MANAGEMENT OF NONULCER DYSPEPSIA

ROBERT S. FISHER, M.D., AND HENRY P. PARKMAN, M.D.

The term “dyspepsia,” derived from the Greek words *dys* (bad) and *pepsis* (digestion), refers to symptoms thought to originate in the upper gastrointestinal tract. Dyspepsia is often used to refer to upper abdominal pain or discomfort but may also encompass symptoms of early satiety, postprandial abdominal bloating or distention, nausea, and vomiting. Dyspepsia can be episodic or persistent and is often exacerbated by eating. The prevalence of dyspepsia ranges from 26 percent in the United States to 41 percent in England. Although only 20 to 25 percent of persons with dyspepsia seek medical care, the problem is responsible for 2 to 5 percent of visits to primary care physicians. Nonulcer dyspepsia results in substantial health care costs — both the direct costs of visits to doctors, expensive tests, and medications, and the indirect costs of absenteeism from work and diminished productivity in the workplace.

DIFFERENTIAL DIAGNOSIS OF DYSPEPSIA

An organic cause is found in 40 percent of patients with dyspeptic symptoms. The most common organic disorders causing dyspepsia are gastroesophageal ulcer, gastroesophageal reflux disease, and gastric cancer (Table 1). In 50 percent of patients, no cause is apparent and the dyspepsia is considered to be idiopathic — that is, the diagnosis is essential, functional, or nonulcer dyspepsia. The history and physical examination do not reliably differentiate organic from nonulcer dyspepsia.

DIAGNOSIS OF NONULCER DYSPEPSIA

The criteria for diagnosing nonulcer dyspepsia, recommended by investigators meeting in Rome in 1991, are chronic or recurrent upper abdominal pain or discomfort for a period of at least one month, with symptoms present more than 25 percent of the time, and an absence of clinical, biochemical, endoscopic, and ultrasonographic evidence of organic disease that would account for the symptoms. Despite these criteria, there is still some overlap between the symptoms of dyspepsia and those of the irritable bowel syndrome.

The Rome group also suggested that it might be useful to subcategorize nonulcer dyspepsia into ulcer-like, reflux-like, dysmotility-like, and nonspecific dyspepsia. Reflux-like dyspepsia is characterized by heartburn, regurgitation, or both, with dyspeptic symptoms and no endoscopic evidence of esophagitis. Epigastric pain is the predominant symptom of ulcer-like dyspepsia. Symptoms of nausea, vomiting, early satiety, and abdominal bloating or distention characterize dysmotility-like dyspepsia. The usefulness of this subclassification based on symptoms has been questioned, since studies have reported a marked overlap among the subtypes. Also, the symptom-based subclassification provides little information about the underlying pathophysiologic abnormality, such as gastroduodenal ulcer or gastroparesis.

THEORIES OF PATHOGENESIS

A number of hypotheses have been proposed to explain the pathogenesis of nonulcer dyspepsia. The gastric acid hypothesis suggests that either hypersecretion of gastric acid or increased sensitivity to it is responsible for dyspeptic symptoms. The motor-disorder hypothesis suggests that motor disorders of the upper gastrointestinal tract, such as gastroesophageal reflux disease, gastroparesis, small-bowel dysmotility, and biliary dyskinesia, cause dyspeptic symptoms. According to the psychiatric hypothesis, the symptoms of dyspepsia may be due to depression, anxiety, or a somatization disorder. The hypothesis of augmented visceral perception suggests that dyspeptic symptoms are exaggerated responses to physical stimuli such as pressure, distention, and temperature. Finally, the food-intolerance hypothesis proposes that certain foods may cause dyspeptic symptoms by triggering secretory motor or allergic responses.

Despite the use of the term “nonulcer dyspepsia,” which suggests an idiopathic functional disorder, a number of nonmotility and motility disorders have been identified as potential causes (Table 2).

Nonmotility Disorders

For years, physicians have cared for patients with pain like that associated with ulcer (epigastric pain...
TABLE 1. DIFFERENTIAL DIAGNOSIS OF DYSPEPSIA.

