

ORIGINAL ARTICLE

## 국내 임상 용량의 양성자펌프억제제에 반응하지 않는 불응성 위식도역류증의 유병률 및 임상양상: 다기관 연구

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### The Prevalence and Clinical Features of Non-responsive Gastroesophageal Reflux Disease to Practical Proton Pump Inhibitor Dose in Korea: A Multicenter Study

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**Background/Aims:** In Korea, there are no available multicenter data concerning the prevalence of or diagnostic approaches for non-responsive gastroesophageal reflux disease (GERD) which does not respond to practical dose of proton pump inhibitor (PPI) in Korea. The purpose of this study is to evaluate the prevalence and the symptom pattern of non-responsive GERD.

**Methods:** A total of 12 hospitals who were members of a Korean GERD research group joined this study. We used the composite score (CS) as a reflux symptom scale which is a standardized questionnaire based on the frequency and severity of typical symptoms of GERD. We defined "non-responsive GERD" as follows: a subject with the erosive reflux disease (ERD) whose CS was not decreased by at least 50% after standard-dose PPIs for 8 weeks or a subject with non-erosive reflux disease (NERD) whose CS was not decreased by at least 50% after half-dose PPIs for 4 weeks.

**Results:** A total of 234 subjects were analyzed. Among them, 87 and 147 were confirmed to have ERD and NERD, respectively. The prevalence of non-responsive GERD was 26.9% (63/234). The rates of non-responsive GERD were not different between the ERD and NERD groups (25.3% vs. 27.9%, respectively,  $p=0.664$ ). There were no differences between the non-responsive GERD and responsive GERD groups for sex ( $p=0.659$ ), age ( $p=0.134$ ), or BMI ( $p=0.209$ ). However, the initial CS for epigastric pain and fullness were higher in the non-responsive GERD group ( $p=0.044$ ,  $p=0.014$ , respectively).

**Conclusions:** In conclusion, this multicenter Korean study showed that the rate of non-responsive GERD was substantially high up to 26%. In addition, the patients with the non-responsive GERD frequently showed dyspeptic symptoms such as epigastric pain and fullness. (Korean J Gastroenterol 2016;68:16-22)

**Key Words:** Gastroesophageal reflux; Reflux esophagitis; Heartburn; Proton pump inhibitors; Gastric acid

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common digestive disease in which reflux of stomach contents into the esophagus through the incompetent lower esophageal sphincter causes troublesome symptoms, mucosal injury in the low esophagus, or both of these.<sup>1</sup> Subtypes of GERD include erosive reflux disease (ERD) and non-erosive reflux disease (NERD), which does not cause erosive changes visible on endoscopy but results from pathological amounts of acid reflux. The prevalence of GERD is approximately 10-20% among Western people and 3-5% among East Asian people, but there has recently been an increase in symptoms of GERD as well as an increase in the prevalence of esophagitis in Asian countries.<sup>2,3</sup> The treatments for GERD are primarily focused on reducing gastric acidity and decreasing the reflux of gastric acid contents into the esophagus. It has been well established that proton pump inhibitors (PPIs) are more effective than are histamine receptor-2 antagonists (H2RAs) for esophageal mucosal healing and symptom relief.<sup>4</sup> It is generally recommended that standard-dose PPIs should be used for 4 to 8 weeks as the initial treatment.<sup>5</sup>

Sometimes, patients with GERD are either partially or completely non-responsive to PPIs. It has been reported that between 10% and 40% of patients with GERD in Western countries have failed to respond to PPI treatment.<sup>6,7</sup> However, intractable or refractory GERD can be difficult to diagnose based on: 1) which regimen failed, and 2) which symptoms failed to respond. Some authors have considered failure to respond to standard doses of once-daily PPIs as intractable GERD, while others consider it to be failure to respond to standard doses of twice-daily PPIs.<sup>6,8,9</sup> In addition, it is difficult to define a refractory or intractable GERD because of the different responses by many GERD symptoms.

It may be difficult to apply Western guidelines to patients in Asian countries because of the differences between Western and Asian countries in the prevalence of GERD, *Helicobacter* infection, and gastric cancer.<sup>10</sup> Especially in Korea, there are no available data concerning the prevalence of or diagnostic approaches for non-responsive GERD which does not respond to practical dose of PPI in Korea. This retrospective multicenter study in Korea was therefore conducted to evaluate the response rate of GERD to PPIs as well the prevalence and the symptom pattern of non-responsive GERD.

