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Original Article

The Therapeutic and Diagnostic Value of 2-week High Dose Proton Pump Inhibitor Treatment in Overlapping Non-erosive Gastroesophageal Reflux Disease and Functional Dyspepsia Patients

Chatchai Kriengkirakul, Tanisa Patcharatrakul and Sutep Gonlachanvit*

Center of Excellence in Neurogastroenterology and Motility, Department of Internal Medicine, Chulalongkorn University, Bangkok, Thailand

Background/Aims
To evaluate the value of a 2-week high dose proton pump inhibitor (PPI) treatment on patients with overlapping non-erosive gastroesophageal reflux disease (NERD) and functional dyspepsia (FD).

Methods
Sixty overlapping NERD and FD patients with symptom onset > 3 months prior underwent 24-hour esophageal pH monitoring studies. All patients received rabeprazole 20 mg b.i.d. for 2 weeks. The reflux and dyspeptic symptoms were evaluated using a symptom questionnaire with 4-point Likert scales before and at the end of treatment. A positive PPI test was defined as score improvement in ≥ 50% from the baseline in the typical reflux symptoms.

Results
The prevalence of each reflux and dyspeptic symptom did not differ significantly between patients with positive and negative pH tests. After the PPI treatment, epigastric burning, acid regurgitation, heartburn, nausea, vomiting and chest discomfort scores were significantly improved compared to pretreatment values ($P < 0.05$), whereas postprandial abdominal fullness, early satiation, belching and food regurgitation were not. The proportion of patients who responded to the PPI treatment did not differ significantly between patients with positive and negative pH tests. The sensitivity, specificity, PPV, NPV and accuracy of 2-week high dose rabeprazole treatment for diagnosing gastroesophageal reflux disease were 47%, 38%, 50%, 35% and 43%, respectively.

Conclusions
The two-week high dose PPI treatment was not effective for early satiation, postprandial abdominal fullness, regurgitation or belching symptoms in patients with overlapping NERD and FD. Acid exposure in the distal esophagus could not predict the response of symptoms to PPI. In addition, the 2-week PPI test provided limited value for gastroesophageal reflux disease diagnosis in patients with overlapping NERD and FD.
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Key Words
Diagnosis; Dyspepsia; Gastroesophageal reflux; Proton pump inhibitors; Therapeutics

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*Correspondence: Sutep Gonlachanvit, MD
Center of Excellence in Neurogastroenterology and Motility, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Rama 4 Road, Patumwan, Bangkok 10330, Thailand
Tel: +66-2-256-3514, Fax: +66-2-252-3540, E-mail: gsutep@hotmail.com
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Conflicts of interest: None.

Introduction

Dyspeptic symptoms are commonly observed among patients with gastroesophageal reflux disease (GERD).[1,2] Patients who experience both dyspeptic and GERD symptoms have been reported to have impaired quality of life compared to patients with only dyspeptic or GERD symptoms.[1,3] The dyspeptic symptoms have heterogeneous presentations that may involve epigastric pain, epigastric burning, abdominal fullness, early satiation, nausea, vomiting, belching and are considered to have various underlying pathophysiologies.[4-6] Gastric acid has been demonstrated to play a role in the pathophysiology of dyspeptic symptoms. Extensive evidence supports the usage of acid-suppressive therapy for functional dyspepsia (FD).[7,8] Meta-analysis also revealed significant dyspeptic symptom improvement in patients treated with proton pump inhibitor (PPI). However, the benefit was observed in particular patients with reflux-like or ulcer-like dyspepsia but not in the patients with dysmotility-like dyspepsia who had postprandial fullness, early satiation, bloating or belching as their dominant symptom.[8-11] Various pathophysiological mechanisms in the esophagus, stomach and duodenum might induce dyspeptic symptoms. Acid reflux into the esophagus might cause dyspepsia without reflux symptoms in some patients, which is effectively treated with acid-secretion inhibitors.[12] Acid in the stomach might also provoke symptoms. Increased acid secretion after the injection of pentagastrin provokes symptoms in patients with non-ulcer dyspepsia.[13] Delayed gastric emptying and impaired gastric accommodation have been shown to be associated with abdominal fullness and early satiation. Due to various pathophysiologies of these upper gastrointestinal (GI) symptoms, the treatment of GERD patients with overlapping dyspeptic symptoms remains as a major challenge.

