INTRODUCTION

Dyspepsia is not a single disease, but rather a complex of symptoms that often overlap with other disease entities. The investigation of undifferentiated dyspepsia poses a diagnostic dilemma for primary care physicians. Because evidence to guide best practices is sparse, it is challenging for the primary care physician to decide the optimal diagnostic and therapeutic plan. Although life-threatening conditions are rare in this setting, a missed diagnosis of esophageal cancer or other serious upper gastrointestinal pathology could be devastating. For this reason, invasive diagnostic tests, including endoscopies, are common in the evaluation of uninvestigated dyspepsia. Given the high prevalence of dyspepsia around the world, developing a prudent and evidence-based method of investigation and treatment of dyspepsia is of the utmost importance to prevent potential harm and unnecessary medical expense.
Dyspepsia affects 25% to 40% of the population over a lifetime and accounts for 3% to 5% of all primary care clinic visits, estimated at 4 million primary care visits a year in the United States alone. One study found that 50% of European and North American patients with dyspepsia are on medication for it, and more than 30% report ever missing work or school because of burdensome symptoms. Another study reported 12.4% of patients with dyspepsia missed work because of their symptoms over a 1-year period. Among active workers with dyspepsia, more than 32% reported their symptoms caused them to be absent from work, and 78% reported reduced productivity because of dyspepsia (presenteeism). That study did not find a difference in lost productivity between those with organic versus those with functional dyspepsia (FD). Nearly 62% of the patients in one study had consulted a physician for their dyspeptic symptoms, and 74% of those went more than once. More than two-thirds of those patients who had consulted

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Fig. 1. Causes of dyspepsia. *(Data from Zagari RM, Fuccio L, Bazzoli F. Investigating dyspepsia. BMJ 2008;337:1–5.)*

Dyspepsia affects 25% to 40% of the population over a lifetime and accounts for 3% to 5% of all primary care clinic visits, estimated at 4 million primary care visits a year in the United States alone. One study found that 50% of European and North American patients with dyspepsia are on medication for it, and more than 30% report ever missing work or school because of burdensome symptoms. Another study reported 12.4% of patients with dyspepsia missed work because of their symptoms over a 1-year period. Among active workers with dyspepsia, more than 32% reported their symptoms caused them to be absent from work, and 78% reported reduced productivity because of dyspepsia (presenteeism). That study did not find a difference in lost productivity between those with organic versus those with functional dyspepsia (FD). Nearly 62% of the patients in one study had consulted a physician for their dyspeptic symptoms, and 74% of those went more than once. More than two-thirds of those patients who had consulted

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Fig. 2. Functional dyspepsia diagnostic criteria. One or more of the listed symptoms, in the absence of structural disease. Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
a physician were taking medications for their dyspepsia, and 36% underwent endoscopy.\textsuperscript{5}

Of patients presenting with dyspepsia symptoms, 50% to 60% have no biochemical or structural lesion to explain their symptoms (Fig. 1). FD, previously referred to as “nonulcer dyspepsia,” describes these symptoms in the absence of an identifiable organic, systemic, or metabolic etiology (Fig. 2).\textsuperscript{2,7–9} FD is divided into two categories by the Rome III criteria, although there is considerable overlap between the two. The first is postprandial distress syndrome (Fig. 3), characterized by bothersome postprandial fullness and early satiation; the second is epigastric pain syndrome (Fig. 4), characterized by epigastric pain and burning, with onset of at

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{Postprandial distress syndrome.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{Epigastric pain syndrome.}
\end{figure}
least 6 months ago, and present during the last 3 months. The symptoms are usu-
ally aggravated by meals. Some older definitions of FD include symptoms of gastro-
esophageal reflux, such as heartburn and belching, whereas the newer Rome III
definition does not include these symptoms. However, there is a great degree of
overlap between FD and coexisting reflux disease. One study revealed 37% of pa-
tients complaining of symptoms that could be characterized as FD actually had
esophageal acid reflux proved by pH monitoring. The exact causes of FD remain
unknown but symptoms are more common in women, smokers, aspirin users, and those with a history of acute gastroenteritis. Coffee and alcohol are not definitively associated with FD, and the role of *Helicobacter pylori* infection in FD is still up for debate.