## SUBJECTS AND METHODS

A total of 12 physicians from 12 hospitals who were members of the Korean GERD research group participated in this study. Previously, the Korean GERD research group discussed an evaluation system for response to PPIs. The group reached a consensus and adopted a GERD composite score (CS) for use as the GERD evaluation system. Thus, all patients were evaluated with the CS for their GERD symptoms and we enrolled GERD patients evaluated with the CS through electrical medical data from each hospital. This retrospective multicenter study protocol was approved by the institutional review board of Wonju Severance Christian Hospital (2014-08-42).

The primary end points of study were the response rate of patients with GERD and the prevalence and symptomatic patterns of non-responsive GERD to practical PPI dose. In addition, we evaluated the characteristics of patients with non-responsive GERD.

### 1. Study population

From January 2014 to May 2014, subjects over 18 years of age with typical troublesome reflux symptoms, such as acid reflux and heartburn, were eligible for study inclusion. Among them, subjects with ERD who were prescribed standard-dose PPIs and revisited after 8 weeks and subjects with NERD who were prescribed half-dose PPIs and revisited after 4 weeks were enrolled.

We excluded subjects with only atypical symptoms, histories of gastrectomy, or previous PPI or H2RA medication use within the previous 4 weeks. Subjects who were prescribed different doses of PPIs for ERD or NERD were not enrolled. Subjects who were prescribed gastrointestinal medications other than PPIs were excluded. And, subjects who did not revisit after 4 weeks for NERD or 8 weeks for ERD were also excluded. In addition, subjects whose compliance with medication and CS could not be measured were excluded. We analyzed the patients with good compliance whose rate of taking drug was above 80%.

### 2. Study variables

A component and dosage of PPIs were reviewed. Standard doses were as follows: 20 mg of omeprazole, 30 mg of lansoprazole, 40 mg of pantoprazole, 20 mg of rabeprazole, and

40 mg of esomeprazole.

We calculated CS before PPI medication (initial) and after medication (final: at 4 weeks in NERD group and at 8 weeks in ERD group). The demographic data of enrolled patients, such as age; sex; underlying diseases; medications (NSAIDs, Cox-2 inhibitors, aspirin, steroids, anti-coagulants, and anti-platelets); social habits, such as smoking and alcohol use; BMI; and endoscopic findings within 6 months were evaluated by review of records. After 4 weeks of PPI medication for NERD patients and 8 weeks of PPI medication for ERD patients, we evaluated the type of PPI, compliance with medications, and changes in CS. If subjects revisited before scheduled, they were excluded, except in cases of revisiting for changing the PPI to another kind of PPI.

### 3. Composite score

We used the CS of reflux symptoms, which were evaluated with a standardized questionnaire based on the frequency and severity of typical symptoms of GERD, such as heartburn and acid reflux.<sup>11</sup> The CS was calculated as the sum of each symptom score, which was determined to be the severity (from 0 to 3) multiplied by the frequency. Symptom severity ratings were classified as follows: No (0), no symptoms; mild (1), reflux symptoms that did not disrupt daily life; moderate (2), reflux symptoms that made daily life uncomfortable; and severe (3), reflux symptoms that disturbed all aspects of daily life. Symptom frequencies were described as the number of times per week the symptom was experienced. CSs were measured before and after PPI medication (Fig. 1). At the initial total CS measurement, all subjects were classified by their CS as follows: symptom index (SI)=0-2, normal; SI=3-7, mild; SI=8-12, moderate; SI ≥ 13, severe. In addition, we calculated the CSs of atypical symptoms, such as epigastric pain and abdominal fullness, in the same manner as for typical symptoms. However, the CS of atypical symptoms was not included in the total CS.

