Epigastric Pain in Dyspepsia and Reflux Disease

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Epigastric pain may occur as a specific and localized symptom, as part of a group of symptoms that include heartburn, or in association with bloating or early satiety. The current classification (Rome II) characterizes ulcer-like dyspepsia by predominant pain centered in the upper abdomen and characterizes dysmotility-like dyspepsia by discomfort. The large number of patients presenting with epigastric pain has led to the development of empirical strategies.
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Epigastric pain is a symptom that has been recognized for thousands of years. Ancient Chinese and Indian texts describe treatments for this affliction. The pain may occur as a specific and localized symptom, in which case it is frequently referred to as "ulcer-type pain." Alternatively, it may be part of a group of symptoms that includes heartburn when it is referred to as "reflux-like" or in association with bloating or early satiety when it is referred to as "dysmotility-like." Until the widespread availability of endoscopy, epigastric pain was thought to be diagnostic of peptic ulcer disease. Endoscopic studies in patients with epigastric pain (including those who reported improvement with antacids) were frequently normal, suggesting that epigastric pain was not a specific symptom for peptic ulcer disease. Studies on gastro-esophageal reflux disease (GERD) have also shown patient-reported epigastric pain that improves with therapy. As a result, the symptoms of epigastric discomfort or pain are best considered as a part of the spectrum of uninvestigated dyspepsia (chronic or recurrent pain and discomfort centered in the upper abdomen). More specific terms such as ulcer disease or erosive esophagitis are more appropriately reserved for patients who have specific findings at endoscopy.

Epidemiology

In the United States, the point prevalence of upper abdominal pain or discomfort is approximately 25%, excluding those people who have typical GERD symptoms.[1] The incidence is not as well documented. In the United States, approximately 9% of people annually who had no symptoms of dyspepsia in the prior year reported new dyspeptic symptoms on a follow-up evaluation.[2] The prevalence appears to remain stable as the number of patients developing new symptoms is matched by the number of patients losing them.

Classification of Epigastric Pain and Other Dyspeptic Symptoms

Many attempts have been made to cluster dyspeptic symptoms and to offer a possible unifying pathogenic mechanism. The first Rome consensus statement party suggested that patients with functional dyspepsia should be stratified into ulcer-like, reflux-like, and dysmotility-like dyspepsia, based on the clusters of symptoms reported.[3] Patients with epigastric pain would therefore be classified as having ulcer-like dyspepsia. While this classification was attractive in theory, it was not useful in clinical practice because it did not reliably predict the pathogenic mechanism for the cluster of symptoms. The subsequent Rome II consensus definition classified functional dyspepsia into two main subclasses based on the predominant symptom located in the central portion of the upper abdomen. In the current classification (Rome II), ulcer-like dyspepsia is characterized by predominant pain centered in the upper abdomen, and dysmotility-like dyspepsia is characterized by symptoms that are different from pain: so-called discomfort (a term used to describe unpleasant or troublesome nonpainful sensations), suggesting dysfunctional gastro-duodenal motility. Patients with predominant symptoms of heartburn were no longer included in the dyspepsia group and are considered to have GERD.[2]

The Role of Gastric Acid in the Genesis of Epigastric Pain

Patients with epigastric pain and matched controls without epigastric pain have similar basal and peak acid outputs.[5,6] Despite this, acid inhibition by pharmacologic intervention alleviates dyspeptic symptoms in some patients. If heartburn is a predominant symptom, the patient is more likely to respond to acid suppression.[7] Although ambulatory pH testing is useful as a diagnostic test, it is not sensitive enough to exclude acid reflux as a mechanistic cause of epigastric pain. Furthermore, some patients may have epigastric pain in response to short episodes of reflux, despite having total distal acid exposure times that are normal. In an interesting study of the sensation of epigastric pain, Earlam and colleagues compared 61 patients with a duodenal ulcer and epigastric pain to 39 patients with an ulcer who did not have epigastric pain.[8] Fifty-three of the 61 patients with epigastric pain developed the symptom when the esophagus was perfused with dilute acid. In contrast, none of the patients who did not have epigastric pain developed this symptom when acid was perfused into the esophagus. These data suggest that even patients with ulcer disease may report epigastric pain due to acid in the esophagus rather than due to acid perfusing the ulcer crater.