- Peptic ulcer disease
- Gastroesophageal reflux disease
- Gastropenia
- Gastric neoplasm
- Cholelithiasis or choledocholithiasis
- Acute or chronic relapsing pancreatitis
- Carbohydrate malabsorption (lactose, sorbitol, fructose, or mannitol)
- Intestinal parasites (giardia or strongyloides)
- Injury caused by acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, antibiotics, iron, or other substances
- Systemic disorders (diabetes, thyroid and parathyroid disorders, and connective-tissue disease)
- Ischemic bowel disease
- Abdominal cancer, especially pancreatic cancer
- Nonulcer dyspepsia

TABLE 2. POTENTIAL CAUSES OF NONULCER DYSPEPSIA.

Nonmotility disorders
- Peptic-ulcer diathesis
- Gastritis
  - Hypersecretion of gastric acid
  - Helicobacter pylori infection
- Bile (enterogastric) reflux
- Viral infection
- Duodenitis
- Malabsorption or malabsorption of carbohydrates
  - Lactose
  - Sorbitol
  - Fructose
  - Mannitol
- Small-intestine parasite
  - Giardia lamblia
  - Strongyloides stercoralis
- Chronic pancreatitis
- Psychiatric disorders
- Augmented perception of visceral pain

Motility disorders
- Nonerosive esophageal reflux disease
- Idiopathic gastroparesis
- Small-intestine dysmotility
- Gallbladder and biliary tract dysmotility

Unexplained upper gastrointestinal symptoms, especially in patients who live in or have traveled to parts of the world where parasitic disorders are endemic, may be caused by giardiasis or strongyloidiasis. Unexplained abdominal pain has been reported in a small number of women in whom the only evidence of chronic pancreatitis (exocrine-pancreatic-function insufficiency) was decreased secretion of bicarbonate into the duodenum. Further surgical treatment for ulcer.

Virus-induced gastritis has been suggested as a cause of unexplained gastrointestinal symptoms, since some patients date the symptoms to a period when they had a viral-like illness. However, there is little objective evidence that any specific virus or viral infection causes dyspeptic symptoms.

Malabsorption or malabsorption of carbohydrates can be associated with a wide range of symptoms, including upper abdominal pain with postprandial nausea and bloating. Not only are these symptoms commonly reported by patients with lactase deficiency, but they may also develop in patients who ingest increased quantities of nonabsorbable sugars, such as sorbitol, mannitol, and fructose, contained in liquid medicinal suspensions, chewing gum, and health foods. Mucosal disorders of the small intestine, such as celiac sprue, may also be associated with dyspeptic symptoms.

Another potential cause of nonulcer dyspepsia is bile reflux into the stomach. However, objective studies have shown that patients with dyspepsia who have not undergone prior surgery do not have elevated bile acid concentrations in the stomach. Furthermore, therapeutic agents to treat bile-reflux gastritis have been unavailable or ineffective. A Roux-en-Y diversion of biliary flow has been used successfully in some patients, especially those with bile reflux after surgical treatment for ulcer.

that occurs after meals and at night and that is relieved with antacids), but with no ulcer on examination. In some patients, subsequent endoscopy may reveal an ulcer, suggesting that the initial symptoms were those of an “ulcer diathesis.” In some patients with dyspeptic symptoms, the duodenal mucosa may appear mottled, hyperemic, or irregular on endoscopy, with duodenitis noted on biopsy. The clinical significance of histologic duodenitis is questionable, since it is often found in healthy adults and since there is little improvement in the appearance of the mucosa with treatment, regardless of the symptomatic response.