**PATHOPHYSIOLOGY**

The pathophysiology of FD is not completely understood, with abnormal gut motility, visceral hypersensitivity, genetic, infectious/postinfectious, and psychosocial factors playing a role.

Delayed gastric emptying occurs in 20% to 50% of patients with FD. Up to two-thirds may have abnormalities of either antral or duodenal motility. Those patients with delayed gastric emptying predominantly have symptoms of postprandial fullness, nausea, and vomiting. Up to 40% of patients with symptoms of early satiety and weight loss have impaired gastric accommodation, which suggests those patients’ dyspeptic symptoms could be caused by increased intragastric pressure after ingestion of a meal. Studies using capsaicin have shown increased sensitivity to visceral stimulation in patients with FD. Several genetic polymorphisms are associated with visceral hypersensitivity and other upper abdominal symptoms in FD.

FD occurs at higher rates in people with a history of acute infectious gastroenteritis (IGE), suggesting a role for gut immune dysregulation. After an episode of IGE, patients with FD are noted to have focal T-cell aggregation with elevated CD8$^+$ cells and macrophages and decreased CD4$^+$ cells in and around the crypts and villi of the duodenum. This suggest that patients with FD are slower, or unable, to terminate the inflammatory response. A meta-analysis investigating the risk of developing FD after an episode of acute IGE found an odds ratio of 4.76 in the first year after a self-reported episode of IGE and 1.97 thereafter, with an overall odds ratio of nearly 2.2. Several studies have also linked eradication of *H pylori* to improvement in FD.

### Table 1

**Differential diagnosis of dyspepsia**

<table>
<thead>
<tr>
<th>Upper Gastrointestinal Tract</th>
<th>Other Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux with or without esophagitis</td>
<td>Gallbladder: cholelithiasis or cholecystitis</td>
</tr>
<tr>
<td>Peptic ulcer disease: gastric or duodenal</td>
<td>Pancreas: pancreatitis or pancreatic malignancy</td>
</tr>
<tr>
<td>Esophageal malignancy</td>
<td>Vascular: ischemic heart disease, mesenteric ischemia</td>
</tr>
<tr>
<td>Gastric malignancy</td>
<td>Medications: NSAIDS, aspirin, steroids, antibiotics, calcium channel blockers, bisphosphonates, SNRIs, theophylline</td>
</tr>
<tr>
<td>Functional dyspepsia</td>
<td>Hepatobiliary: hepatitis and hepatic malignancy</td>
</tr>
</tbody>
</table>

*Abbreviations:* NSAIDS, nonsteroidal antiinflammatory drugs; SNRIs, serotonin-norepinephrine reuptake inhibitors.
FD is more common in patients with concomitant depression or anxiety, and those with a history of abuse. A recent prospective cohort study of nearly 1200 patients demonstrated that high baseline levels of anxiety were an independent predictor of developing FD in the future. Patients with anxiety and depression are more likely to seek treatment of their dyspepsia, and are also more likely to experience their symptoms as more severe than those without a comorbid psychiatric condition. As with any functional gastrointestinal disorder, somatization is a potential cause (Table 1).

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is one of the most common upper gastrointestinal disorders in the developed world. It is caused by prolonged gastric acid exposure in the esophagus due to poor esophageal motility, decreased lower esophageal sphincter tone, and impairments in gastroesophageal junctions. Obesity, smoking, alcohol, pregnancy, certain foods, and a recumbent position shortly after eating can all cause GERD or make it worse. There is a great deal of overlap between GERD and FD. A study of prevalence of pathologic esophageal acid reflux in patients with FD found that nearly 32% of patients with FD had pathologic esophageal acid reflux. The prevalence is approximately 50% in patients who complained predominantly of epigastric burning.