Previous studies reported that acid-suppressive therapy by PPI could delay gastric emptying in humans.[14,15] This may produce negative effects on some dyspeptic symptoms associated with delayed gastric emptying such as postprandial abdominal fullness. Therefore, PPI may provide benefits in the treatment of acid-related symptoms such as heartburn, acid regurgitation, chest discomfort and epigastrium burning/pain but not in non-acid related symptoms such as postprandial abdominal fullness or early satiety symptoms. However, limited data have been published regarding the therapeutic and diagnostic value of short-term PPI treatment in patients with overlapping GERD and FD. The primary objectives of this study were: (1) to investigate the response of each individual GERD and dyspeptic symptom to treatment with high dose PPI in patients with overlapping NERD and FD and (2) to compare the treatment responses between patients with and without abnormal 24-hour pH monitoring. The secondary objective was to compare the 2-week PPI test results and the results from 24-hour esophageal pH monitoring for the diagnosis of GERD in this patient group.

Materials and Methods

Study Population

The adult patients, 18-80 years old, who had disturbing typical reflux symptoms (heartburn and/or acid regurgitation) and dyspeptic symptoms for more than 3 months were evaluated prospectively during from 2004 to 2008 at the gastrointestinal clinic, GI motility research Unit, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand. All patients underwent upper endoscopy within 1 month prior to the enrollment. Exclusion criteria were as follows: patients who had significant reflux esophagitis (Los Angeles classification: grade B, C or D), peptic ulcer or esophageal/peptic stricture or gastric cancer visible on upper endoscopy, alarm features (including persistent dysphagia, unintentional weight loss, anemia, GI bleeding and jaundice), irritable bowel syndrome, chronic severe constipation, alcohol or drug abuse, pregnancy, lactation, diabetes mellitus, neurological diseases, history of GI surgery (except appendectomy) and/or had recently taken acid suppressants or prokinetics within 1 month prior to the study. This study was approved by the institution review board, and all participants provided their written informed consent.

Study Design

All patients were interviewed regarding the presence and severity of each individual esophageal or other upper GI symptom including heartburn, acid regurgitation, chest discomfort, postprandial abdominal fullness, nausea, vomiting, early satiation, epigastric burning, food regurgitation and belching using a symptom questionnaire. The severity of each of the upper GI symptoms was evaluated with a 4-point Likert scale before and at the end of treatment (0 = no symptoms, 1 = mild symptoms [occasionally symptoms that do not influence daily activities or sleeping], 2 = moderate symptoms [occasionally influence daily activities but do not induce changes in daily activities or sleeping] and 3 = severe [influence on daily activities and induce changes in daily activities or sleeping]).[16] After at least 6 hours of overnight fasting, all patients underwent water perfusion esophageal

manometry for location of the lower esophageal sphincter. The pH catheter (GeroFlex™/M; Sierra Scientific Instruments, CA, USA) was placed with a pH sensor located at 5 cm above the lower esophageal sphincter for ambulatory, 24-hour esophageal pH monitoring (Digitrapper; Medtronic A/S, Skovlunde, Denmark). After the tests, all patients received Rabeprazole (Pariet®; Easai Co., Ltd, Bangkok, Thailand) 20 mg twice daily for 2 weeks. A positive 24-hour esophageal pH monitoring test was defined as a total percentage of time with pH < 4 for greater than 4.5%. The complete response of each upper GI symptom was defined as a 2 point decrease compared to pretreatment symptom scores or the absence of symptoms (score = 0) at the end of treatment.

Statistical Methods

All data were recorded and analyzed using SPSS version 17.0 (SPSS Inc, Chicago, IL, USA). Data were expressed as mean and standard deviation. We used the paired and unpaired *t* tests to analyze the score differences in dyspeptic and other upper GI symptoms for dependent and independent samples, respectively. The Chi-square test was conducted to identify significant differences of the proportion between 2 categorical variables. A *P*-value < 0.05 indicated statistical significance.