Some cases of dyspepsia may represent various stages of Helicobacter pylori infection and may subsequently progress to ulcer disease. In the United States, H. pylori infection has a prevalence of up to 1 percent per year of age. The age-related prevalence may be higher in patients with nonulcer dyspepsia, but this finding has not been confirmed by all investigators. Dyspeptic symptoms have been reported after intentional self-infection with H. pylori. Although some studies have demonstrated an improvement in dyspeptic symptoms after the eradication of H. pylori, an equal number of studies have not.

that occurs after meals and at night and that is relieved with antacids), but with no ulcer on examination. In some patients, subsequent endoscopy may reveal an ulcer, suggesting that the initial symptoms were those of an “ulcer diathesis.” In some patients with dyspeptic symptoms, the duodenal mucosa may appear mottled, hyperemic, or irregular on endoscopy, with duodenitis noted on biopsy. The clinical significance of histologic duodenitis is questionable, since it is often found in healthy adults and since there is little improvement in the appearance of the mucosa with treatment, regardless of the symptomatic response.

Some cases of dyspepsia may represent various stages of Helicobacter pylori infection and may subsequently progress to ulcer disease. In the United States, H. pylori infection has a prevalence of up to 1 percent per year of age. The age-related prevalence may be higher in patients with nonulcer dyspepsia, but this finding has not been confirmed by all investigators. Dyspeptic symptoms have been reported after intentional self-infection with H. pylori. Although some studies have demonstrated an improvement in dyspeptic symptoms after the eradication of H. pylori, an equal number of studies have not.

Another potential cause of nonulcer dyspepsia is bile reflux into the stomach. However, objective studies have shown that patients with dyspepsia who have not undergone prior surgery do not have elevated bile acid concentrations in the stomach. Furthermore, therapeutic agents to treat bile-reflux gastritis have been unavailable or ineffective. A Roux-en-Y diversion of biliary flow has been used successfully in some patients, especially those with bile reflux after surgical treatment for ulcer.

Virus-induced gastritis has been suggested as a cause of unexplained gastrointestinal symptoms, since some patients date the symptoms to a period when they had a viral-like illness. However, there is little objective evidence that any specific virus or viral infection causes dyspeptic symptoms.

Malabsorption or malabsorption of carbohydrates can be associated with a wide range of symptoms, including upper abdominal pain with postprandial nausea and bloating. Not only are these symptoms commonly reported by patients with lactase deficiency, but they may also develop in patients who ingest increased quantities of nonabsorbable sugars, such as sorbitol, mannitol, and fructose, contained in liquid medicinal suspensions, chewing gum, and health foods. Mucosal disorders of the small intestine, such as celiac sprue, may also be associated with dyspeptic symptoms.

Another potential cause of nonulcer dyspepsia is bile reflux into the stomach. However, objective studies have shown that patients with dyspepsia who have not undergone prior surgery do not have elevated bile acid concentrations in the stomach. Furthermore, therapeutic agents to treat bile-reflux gastritis have been unavailable or ineffective. A Roux-en-Y diversion of biliary flow has been used successfully in some patients, especially those with bile reflux after surgical treatment for ulcer.

Virus-induced gastritis has been suggested as a cause of unexplained gastrointestinal symptoms, since some patients date the symptoms to a period when they had a viral-like illness. However, there is little objective evidence that any specific virus or viral infection causes dyspeptic symptoms.

Malabsorption or malabsorption of carbohydrates can be associated with a wide range of symptoms, including upper abdominal pain with postprandial nausea and bloating. Not only are these symptoms commonly reported by patients with lactase deficiency, but they may also develop in patients who ingest increased quantities of nonabsorbable sugars, such as sorbitol, mannitol, and fructose, contained in liquid medicinal suspensions, chewing gum, and health foods. Mucosal disorders of the small intestine, such as celiac sprue, may also be associated with dyspeptic symptoms.

Unexplained upper gastrointestinal symptoms, especially in patients who live in or have traveled to parts of the world where parasitic disorders are endemic, may be caused by giardiasis or strongyloidiasis. Unexplained abdominal pain has been reported in a small number of women in whom the only evidence of chronic pancreatitis (exocrine-pancreatic-function insufficiency) was decreased secretion of bicarbonate into the duodenum. The pain was relieved by treatment with pancreatic-enzyme replacement.