### 4. Definitions

#### 1) Responsiveness to practical PPI dose

We defined “which does not respond to practical dose of PPI in Korea (non-responsive GERD group)” as follows: a subject with ERD whose CS was not decreased by at least 50% after standard-dose PPIs for 8 weeks or a subject with NERD whose CS was not decreased by at least 50% after half-dose

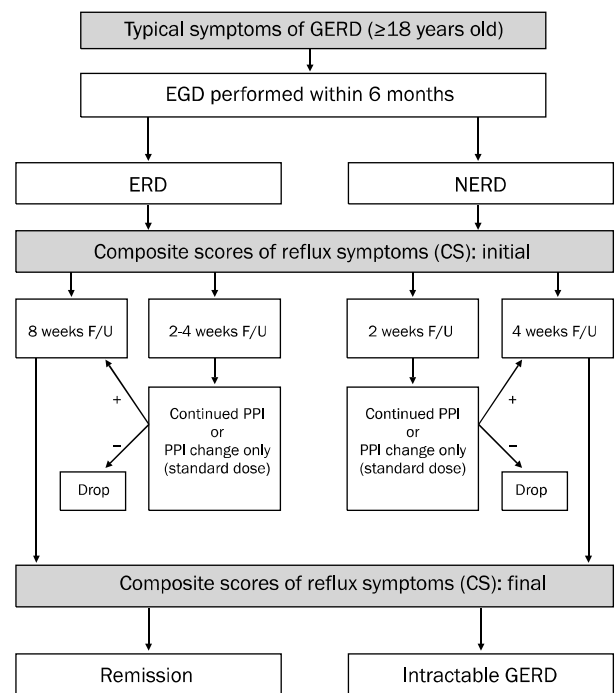
PPIs for 4 weeks.

“Responsive GERD to practical PPI dose (responsive GERD group)” was defined for subjects whose CSs had decreased more than 50% after standard-dose PPIs for 8 weeks for ERD and after half-dose PPIs for 4 weeks for NERD. The clinical PPI doses of ERD and NERD were the doses which were limited by National Health Insurance support in Korea.

We evaluated endoscopic findings performed within 6 months for such conditions as erosions on the esophagogastric junction (EGJ), hiatal hernia, and Barrett’s esophagus. Hiatal hernia was defined as a hiatal sac more than 2 cm in length from the opening of the sac to the EGJ (proximal end of gastric fold). Barrett’s esophagus, diagnosed by specialized columnar epithelium on pathologic findings, was described according to the Prague criteria.

### 5. Statistics

The proportions of non-responsive GERD to practical PPI dose in ERD and in NERD patients were calculated. Categorical variables, such as sex and transition to another PPI, were analyzed by the chi-squared test, and continuous variables, such as age and CS, were presented as the



**Fig. 1.** Diagram of study process. GERD, gastroesophageal reflux disease; ERD, erosive reflux disease; NERD, non-erosive reflux disease; F/U, follow up.

mean±SD. Chi-square test was used to analyze differences of categorical data among subjects with non-responsive GERD who needed maintenance of PPIs, and responders who did not need maintenance of PPIs. A p-value of less than 0.05 was considered statistically significant. All analyses were performed with the use of IBM SPSS Statistics software, version 20.0 for Windows (IBM Co., Armonk, NY, USA).

## RESULTS

### 1. Patient characteristics

Among a total of 256 eligible subjects, a total of 234 subjects were finally analyzed. The compliance rate was 91.0% (ERD, 87.0%; NERD, 94.0%). Among them, 87 (37.2%) were confirmed to have ERD, and 147 (62.8%) were confirmed to have NERD. Mean age was significantly lower in the NERD group than that in the ERD group (50.5±14.0 years vs. 55.7±13.4 years, respectively;  $p=0.006$ ), and there was a higher proportion of women in the NERD group than there were in the ERD group (59% vs. 45%, respectively;  $p=0.043$ ). BMI was significantly lower in the NERD group (24.6±3.5 kg/m<sup>2</sup> vs. 23.3±3.0 kg/m<sup>2</sup>, respectively;  $p=0.002$ ). The following were less common in the NERD group than they were in the ERD group: hypertension (20% vs. 34%, respectively;  $p=0.017$ ), diabetes (6% vs. 16%, respectively;  $p=0.013$ ), and history of anti-platelet medication (2% vs. 9%, respectively;  $p=0.013$ ). Other underlying diseases, medication histories, and smoking and alcohol use were not different between groups. In addition, moderate-to-severe GERD (initial total CS  $\geq 8$ ) was evenly distributed in both groups (41.4% in ERD vs. 35.4% in NERD,  $p=0.359$ ).