Table 1. Baseline Patient Characteristics of 60 Patients

Patients characteristics	
Gender (male:female [%])	22:78
Age (yr)	49.2 ± 13.4
BMI	23.6 ± 3.3
Alcohol drinking (n [%])	8 (13.0)
Smoking (n [%])	6 (10.0)
Symptoms (n [%])	
Heartburn	42 (70.0)
Acid regurgitation	47 (78.3)
Chest discomfort	43 (71.7)
Epigastric burning	43 (71.7)
Postprandial fullness	51 (85.0)
Early satiation	37 (61.7)
Belching	47 (78.3)
Nausea	26 (43.3)
Vomiting	13 (21.7)
Food regurgitation	38 (63.0)
24-hour pH monitoring result	
Positive	34 (56.7)
Negative	26 (43.3)
Esophageal manometry result	
Normal	33 (55.0)
Abnormal	27 (45.0)
Ineffective esophageal motility disorder	10 (16.7)
Diffuse esophageal spasm	5 (8.3)
Nutcracker esophagus	5 (8.3)
Hypertensive LES pressure	2 (3.3)
Scleroderma-like esophagus	2 (3.3)
Impaired LES relaxation	2 (3.3)
Hypotensive LES pressure	1 (1.8)

BMI, body mass index; LES, lower esophageal sphincter.

Results

Sixty patients were enrolled. The median duration of symptoms in the patients was 24 (3-60) months (median [range]). All patients underwent upper GI endoscopy: 56 and 4 patients had normal endoscopic findings and mild reflux esophagitis (Los Angeles classification: grade A), respectively. All patients underwent esophageal manometry, 24-hour esophageal pH monitoring and PPI test. The presence of each upper GI symptom at baseline, esophageal manometry results, and the 24-hour esophageal pH monitoring results are described in Table 1.

Relationship Between 24-hour Esophageal pH Monitoring Results and Baseline Upper Gastrointestinal Symptoms

The prevalence of heartburn, acid regurgitation and other upper GI symptoms did not differ significantly between patients with positive and negative pH test results, except for those with

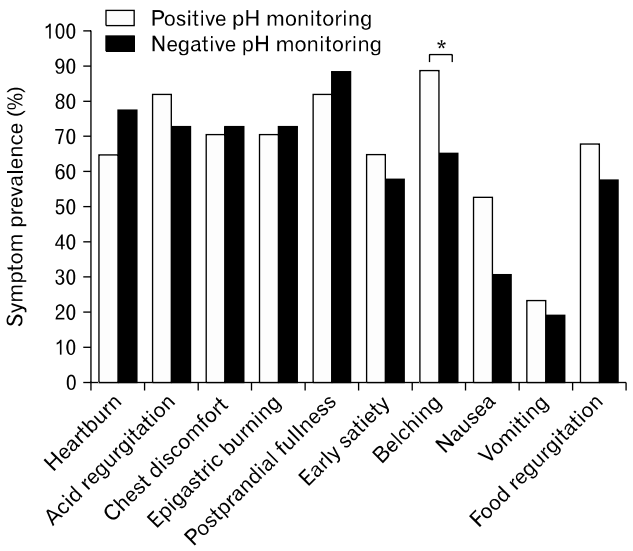

Figure 1. Baseline prevalence of each upper gastrointestinal symptom among patients with positive and negative 24-hour esophageal pH monitoring results (*$P < 0.05$).

belching symptoms (Fig. 1). Patients who had positive 24-hour esophageal pH monitoring results were more likely to suffer from unwanted belching than the patients with negative pH results ($P < 0.05$).

Effect of Proton Pump Inhibitor on Upper Gastrointestinal Symptoms

Heartburn, acid regurgitation, chest discomfort, epigastric burning, nausea and vomiting were significantly improved after the 2-week rabeprazole treatment compared to pretreatment levels. However, postprandial abdominal fullness, early satiation, belching and food regurgitation did not improve significantly (Fig. 2).

The Association Between 24-hour Esophageal pH Monitoring Results and the Response of Upper Gastrointestinal Symptoms to Proton Pump Inhibitor Treatment

After the 2-week rabeprazole treatment, the proportion of patients who experienced the complete response of each GERD and FD symptom was not significantly different between patients with positive and negative 24-hour pH monitoring results ($P > 0.05$) (Table 2).