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Mucosal Inflammation, *Helicobacter Pylori* Infection, and Epigastric Pain

Helicobacter pylori (*H. pylori*) infection is associated with epigastric pain for two reasons: first, because it causes peptic ulcer disease, and second, because the eradication of *H. pylori* relieves symptoms in a substantial proportion of infected patients.[9] Persistence of epigastric pain has been shown to be a marker of failed eradication. The association with epigastric pain is less clear in the absence of peptic ulcer disease. This is because most infected individuals have no symptoms, despite the presence of histologic gastritis. Furthermore, eradication therapy in patients with symptoms does not alleviate these symptoms in the majority of patients.[10]

Visceral Hypersensitivity and Epigastric Pain

There is evidence that the stomach and other regions of the gut including the duodenum and esophagus are hypersensitive in some patients with upper abdominal discomfort or pain.[11,12] Tack and colleagues recently reported that in 160 patients with functional dyspepsia, one third had gastric hypersensitivity. This abnormality was associated with increased postprandial epigastric pain as well as belching and weight loss.[13]

Diagnostic Strategies in Epigastric Pain

The Unaided Clinical Diagnosis

In a prospective study of the diagnostic value of the clinical interview

and examination in primary care, the Danish Dyspepsia Study Group found that the clinical diagnosis was not particularly reliable in patients with epigastric pain or discomfort.[14] The clinical diagnoses of both gastroenterologists and primary care physicians had a relatively poor positive predictive value ranging from 28%–37% for a diagnosis of peptic ulcer disease, but both primary care physicians and gastroenterologists were able to predict if the symptoms were acid related with a high degree of accuracy.

Endoscopy

Large studies of unselected, consecutive patients presenting to primary care physicians with upper abdominal pain have shown that 10%–20% of them have peptic ulcer disease, 5%–15% have esophagitis, 10%–12% have abnormalities that are less specific (gastritis, duodenitis), and approximately 50% have no visible abnormalities at endoscopy. Kagevi and colleagues[15] studied 172 patients with dyspepsia who were evaluated in a primary care center. After appropriate history and physical, as well as laboratory tests, upper endoscopy, and flexible sigmoidoscopy, a final diagnosis was established. Six percent of patients had esophagitis, 13% had peptic ulcer disease, and 64% had non-ulcer dyspepsia. In another study, Gear et al[16] studied 346 patients and found that a gastric ulcer was present in 6% of cases and a duodenal ulcer in 12% of cases presenting with dyspepsia in primary care. Sixty percent of patients in that study did not have specific findings at endoscopy. With the general decline in peptic ulcer disease caused by the eradication of *H. pylori* and the widespread use of acid-inhibitory agents in many developed countries, the prevalence of endoscopic lesions is likely to be even lower than reported in these studies.