### 2. CS in the ERD and NERD groups

The initial and final CSs for both groups are shown in Table 1. Total initial CSs were not different between groups (6.3±3.4 in the ERD group and 6.2±3.4 in the NERD group,  $p=0.861$ ). Regarding atypical symptoms, epigastric pain was non-significantly more frequent in the ERD group (3.4±2.9 in the ERD group vs. 2.7±2.4 in the NERD group,  $p=0.052$ ), and fullness was non-significantly more common in the NERD group (1.9±2.1 in the ERD group vs. 2.5±2.3 in the NERD group,  $p=0.053$ ). After PPI medication, the final total CSs were significantly decreased for both groups (6.3±3.4 to 0.5±0.9 in the ERD group,  $p < 0.001$ ; and 6.2±3.4 to 1.7±2.1

in the NERD group,  $p < 0.001$ ), with significant improvement of atypical symptoms in both groups. However, the final total CS was higher in the NERD group than that in the ERD group (1.1±1.9 in the ERD group vs. 1.7±2.1 in the NERD group,  $p=0.036$ ) (Table 2). The CS for epigastric pain after PPI treatment was higher in the NERD group than in the ERD group (0.5±0.9 in the ERD group vs. 1.0±1.8 in the NERD group,  $p=0.006$ ).

### 3. Non-responsive GERD

Among all subjects, 26.9% (63/234) had non-responsive GERD (non-responders, 26.9% vs. responders, 73.1%). The rate of non-responsive GERD were not different between the ERD and NERD groups (25.3% in the ERD group vs. 27.9% in the NERD group,  $p=0.664$ ). The initial total CSs in the non-responsive GERD group and that in the responsive GERD group were not different (5.7±2.5 in the non-responder group vs. 6.4±3.7 in the responder group,  $p=0.095$ ). According to individual symptoms, the CS for heartburn was initially higher in the responsive GERD group than in the non-responsive GERD group ( $p=0.028$ ). In contrast, the initial CSs for epigastric pain and fullness were higher in non-responsive

**Table 1.** Characteristics of Subjects

| Characteristic           | ERD<br>(n=87) | NERD<br>(n=147) | p-value |
|--------------------------|---------------|-----------------|---------|
| Age (yr)                 | 55.7±13.4     | 50.5±14.0       | 0.006   |
| Sex (%), male/female     | 55/45         | 42/59           | 0.043   |
| BMI (kg/m <sup>2</sup> ) | 24.6±3.5      | 23.3±3.0        | 0.002   |
| Underlying disease       |               |                 |         |
| Angina                   | 7 (8.0)       | 5 (3.4)         | 0.135   |
| Diabetes mellitus        | 14 (16.1)     | 9 (6.1)         | 0.013   |
| Hypertension             | 29 (33.7)     | 29 (19.2)       | 0.017   |
| Liver disease            | 1 (1.1)       | 5 (3.4)         | 0.416   |
| Renal disease            | 2 (2.3)       | 0 (0)           | 0.137   |
| Lung disease             | 4 (4.6)       | 3 (2.0)         | 0.429   |
| Social habit             |               |                 |         |
| Smoking                  | 24 (27.9)     | 27 (18.4)       | 0.089   |
| Alcohol                  | 37 (42.5)     | 46 (31.3)       | 0.083   |
| Medication               |               |                 |         |
| NSAID                    | 1 (1.1)       | 3 (2.0)         | >0.999  |
| Cox-2                    | 0 (0.0)       | 2 (1.3)         | 0.531   |
| Aspirin                  | 11 (12.6)     | 14 (9.5)        | 0.455   |
| Steroid                  | 1 (1.1)       | 1 (0.7)         | >0.999  |
| Anti-coagulant           | 0 (0)         | 0 (0)           | NA      |
| Anti-platelet            | 8 (9.2)       | 3 (2.1)         | 0.013   |

Values are presented as mean±SD or n (%).

ERD, erosive reflux disease; NERD, non-erosive reflux disease; NA, not available.

GERD group ( $p=0.044$  and  $p=0.014$ , respectively) (Fig. 2A).

The final CS in the responsive GERD group decreased by up to 93%, whereas that in the non-responsive GERD group decreased by only 27% ( $p < 0.001$ ). The responsive GERD group showed significant decrease of the CS for epigastric pain (80%) and the CS for fullness (76%) compared with decreases of CSs (53% for epigastric pain, 40% for fullness respectively) in non-responsive GERD groups (Fig. 2B).