However, among each symptom score analyzed; in the patients with positive 24-hour esophageal pH monitoring results, heartburn, acid regurgitation, epigastric burning, nausea, chest discomfort and belching symptom scores at the end of treatment were significantly improved compared to pretreatment level ($P < 0.05$) (Fig. 3A). In patients with negative pH monitoring results, only acid regurgitation and heartburn were significantly improved, but other dyspeptic symptoms were not (Fig. 3B).

The 2-week Proton Pump Inhibitor Test Versus 24-hour Esophageal pH Monitoring for the Diagnosis of Gastroesophageal Reflux Disease

After a 2-week treatment with high dose rabeprazole, 32 patients (57%) exhibited a greater than 50% improvement in typical reflux symptoms (heartburn and acid regurgitation); these patients were classified as the positive PPI test group. When using 24-hour esophageal pH monitoring as the gold standard for GERD diagnosis, sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the 2-week high dose rabeprazole treatment for GERD diagnosis was 47%, 38%, 50%, 35% and 43%, respectively.

Discussion

NERD and dyspeptic symptoms often coexist.[17] Patients with these overlapping conditions have lower quality of life[3] and higher health care costs than patients who suffer from either GERD or FD.[2] Acid suppression medications are usually effective for a subset of dyspeptic patients with typical reflux symptoms including heartburn and acid regurgitation. However, their efficacy in the treatment of particular upper GI symptoms such as post-prandial abdominal burning/pain, abdominal fullness, early

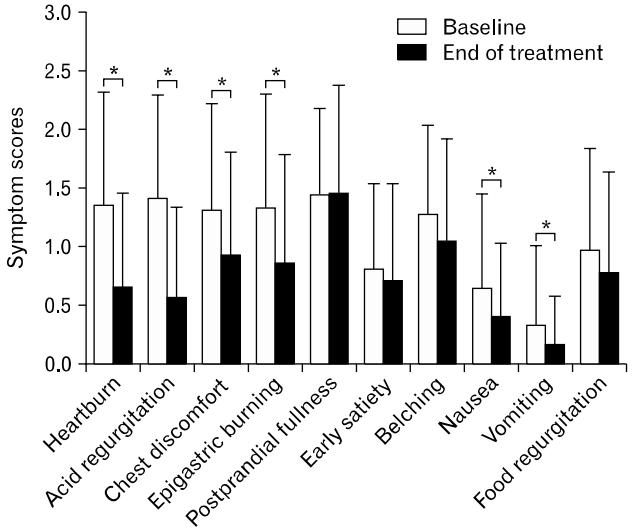

Figure 2. Effects of the 2-week high dose proton pump inhibitor treatment on upper gastrointestinal symptom scores (*$P < 0.05$).

Table 2. Proportion of Patients With a Complete Response For Each Individual Symptom After the 2-week High dose Proton Pump Inhibitor Treatment

Symptoms	Complete response to PPI (N/N [%])	
	Positive pH test	Negative pH test
Heartburn	13/21 (62)	13/20 (65)
Acid regurgitation	16/28 (57)	13/17 (76)
Chest discomfort	9/22 (40)	7/19 (36)
Epigastric burning	13/24 (54)	8/17 (47)
Postprandial fullness	5/26 (19)	7/22 (32)
Early satiety sensation	7/21 (33)	6/15 (40)
Belching	13/30 (43)	6/18 (33)
Nausea	13/18 (72)	5/8 (62)
Vomiting	6/7 (85)	3/5 (60)
Food regurgitation	14/23 (60)	5/15 (33)

PPI, proton pump inhibitor.
Positive pH test vs negative pH test, $P > 0.05$.