When one cannot explain a patient’s intractable symptoms, there is often speculation that they may be a manifestation of an underlying psychiatric disorder. Regardless of whether the cause is functional or organic, however, patients with abdominal pain...
MoLife Disorders

Patients with gastroesophageal reflux disease and no endoscopic evidence of esophagitis often have heartburn. Thirty to 50 percent of patients with heartburn as the predominant symptom also report postprandial dyspeptic symptoms. In addition, up to 25 percent of patients with predominantly dyspeptic symptoms also report heartburn. Many investigators refer to the latter condition as reflux-like dyspepsia. The relation between dyspeptic symptoms and gastric motor dysfunction is not always straightforward. In some patients, both gastric emptying and symptoms of dyspepsia improve with prokinetic therapy; in some, symptoms improve but with no change in gastric emptying; and in others, gastric emptying improves without any change in symptoms. Abnormalities in regional gastric emptying may be correlated with symptoms. Decreased compliance in the proximal stomach, with rapid proximal gastric transit and subsequent antral distention, has been reported in some patients with dyspepsia.

Gallbladder and biliary tract motor dysfunction may also cause nonspecific dyspeptic symptoms. Although delayed gallbladder emptying is an important factor in the development of cholesterol gallstones, its association with dyspeptic symptoms remains controversial. Two types of dysfunction of the sphincter of Oddi cause dyspeptic symptoms; both are often referred to as biliary dyskinesia. One type is characterized by an increased resting pressure of the sphincter of Oddi. The second is characterized by incoordination between either bile acid secretion or gallbladder contraction and relaxation of the sphincter of Oddi, resulting in bile-duct distention.

TREATMENT

There are extensive and sometimes inconsistent data on the treatment of nonulcer dyspepsia. Treatment approaches that have been tested extensively include the use of antisecretory agents, the use of prokinetic agents, and the eradication of *H. pylori*. Several careful meta-analyses have been performed, allowing some general statements about treatment for nonulcer dyspepsia.

Gastric Acid–Suppressing Agents

Extensive studies of gastric acid suppression in the treatment of nonulcer dyspepsia show, in general, that antacids provide little help. Consumers appear to use over-the-counter histamine H2-receptor antagonists more for gastroesophageal reflux and ulcer disease than for dyspepsia.

In 14 of 24 studies, higher doses of acid-suppressing agents than those available without a prescription had a positive effect on symptoms, with improvement reported in 35 to 80 percent of patients receiving the acid-suppressing agents, as compared with 30 to 60 percent of those receiving placebo. In two preliminary studies of omeprazole, a proton-pump inhibitor, for the treatment of nonulcer dyspepsia, only 50 percent of the patients treated with omeprazole had a response, as compared with 25 percent of those receiving placebo. In general, the improvement in dyspeptic symptoms with acid-suppressing agents as compared with placebo has been moderate, with an average difference of only 25 percentage points in the proportions with improvement.

Prokinetic Agents

Prokinetic agents have been more effective than placebo in 16 of 21 studies (metoclopramide has been more effective than placebo in 2 of 2 studies; cisapride in 7 of 12, and domperidone in 7 of 7). In general, the improvement in dyspeptic symptoms with prokinetic agents has been 40 to 45 percentage points greater than with placebo. The few studies that have directly compared acid-suppressing and prokinetic agents have suggested that the prokinetic agents are more effective.

Treatment of *H. pylori* Infection

In 8 of 16 studies, the eradication of *H. pylori* significantly improved symptoms in patients with nonulcer dyspepsia. Although the 1994 National Institutes of Health consensus conference concluded that *H. pylori* should not be eradicated in patients with nonulcer dyspepsia, some investigators and clinicians have recommended that this directive be reconsidered for several reasons. First, some studies have found that the frequency of *H. pylori* infection is higher among patients with nonulcer dyspepsia than among age-matched controls. Second, inten-
tional self-infection with *H. pylori* has caused dyspeptic symptoms. Third, some patients with dyspeptic symptoms may have antral gastritis, which can eventually progress to ulcer disease; this progression may be prevented by the eradication of *H. pylori*. Fourth, *H. pylori* infection may be associated with the development of gastric adenocarcinoma.