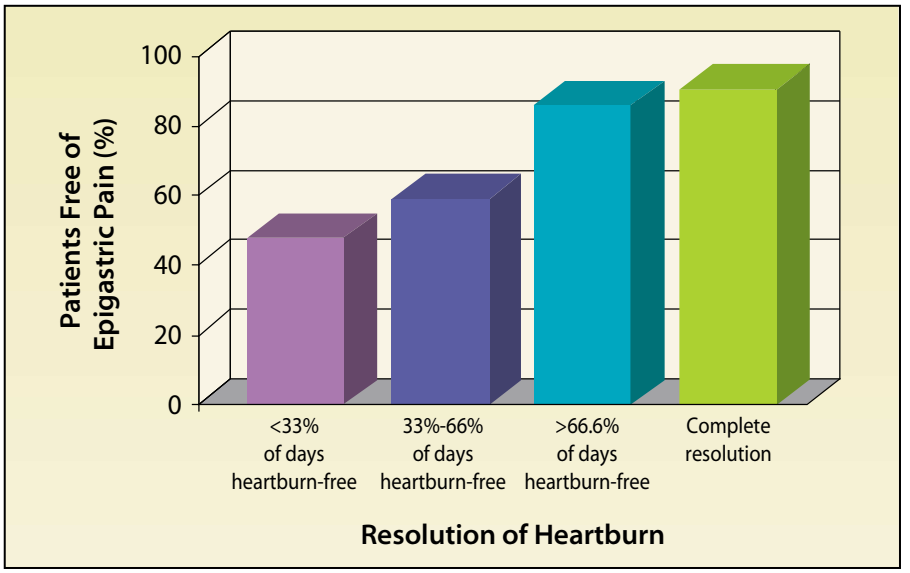

Figure 1. *Resolution of epigastric pain with the resolution of heartburn in non-erosive reflux disease from two randomized, controlled trials with esomeprazole. Values represent the number of days the patient was heartburn free by diary card. Note that as the proportion of heartburn-free days increases, the proportion of patients reporting epigastric pain falls in tandem.*

The Rationale for Empirical Strategies in the Management of Patients With Epigastric Pain/Discomfort

Empirical treatment strategies have been developed in the management of epigastric pain. For the most part, this empiricism is driven by the large numbers of patients presenting with this symptom, the relatively poor yield of diagnostic tests like endoscopy, and the poor predictive value of the unaided clinical diagnosis. In the majority of younger patients who lack alarm symptoms, such as bleeding and weight loss, diagnostic testing is unrevealing and a short course of empirical therapy could be a useful strategy. The major rationale for this strategy remains that upper gastrointestinal cancer is very rare in individuals younger than 50 years of age. The incidence does, however, increase with age thereafter. Some studies have reported that older age is an independent risk factor for identifying underlying structural abnormalities, but the results have not been consistent.[17-20]

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Management Strategies in Epigastric Pain

Test-and-Treat Strategy for H. pylori

There is a considerable body of evidence that a test-and-treat strategy is as effective as endoscopy-driven treatment in young patients with epigastric pain/discomfort. Lassen and associates randomized 500 patients in primary care with dyspepsia to either *H. pylori* test-and-treat or prompt endoscopy.[21] They found that there were no differences

in symptomatic outcomes or quality of life between the groups at 1 year. There was, however, a substantial reduction in the number of endoscopic procedures performed in the test-and-treat arm. McColl et al studied 708 patients under age 55 who were referred for endoscopy and who were randomized to either *H. pylori* test-and-treat or endoscopy (including *H. pylori* testing).[22] They found no significant difference in dyspepsia scores at 12 months follow-up in the two groups. Furthermore, only 8% of patients who had testing and treatment eventually underwent endoscopy. Overall patient satisfaction and quality of life was similar in both groups.

The major disadvantage of the test-and-treat strategy is that cure of *H. pylori* infection will only lead to a minority percentage of patients reporting symptomatic improvement. A recent study from California illustrates this point. An open-label, randomized trial was conducted in which patients were randomized either to a test-and-treat strategy or diagnostic investigation.[23] Only 17% of study participants had peptic ulcer disease confirmed by radiography or endoscopy in the investigation-first arm, and only 38% were infected with *H. pylori*. At 12 months, patients in the test-and-treat group were less likely to report ulcer-like pain or the use of acid-reducing medication. Seventy-five percent of the test-and-treat group, however, used acid-reducing medication during the second half of the 12-month follow-up. In the 12 months after randomization, the test-and-treat group had higher total acid-peptic-related costs than the usual care group. This study demonstrated that most patients have *H. pylori*–negative dyspepsia and that the impact of a test-and-treat strategy is small but significant.

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Acid-Suppressive Therapy

H_2 Receptor Antagonists. A recent meta-analysis concluded that there was some benefit with these agents, but a large number of the studies had to be excluded from the analysis (only 18 of 150 studies met the inclusion criteria).[24] This suggests that many studies have been poorly conducted. The overall results suggest that H_2 receptor antagonists have a modest effect. With cimetidine the therapeutic benefit above placebo was 14% (95% CI, 3%–24%) and with ranitidine the therapeutic benefit was 33% (95% CI, 23%–43%).