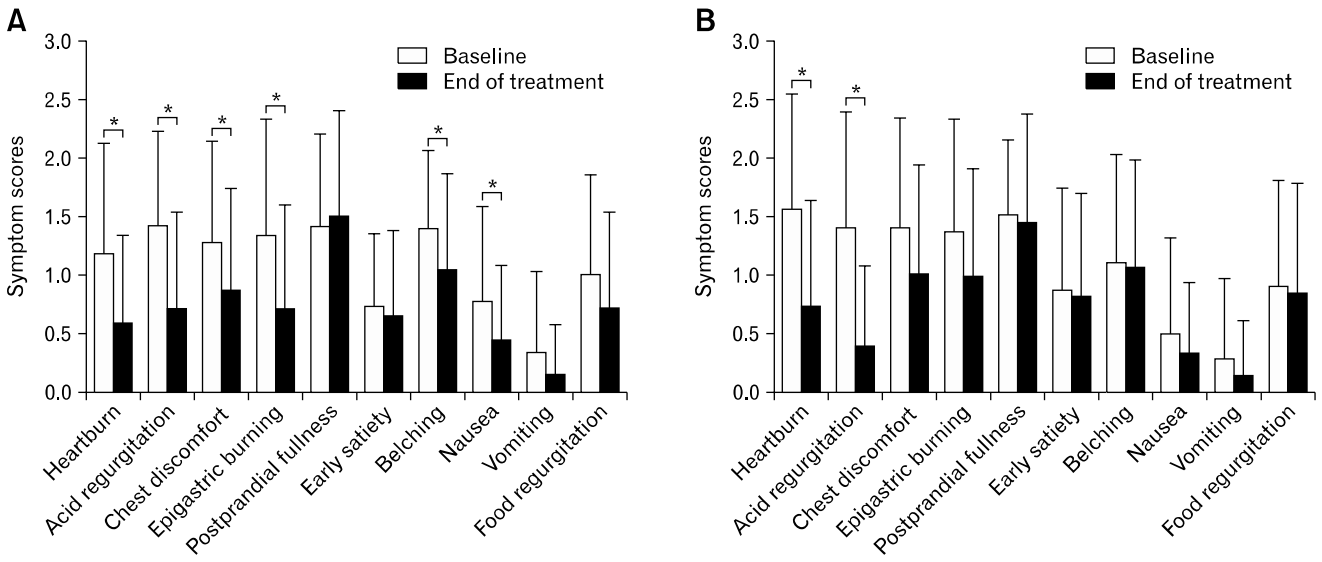

Figure 3. Effects of the 2-week high dose proton pump inhibitor treatment on gastroesophageal reflux disease and functional dyspepsia symptom scores in patients with positive (A) and negative (B) 24-hour esophageal pH monitoring results (*$P < 0.05$).

satiation and nausea has been questioned.[18,19] Our study was designed to investigate whether gastric acid inhibition with a high dose of rabeprazole would relieve each individual upper GI symptom differently in non-erosive gastroesophageal reflux disease (NERD) patients with overlapping FD and to compare the treatment responses between patient with and without abnormal 24-hour esophageal pH monitoring.

Our study demonstrated that in NERD patients with dyspeptic symptoms, 2-week high dose PPI treatment significantly improved epigastrium burning, nausea, vomiting, chest discomfort and typical reflux symptoms including acid regurgitation and heartburn. However, postprandial abdominal fullness, early satiation, belching and food regurgitation were not significantly improved. We used high dose PPI to secure that acid was adequately suppressed and this suggests that postprandial fullness, early satiation, belching and food regurgitation symptoms may not be acid-related symptoms. This finding supports the use of other medication(s) in combination with PPI as an initial treatment for controlling both PPI-sensitive and PPI-resistant symptoms in this patient group. Two previous studies in western countries also demonstrated improvements of dyspeptic symptoms in FD patients who had overlapping reflux symptoms. Epigastric burning or pain and reflux symptoms improved after treatment with omeprazole (both standard dose and high dose treatment for 2-4 weeks), but there was no significant benefit for dysmotility-like symptoms including early satiety and postprandial abdominal fullness.[7,8] Different results regarding regurgitation, belching and early satiety symptom responses to standard dose PPI treatment were demonstrated in previous studies.[20,21] These could be from different patients group enrolled. All patients enrolled in our study had moderate dyspepsia and moderate reflux symptoms combined but previous studies included patients with predominant reflux symptoms, not the overlapping GERD and dyspepsia patients.

Acid suppressants including ranitidine, famotidine and omeprazole at therapeutic doses delayed solid gastric emptying in healthy controls.[14] A recent systematic review also found that PPI delayed solid gastric emptying but had an inconsistent effect on liquid gastric emptying.[15] Whether this slowing produces poorer response of delayed gastric emptying related symptoms to PPI treatment remains to be determined. Our study demonstrated that postprandial abdominal fullness, which has been shown to be associated with delayed gastric emptying,[22] did not respond to the 2-week high dose PPI treatment.