The controversy over whether to eradicate *H. pylori* in patients with nonulcer dyspepsia is reflected in a recent survey of British gastroenterologists. Although only 25 percent of the respondents considered *H. pylori* infection a major etiologic factor in nonulcer dyspepsia, 69 percent would eradicate it. It is important to remember that primary care physicians manage dyspeptic symptoms without knowing whether organic disorders are present and without the benefit of endoscopy. In this setting, the eradication of *H. pylori* is reasonable even if it is not effective in treating dyspepsia caused by ulcer disease.

**Psychotropic Medications**

Psychotropic medications include tricyclic antidepressants, serotonin-receptor–reuptake inhibitors, and anxiolytic agents. Although there is a substantial literature on the successful use of tricyclic antidepressants in low and full doses to treat depression, noncardiac chest pain, the irritable bowel syndrome, fibromyalgia, and interstitial cystitis, there are no data from controlled studies of these agents for the treatment of nonulcer dyspepsia. Patients with nonulcer dyspepsia may have a response to these agents that is similar to the favorable response in patients with noncardiac chest pain or the irritable bowel syndrome. Anxiolytic agents, such as the benzodiazepines, should be avoided because of potential addiction.

**Antinociceptive Agents**

Agents used to inhibit pain or its perception include low-dose tricyclic antidepressants, kappa opioid agonists (e.g., fedotozine), serotonin-receptor antagonists (e.g., ondansetron and granisetron), and somatostatin analogues (e.g., octreotide). Visceral nociception is receiving much attention because of recent studies showing augmented visceral perception of balloon distention in the rectum, the esophagus, and the stomach or small intestine in patients with the irritable bowel syndrome, noncardiac chest pain, and nonulcer dyspepsia, respectively. Fedotozine has been used in studies in Europe for the treatment of nonulcer dyspepsia. Patients with nonulcer dyspepsia may have an antral gastritis, which can eventually progress to ulcer disease; this progression may be prevented by the eradication of *H. pylori*. The controversy over whether to eradicate *H. pylori* in patients with nonulcer dyspepsia is reflected in a recent survey of British gastroenterologists. Although only 25 percent of the respondents considered *H. pylori* infection a major etiologic factor in nonulcer dyspepsia, 69 percent would eradicate it. It is important to remember that primary care physicians manage dyspeptic symptoms without knowing whether organic disorders are present and without the benefit of endoscopy. In this setting, the eradication of *H. pylori* is reasonable even if it is not effective in treating dyspepsia caused by ulcer disease.

**Role of Endoscopy**

Whether and, if so, when to perform endoscopy in patients with dyspeptic symptoms are controversial questions. Gastroduodenal ulcer, reflux esophagitis, and upper gastrointestinal cancer are detected by endoscopy, which is more sensitive than upper gastrointestinal contrast radiography and allows biopsy, if needed. Since approximately 40 percent of cases of dyspepsia have an organic cause, some investigators have argued that all patients should undergo endoscopy and abdominal ultrasonography before empirical therapy is administered. In addition, a number of cost–benefit studies suggest that the use of endoscopy before treatment may decrease rather than increase the overall cost of care. Since dyspepsia occurs in 25 percent or more of the general population and since endoscopy is expensive, a number of factors should be considered in deciding whether to perform endoscopy before treatment. First, are there signs or symptoms that suggest an important underlying organic cause of the dyspepsia, especially gastric cancer (Table 3)? If so, an endoscopic examination should be performed promptly to determine whether the patient has a gastric tumor or a peptic ulcer. Second, how high a risk of an incorrect or overlooked diagnosis is the patient, his or her family, and the physician willing to tolerate? Third, what is the patient’s expectation? Many patients fear that they have cancer. Endoscopy often helps reassure them that cancer has been ruled out, and this reassurance in itself may have a therapeutic effect.