The hallmark of GERD is heartburn and regurgitation, particularly after meals. Patients may also have extraesophageal symptoms, such as cough or laryngitis. Endoscopy is 90% to 100% specific for diagnosing esophagitis in reflux disease. However, 50% to 70% of patients with the classic heartburn and regurgitation symptoms of GERD have no esophagitis on endoscopy, making it a rather insensitive screening tool. When typical heartburn and regurgitation occur together, a diagnosis of GERD can be made without further testing with greater than 90% accuracy. A study comparing a 2-week course of high-dose omeprazole versus 24-hour esophageal pH monitoring found the two interventions to be equally sensitive in diagnosing GERD in patients with erosive esophagitis. Thus, for those patients presenting with heartburn and regurgitation, an empiric therapeutic trial of a standard-dose proton pump inhibitor (PPI) for 2 weeks or a double-dose of PPI therapy for 1 week is appropriate. If patients respond to an appropriate trial of antisecretory therapy, a diagnosis can be made and no further testing is warranted. However, if patients do not respond to empiric therapy, have chronic symptoms, or have alarm symptoms, endoscopy should be considered to evaluate for Barrett esophagus, stricture, ulcers, or malignancy.

Dietary and lifestyle modifications are often recommended as first-line treatment of GERD. Suggested dietary changes include avoiding foods and drinks that decrease lower esophageal sphincter pressure, delay gastric emptying, or provoke reflux symptoms. These foods include chocolate, mint, alcohol, tomato, citrus juice, carbonated beverages, garlic, onions, and fatty meals. Additionally, instituting behavioral modifications might also decrease reflux symptoms. These modifications include elevating the head of the bed while sleeping, avoiding a recumbent position for 3 hours after meals, sleeping in the left lateral position, smoking cessation, and avoidance of alcohol. Although these recommendations are almost universally accepted, the evidence to support their effectiveness is not strong.

After the diagnosis of GERD is made, patients and providers can engage in shared decision making to determine if a step-up or a step-down approach to therapy is appropriate. A step-up approach starts with over-the-counter therapy with an H2-receptor antagonist (H2RA) and steps up therapy to medications with a
higher degree of efficacy (standard-dose PPI, then high-dose PPI) if symptoms persist (Table 2). A step-down approach to therapy starts with daily or twice-daily PPI therapy and steps down to therapies with lower degree of efficacy as symptoms allow. With each model, the therapy is maintained at the lowest level that completely controls symptoms. Clinicians should choose the most cost-effective medication at the lowest effective dose for the shortest amount of time possible.

HELICOBACTER PYLORI AND PEPTIC ULCER DISEASE

Helicobacter pylori infection is associated with 90% to 95% of duodenal ulcers and 60% to 80% of gastric ulcers. The prevalence of H pylori ranges from 20% in North America and western Europe to more than 80% in eastern Europe, Asia, and most of the developing world. H pylori can progress rapidly in high-prevalence areas or slowly in low-prevalence areas toward atrophic gastritis. A fast rate of progression toward gastritis is associated with a higher incidence of gastric cancer, whereas a slower rate of progression is more closely associated with peptic (duodenal) ulcer disease. H pylori are a known carcinogen. The International Agency for Research on Cancer estimates 43% of the global burden of gastric cancer to be related to H pylori, and this is likely an underestimation.

There is, however, some uncertainty as to whether chronic H pylori infection plays a role in dyspepsia in the absence of peptic ulcer disease or gastric cancer. Indeed, multiple systematic reviews and meta-analyses have looked into this question with conflicting results. One trial of H pylori eradication found that patients with complete or satisfactory response to a proton pump–based eradication therapy had decreased gastritis and improvement of dyspepsia symptoms at 1 year. Some randomized controlled trials have shown a test-and-treat strategy is equally as effective as prompt endoscopy in reducing the severity of dyspepsia symptoms but with much lower medical costs. Recently, the HEROES trial identified H pylori–positive adults with FD by Rome III criteria, and randomized them to H pylori triple therapy or omeprazole plus placebo. The main outcome was at least 50% symptomatic improvement at 12 months. Forty-nine percent of the patients in the antibiotics group reached the primary outcome, as opposed to 36.5% in the PPI plus placebo group. Overall, 78% in the antibiotics group and 67.5% in the control group reported some symptomatic improvement. Based on a large Cochrane review, the number needed to treat to achieve a complete symptomatic response in one patient is 14. Some studies suggest a trend toward higher symptom response by H pylori eradication treatment in high-prevalence populations. However, a recent meta-analysis of randomized