Patients who receive PPI treatment may develop small bowel bacterial overgrowth (SIBO)[23,24] which may generate more intestinal gases and cause bloating. A recent study demonstrated that GERD patients who received esomeprazole 20 mg bid for 8 weeks complained more of bloating and flatulence. In addition, at 6 months after the PPI treatment, 26% of the patients developed SIBO.[25] The effect of PPI on the development of delayed gastric emptying and SIBO may explain why patients with post-prandial fullness, bloating, nausea/vomiting or early satiation did not respond or their symptom even worsened after PPI treatment in

clinical practice.

In this study, we found that 24-hour esophageal pH monitoring results had no significant association with any improvement in GERD or dyspeptic symptoms in overlapping GERD and FD. Tack et al[26] studied 24-hour esophageal pH monitoring in patients with FD without predominant heartburn symptoms and revealed that pathologic esophageal acid exposure was present in 18.5% of FD patients without heartburn. This study also included gastric emptying breath test and gastric barostat study and demonstrated that the demographic features and the presence of putative pathophysiological mechanisms such as delayed gastric emptying, hypersensitivity to gastric distention, or impaired accommodation did not distinguish patients with and without pathological esophageal acid exposure. However, epigastric pain was significantly more prevalent and more severe among patients with abnormal esophageal acid exposure than in patients with normal esophageal acid exposure, but the authors did not assess the effects of acid suppression on the symptoms. The other study evaluated the correlation between each dyspeptic symptom and esophageal acid exposure in non-erosive reflux disease patients, but they failed to find significant association between the prevalence of each dyspeptic symptom or dyspeptic symptom severity and esophageal acid exposure.[27] This study also included a 4-week trial of esomeprazole treatment (20 mg twice daily). The authors found that esomeprazole significantly improved dyspepsia symptoms independent of the improvement in reflux-related symptoms and achieved similar degrees of dyspepsia improvement in patients with and without abnormal esophageal acid exposure. A previous randomized controlled study also showed that the level of esophageal acid exposure had no influence on upper abdominal pain or abdominal discomfort improvement after the 2-week high dose treatment with PPI among patients with FD. These results were similar to those reported here.[7]

The secondary aim of our study was to compare the 2-week PPI test and 24-hour pH monitoring for the diagnosis of GERD in patients with overlapping typical reflux and dyspeptic symptoms. We found that the PPI test had very limited value for GERD diagnosis in this patient group at our tertiary hospital. The lower sensitivity and specificity of the PPI test with respect to the diagnosis of GERD in our study may have been caused by visceral hypersensitivity, which is commonly found in NERD and FD.[28,29]

There was no placebo group in comparison with the PPI group in this present study, therefore, it is difficult to conclude whether the symptom improvement was truly a benefit from the acid suppression or placebo effect. Previous randomized control studies[7,8] using standard dose or high dose omeprazole in patients with overlapping GERD and FD also demonstrated similar symptom improvement but lower response rate than our study. Another limitation was the relatively high prevalence of esophageal dysmotility which may associate with refractory regurgitation in our patients. This could be due to our hospital which is a tertiary care center and most of the subjects being refractory cases. The prevalence of esophageal dysmotility has been reported in 35%-44% of NERD patients in tertiary hospital[30,31] which is comparable to the result in our study. Most of the esophageal dysmotilities in our study were ineffective esophageal motility which has been reported its association with GERD. There is no recommendation that patients with such abnormal esophageal manometry results should be excluded before making the diagnosis of NERD or GERD.

In conclusion, this study suggests that in patients with overlapping NERD and FD, high dose PPI (rabeprazole) is effective for treating the typical reflux symptoms, epigastric burning, nausea, vomiting and chest discomfort but not for postprandial abdominal fullness, early satiation, food regurgitation and belching symptoms. The assessment of distal esophageal acid exposure in patients with overlapping NERD and dyspepsia did not predict the response of symptoms to PPI. In addition, the 2-week high dose PPI test provides low sensitivity and low specificity for the diagnosis of GERD in these patients. Further randomized control studies with placebo are needed to assess which upper GI symptoms would truly benefit from acid-suppressive treatment and whether the combination of PPI and other medication(s) such as prokinetics as an initial treatment for overlapping NERD and FD is appropriate.

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