Proton Pump Inhibitors. While the efficacy of H_2 blockers is questionable, two recent studies have been performed on the effectiveness of proton pump inhibitors (PPIs) in functional dyspepsia.[25,26] A total of 1262 patients with functional dyspepsia were enrolled in two studies (BOND or OPERA studies) and randomized to omeprazole 20 mg or 10 mg a day or identical placebo for 4 weeks.[25] Complete symptom relief was seen on the last 3 days of therapy in 38% of patients receiving omeprazole 20 mg, 36% in patients receiving omeprazole 10 mg, and 28% on placebo ($P = .002$). Symptom relief was similar in patients who were *H. pylori*–positive or –negative. Similar data have been reported in preliminary form with lansoprazole

Main Points

- Epigastric pain may be considered "ulcer-type," "reflux-like," or "dysmotility-like."
- Data suggest that even patients with ulcer disease may report epigastric pain due to acid in the esophagus rather than due to acid perfusing the ulcer crater.
- The symptoms of epigastric pain or discomfort should be considered part of the spectrum of uninvestigated dyspepsia.
- A study of the diagnostic value of the clinical interview and examination in primary care found that an "unaided" clinical diagnosis is not particularly reliable in patients with epigastric pain/discomfort.
- Data suggest that a test-and-treat strategy is as effective as endoscopy-driven treatment in young patients with epigastric pain/discomfort; however, cure of *H. pylori* infection will only lead to a minority percentage of patients reporting symptomatic improvement.
- Testing and treating for *H. pylori*, followed by an empirical course with a PPI in nonresponders or patients testing negative for *H. pylori,* costs less per additional symptomatic cure than the test-and-treat method followed by endoscopy for nonresponders and *H. pylori*–negative patients.
- Recent studies have demonstrated that epigastric pain is a frequent symptom in patients with gastroesophageal reflux disease, and—like heartburn and regurgitation—is responsive to effective acid-suppressive therapy.

in a US population. Peura and colleagues reported complete symptom relief in 44% of patients given lansoprazole 30 mg for 8 weeks compared to 33% of controls given placebo. A major limitation of these studies is that they were of relatively short duration. Long-term studies with PPIs are clearly needed.

Cost-Effectiveness and the Management of Epigastric Pain

Clinical guidelines in the management of dyspepsia have been quite limited because they propose initial treatment with a test-and-treat strategy but provide no alternatives for the many patients who test negative for *H. pylori* or who do not have symptomatic relief with eradication therapy.[27] We studied several alternative strategies in an economic model that incorporated a number of combinations of endoscopy, testing and treatment for *H. pylori,* and empirical PPI use.[28] Compared to the current American Gastroenterologic Association guidelines (as a standard of care) empirical PPI administration appeared to reduce unnecessary diagnostic procedures while achieving improved symptom control and quality of life at a lower overall cost. We estimated that testing and treating for *H. pylori*, followed by an empirical course with a PPI in nonresponders or patients testing negative for *H. pylori*, with endoscopy reserved only for failures of both these empirical treatments, would cost $2500 *less* per *additional* symptomatic cure than the test-and-treat method followed by endoscopy for nonresponders or those who test negative, as is currently recommended. [26] The analysis also suggested that PPI therapy alone may be cost-effective compared to the combination of PPI therapy and *H. pylori* eradication when there is a high likelihood of underlying erosive esophagitis, a low likelihood of *H. pylori* prevalence, or a low symptom severity. Selecting the optimal treatment strategy for the patient with dyspepsia may therefore ultimately depend upon several individual factors, including the pre-test likelihood of a specific underlying condition, the local prevalence of *H. pylori*, the effectiveness of anti–*H. pylori* therapy, and the severity of dyspepsia symptoms.