<table>
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<tr>
<th>Drug</th>
<th>Standard Dose</th>
<th>High Dose</th>
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<tr>
<td>Dexlansoprazole</td>
<td>30 mg daily</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 mg daily</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>15–30 mg daily</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>omeprazole</td>
<td>20–40 mg daily</td>
<td>20–40 mg twice daily</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20–40 mg daily</td>
<td>40 mg twice daily</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg daily</td>
<td>20 mg twice daily</td>
</tr>
</tbody>
</table>

controlled trials of *H pylori* eradication therapy on symptoms of FD demonstrated improvement in symptoms and a similar rate of response across Asian, European, and American populations. Test-and-treat will cure most cases of underlying peptic ulcer disease, and will prevent most cases of gastric cancer. Although it does not resolve most cases of FD, at least a significant minority of patients will have significant improvements in their dyspepsia symptoms with this intervention. A test-and-treat strategy for *H pylori*, especially in populations with a high prevalence of the disease, is a reasonable approach (Fig. 5).

The $^{13}$C-urea breath test is 95% sensitive and specific for *H pylori*; however, it is not universally available. The *H pylori* stool antigen test has similar sensitivity (91%) and specificity (93%), but patients have to remain off their PPI therapy for 2 weeks, and antibiotics for 4 weeks, before performing either of these tests. *H pylori* serology is widely available but is considerably less sensitive and specific (85% and 79%, respectively) than the other testing (Table 3). However, patients do not need to be off therapies to obtain serology, and the ease with which it is administered (a simple blood draw) makes for improved adherence. In populations with a high prevalence of *H pylori* and challenges with follow through, *H pylori* serology is a reasonable compromise.

**Table 3**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{13}$C-urea breath test</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Stool antigen test</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Serology</td>
<td>85</td>
<td>79</td>
</tr>
</tbody>
</table>

NON–UPPER GASTROINTESTINAL MIMICS

Diseases that can mimic symptoms of dyspepsia include cholelithiasis and cholecystitis, chronic pancreatitis, cardiac and mesenteric ischemia, irritable bowel syndrome, and medication side effects. These alternate diagnoses should be considered throughout the work-up of dyspepsia, especially if patients are not reporting symptom improvement with the prescribed therapies.

There are five key decision points in investigating dyspepsia (Fig. 6). The first, and most important, is to identify any alarm signs and symptoms. They include bleeding, iron-deficiency anemia, persistent vomiting, an epigastric mass, unexplained weight loss, and persistent dysphagia (Fig. 7). Age older than 55 years at the time of onset should also be considered an alarm feature. Patients who present with dysphagia and one or more of these clinical features should be referred for emergent (in the case of hemorrhage) or urgent endoscopy.

For those patients without alarm signs and symptoms, the other key questions are as follows: (1) Are there other possible mimics of the dyspepsia, such as cardiac, hepatobiliary, pancreatic, or vascular? (2) Is the patient on any potentially offending medications? (3) Does the patient have predominant symptoms of heartburn and regurgitation? (4) Has the patient been tested for *H. pylori*? Those who are determined to have an alternative source of their dyspepsia should be treated accordingly. If a patient is found to be taking a potentially offending medication, all efforts should be made to find alternative therapies. If this is not possible, then antisecretory therapy, such as a PPI, should be added to the patient’s therapy.