Studies of chronic dyspepsia suggest that endoscopy should be performed primarily in older patients (55 years of age or older), particularly those with a recent onset of dyspepsia or a change in symptoms. Endoscopy in persons younger than 55 years may be unnecessary, unless there are signs or symptoms of an important underlying disorder, because of the very low likelihood of gastric cancer in this age group.

**Empirical Therapy**

If there are no signs or symptoms of a serious organic disorder or when no cause is found after rou-

---

**Table 3. Characteristics, Symptoms, and Signs That May Suggest a Serious Underlying Organic Disorder.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Symptom</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50 yr</td>
<td>Anorexia or weight loss</td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td>Dysphagia or odynophagia</td>
<td>Failure of several treatments</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Strong history of familial cancer</td>
</tr>
<tr>
<td></td>
<td>Anemia or positive fecal occult-blood test</td>
<td></td>
</tr>
</tbody>
</table>

---
tine diagnostic testing (upper endoscopy and biliary tract ultrasonography), empirical treatment is a reasonable approach, as suggested in 1985 by the Health and Public Policy Committee of the American College of Physicians. It is important to realize that the presence of *H. pylori* infection as well as its relation to ulcer disease influences the treatment approach for dyspepsia.

In young patients without signs or symptoms of a serious underlying disorder, a reasonable approach is to determine whether *H. pylori* infection is present by performing either a serologic test for IgG antibodies or possibly a uracil breath test, which can be used to determine whether active infection is present. Patients with negative results are unlikely to have serious organic gastroduodenal disease. Those with positive results should be treated with anti-*H. pylori* agents. If the symptoms resolve, it may mean that an ulcer or ulcer diathesis has been treated and cured and that no further investigation is needed. The drawbacks of evaluation and treatment of *H. pylori* infection in patients with dyspepsia are that many patients may not have a response to treatment and that bacteria with antibiotic resistance may emerge.

An initial trial with a gastric acid-suppressing agent such as a histamine H2-receptor antagonist or a prokinetic agent is suggested as a first course of empirical treatment in most algorithms for the treatment of nonulcer dyspepsia in patients who do not have *H. pylori* infection or who have infection but do not have a response to anti-*H. pylori* agents. If there is no response to this initial empirical treatment, endoscopy and more specialized testing may be indicated to guide future treatment.

A prokinetic agent used as empirical therapy for nonulcer dyspepsia may be effective in patients with reflux-like or dysmotility-like dyspepsia. Cisapride has significantly fewer side effects than metoclopramide.

Gastric acid suppressants, such as histamine H2-receptor antagonists, may relieve symptoms in patients with ulcer-like or reflux-like dyspepsia. Proton-pump inhibitors are sometimes used as a diagnostic tool to rule out gastroesophageal reflux disease in patients with dyspepsia.

In general, subclassification of dyspepsia as a reflux-like, dysmotility-like, or ulcer-like disorder may be useful in choosing the initial agent for empirical treatment. It may be prudent to refer patients with psychiatric symptoms to a psychologist or a psychiatrist for evaluation and treatment.

**SUMMARY**

Nonulcer dyspepsia is a common disorder with a wide array of symptoms. It is not advisable to perform extensive diagnostic tests such as esophagogastroduodenoscopy, biliary tract ultrasonography, or even abdominal computed tomography in all patients. Whether all patients who present with dyspeptic symptoms should at least undergo initial endoscopy is controversial. Empirical therapy is advisable in patients who do not have signs or symptoms of an underlying organic disorder, such as gastric ulcer or cancer. If empirical therapy is indicated without diagnostic testing, where does one begin? Which approach — prokinetic therapy, acid suppression, eradication of *H. pylori*, psychotropic therapy, or anti-nociceptive therapy — is most effective? The answer to this question will be determined by studies of the short- and long-term effects of the various therapies on symptoms and quality of life and by cost–benefit analyses.

**REFERENCES**