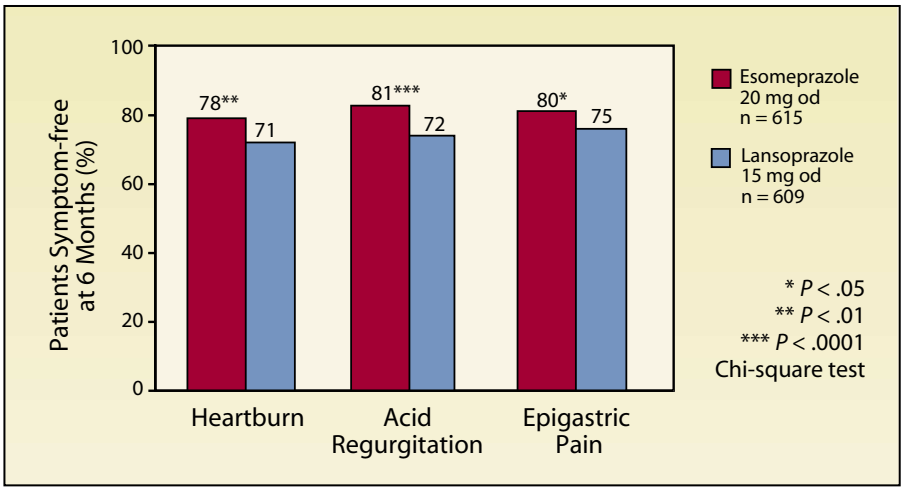

Figure 2. *Epigastric pain in patients with healed reflux esophagitis on maintenance therapy with esomeprazole 20 mg and lansoprazole 15 mg. Note the similarities in symptom relief for each drug. Reprinted with permission from Lauritsen et al.*[31]

Epigastric Pain in Reflux Disease

While it is recognized that patients with reflux disease may present with epigastric pain or dyspepsia, there are few data on the incidence of epigastric pain in reflux disease. Some authors have suggested that most patients with dyspeptic symptoms who respond to acid suppression have acid reflux when they undergo pH testing.[29] Recent studies have demonstrated the importance of epigastric pain in gastro-esophageal reflux disease. While epigastric pain is not generally recognized as a symptom of reflux disease, it is very prevalent in patients with GERD. In two large, randomized, controlled trials of esomeprazole in non-erosive reflux disease, 69% of patients had epigastric pain in addition to symptoms of heartburn.[30] All patients had undergone endoscopy to rule out the presence of significant mucosal disease. Acid-suppressive therapy resolved heartburn and epigastric pain in these patients and there was a strong correlation between the resolution of heartburn and the resolution of epigastric pain (see Figure 1). As most endoscopic tests in patients with epigastric pain do not reveal any significant abnormalities, studies such as these raise the question of whether non-erosive reflux disease is the principal cause of epigastric pain in non-ulcer dyspepsia. This question deserves further study. In a 6-month follow-up study of maintenance therapy for reflux disease, relief of epigastric pain was associated with relief of heartburn and acid regurgitation, suggesting a common pathogenic mechanism for these symptoms (Figure 2).[31] This study also suggested that recurrence or persistence of epigastric pain is a symptom of relapse.

Summary

Epigastric pain is a common manifestation of dyspepsia and is also fre-

quently encountered in gastro-esophageal reflux disease. Like heartburn and regurgitation, epigastric pain improves with maintenance therapy, and persistence or reoccurrence of these symptoms is suggestive of relapse. Epigastric pain responds to acid suppression both in the dyspeptic population and in patients with non-erosive reflux disease. The unaided clinical diagnosis is of limited utility in predicting the source of symptoms, and endoscopy is frequently unrewarding in young individuals. Empirical strategies that sequentially manage patients—first testing and treating those who are infected with *H. pylori* and empirically treating those who test negative or those who fail to respond to eradication therapy—appear to have the greatest promise but need formal study in controlled trials. Clearly, however, epigastric pain should be added to the list of symptoms potentially attributed to the vast spectrum of symptomatic GERD. ■

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