Those who have symptoms of heartburn or regurgitation, even if they also have symptoms of epigastric pain and postprandial fullness, deserve a 4- to 6-week trial of a PPI. All others should be tested, and treated if positive, for *H. pylori* with the

Fig. 6. Diagnosis algorithm. CBT, cognitive behavioral therapy; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; NSAIDs, nonsteroidal antiinflammatory drugs; PPI, proton pump inhibitor.
most sensitive and specific test available. Those who are negative for *H pylori* should be given a 4- to 6-week trial of antisecretory therapy. If patients fail to respond to these measures, endoscopy is an appropriate next step, and if the endoscopy is negative, gastric emptying studies can be considered. A gastric emptying study can help guide therapy if it demonstrates rapid or delayed emptying. After that, alternate therapies can be explored, including antidepressants, psychotherapy, cognitive behavioral therapy, hypnosis, and acupuncture.

**TREATMENT OF FD**

Fewer than 60% of patients with FD improve with medication alone.41

**Acid-suppression Therapy**

Various forms of acid-suppression therapy are available, including over-the-counter antacids, H2RAs, and PPIs. Antacids are commonly used but have the least compelling evidence for effectiveness, and PPIs have the strongest evidence of effectiveness.

The evidence to support the use of H2RAs for FD is conflicting. Some trials have demonstrated superiority of H2RAs over placebo, whereas others have not. In a small crossover study, nizatidine was shown to improve postprandial fullness and early satiation over placebo (70% response vs 10% response). The treatment also improved gastroesophageal reflux symptoms over placebo (53% vs 0%). This study evaluated gastric motility and ghrelin levels, and found that the H2RA improved gastric emptying but had no impact on ghrelin levels.42 A Cochrane review from 2006 showed H2RAs improved dyspepsia symptoms in 54% of patients, compared with 40% for placebo. However, some of the studies included in this meta-analysis were of poor quality.43

PPIs have been shown to be effective in the treatment of FD in several placebo-controlled, randomized controlled trials. Symptom improvement ranges from 32% in one study44 to 68% in another.45 Notably, the response to PPIs tends to be higher in patients with reflux-like dyspepsia, epigastric pain, or burning.46 The subset of patients with postprandial distress symptoms did not tend to respond to PPI therapy.47
Interestingly, the response rate to placebo across several studies ranged from 19% to 49%, which overlaps considerably with the range of responders to PPI therapy.43–48 A Cochrane review demonstrated overall symptom relief rates of 34% in patients receiving PPI therapy, compared with 25% in patients receiving placebo.43

Prokinetics

A brief randomized controlled trial comparing efficacy of PPIs versus prokinetic therapy in relieving the symptoms of patients with FD did not demonstrate a difference between the two, with 50.6% of the PPI group and 47.85% of the prokinetic group achieving meaningful symptom relief. The therapeutic response did not differ in subgroup analyses of patients fulfilling criteria of either epigastric pain syndrome or postprandial distress syndrome.49 A meta-analysis of 27 randomized, controlled trials of prokinetic agents for treatment of FD symptoms found the prokinetics were significantly more likely to improve symptoms over placebo. However, most of the trials included in this analysis studied cisapride, which is off the market, and domperidone, which is not available in the United States. Only one of the studies included metoclopramide.50 Thus, although prokinetic agents are likely equally efficacious to PPIs for the treatment of FD, given the risk of tardive dyskinesia with use of metoclopramide, this medication is not generally recommended for prolonged use.

Acotiamide, an acetylcholinesterase inhibitor that works by accelerating gastric motility,51 has been shown in several placebo-controlled trials to improve FD symptoms and gastric emptying. The number need to treat to improve symptoms was six, and the number needed to treat to eliminate symptoms was 16.52–54 This medication is still undergoing investigation and has not yet been approved by the Food and Drug Administration.

Anxiolytics and Antidepressants

Several studies have shown possible efficacy of anxiolytics and antidepressants for treatment of FD. A systematic review of studies comparing antidepressants and anxiolytics with placebo in the treatment of FD found benefit with the study drugs. Although there were limitations to the studies included in the review, the therapies (which included tricyclic antidepressant agents, levosulpiride [a dopamine-2 receptor agonist], and anticholinergic and anxiolytic medications) were approximately equivalent to studies of antisecretory agents and prokinetic agents (overall relative risk reduction of 0.45).55 A more recent review again showed that antidepressants and anxiolytics are associated with significant pain reduction in patients with FD, and are as effective as classic antisecretory and prokinetic agents.56 Several randomized controlled trials have demonstrated modest efficacy of tricyclic antidepressants in treating FD.57,58

Theoretically, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants should decrease neuropathic pain and address underlying psychiatric issues, which would address at least two of the potential pathophysiologic mechanisms of FD. Furthermore, selective serotonin reuptake inhibitors may enhance gut transit and alter gastric accommodation.59 However, study data to support the use of newer antidepressants for FD have been mixed. A randomized clinical trial of venlafaxine, a serotonin-norepinephrine reuptake inhibitor, failed to demonstrate improvement over placebo.60 The Functional Dyspepsia Treatment Trial, an international multicenter, parallel group, randomized, double-blind, placebo-controlled trial, is ongoing to evaluate whether 12 weeks of treatment with escitalopram or amitriptyline improves FD symptoms compared with treatment with placebo.61
Buspirone, an anxiolytic medication with fundus-relaxing properties, was compared with placebo in a small double-blind, randomized, controlled crossover trial. Patients were given the study drug 15 minutes before meals. Buspirone significantly reduced the overall severity of dyspepsia symptoms, including postprandial fullness, early satiation, and upper abdominal bloating. Buspirone increased gastric accommodation but did not alter the rate of gastric emptying.62

Other Medications

An industry-sponsored study out of France of 276 general practice patients with dyspepsia compared a combination pill (simethicone, activated charcoal, and magnesium oxide) with placebo. Those receiving the study drug had decreased postprandial fullness, epigastric pain, epigastric burning, and abdominal bloating compared with placebo. The number needed to treat to achieve a 70% decrease in overall dyspeptic symptoms was seven.63 Although this combination pill is not commercially available in the United States, an interested patient or practitioner could conceivably prescribe the components separately.

Psychotherapy

A recent study out of Japan randomized patients with FD to medical therapy alone or medical therapy with brief psychodynamic therapy. The results demonstrated brief psychodynamic therapy improved all gastrointestinal symptoms, including heartburn, nausea, postprandial fullness, bloating, and upper and lower abdominal pain, over medical therapy alone.64 Another randomized, controlled trial compared cognitive psychotherapy with usual care and found the intervention group had fewer days of epigastric pain, and less nausea, heartburn, and diarrhea.65 A randomized controlled trial of psychodynamic-interpersonal therapy versus supportive therapy demonstrated significant improvement with psychodynamic-interpersonal therapy over supportive therapy. However, the differences had disappeared at 1-year poststudy, unless the group with severe heartburn was excluded, in which case the psychodynamic-interpersonal group still did better.66 However, a systematic review of psychological therapies for FD found insufficient evidence on the efficacy of psychological therapies for FD, noting that the sample sizes were small and the study designs variable. All of the included studies in that review had to adjust for baseline differences to achieve statistical significance.67

Acupuncture

Some research has suggested that acupuncture might improve gastric emptying and accommodation.68 A Cochrane review is underway to survey the available evidence on the effectiveness and safety of this intervention for FD.

SUMMARY

Dyspepsia is a complex disorder with several distinct pathophysiologic mechanisms that are still poorly understood (Fig. 8). Patients who experience dyspepsia have a high burden of disease, with significant personal and economic costs. Although serious pathology presenting as dyspepsia is rare, clinicians need to be aware of alarm features that should trigger prompt referral for subspecialty care. Those without alarm features can be managed in a rational way with either empiric antisecretory therapy, test-and-treat for H pylori eradication, antidepressants, and psychotherapy, or a combination of these. Given the heterogeneity of symptoms and large variability in
response to different treatments, more research into specific pathophysiologic mechanisms will likely help guide diagnosis and treatment choices in the future.

REFERENCES

45. Meineche-Schmidt V, Christensen E, Bytzer P. Randomised clinical trial: identification of responders to short-term treatment with esomeprazole for dyspepsia