There were no differences in sex ( $p=0.659$ ), age ( $p=0.134$ ), and BMI ( $p=0.209$ ) between the non-responsive GERD and responsive GERD groups. Medical illness and history of medication usage including NSAIDs, aspirin, antiplatelets, and anticoagulants were not different between the groups, with the exception of diabetes, which was more prevalent in responsive GERD group.

**Table 2.** Initial and Final Composite Scores in Both Groups

| Composite score         | ERD (n=87) | NERD (n=147) | p-value |
|-------------------------|------------|--------------|---------|
| Initial composite score |            |              |         |
| Reflux                  | 3.4±2.0    | 3.0±2.4      | 0.192   |
| Heart burn              | 2.9±2.6    | 3.1±2.5      | 0.465   |
| Total                   | 6.3±3.4    | 6.2±3.4      | 0.751   |
| Epigastric discomfort   | 3.4±2.9    | 2.7±2.4      | 0.052   |
| Fullness                | 1.9±2.1    | 2.5±2.3      | 0.053   |
| Final composite score   |            |              |         |
| Reflux                  | 0.7±1.1    | 1.0±1.4      | 0.081   |
| Heart burn              | 0.5±1.1    | 0.7±1.1      | 0.061   |
| Total                   | 1.1±1.9    | 1.7±2.1      | 0.036   |
| Epigastric discomfort   | 0.5±0.9    | 1.0±1.8      | 0.006   |
| Fullness                | 0.6±1.2    | 0.9±1.5      | 0.095   |

Values are presented as mean±SD.  
ERD, erosive reflux disease; NERD, non-erosive reflux disease.

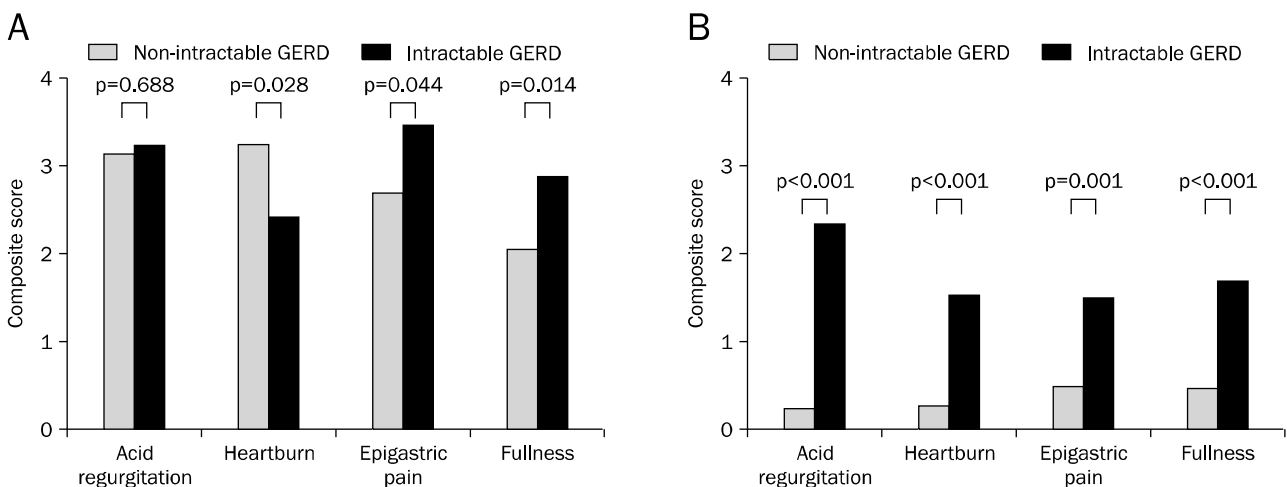
## DISCUSSION

Population-based studies in Korea have revealed an increasing trend in the prevalence of GERD.<sup>12,13</sup> Moreover, it has been reported that many people with GERD did not respond to PPI treatment in Western countries. However, there are no available multicenter data concerning the prevalence and diagnostic approaches for non-responsive in Korea.<sup>6,7</sup> In this multicenter study, the prevalence of non-responsive GERD to practical PPI dose was 26.9% (63/234), higher than the reported rates of 9.7% to 10.1% for refractory GERD reported in previous single-center studies in Korea.<sup>14,15</sup>

In this study, we defined GERD with symptomatic improvement of less than 50% as non-responsive GERD, which included patients who would be classified as “refractory GERD” and “partial or unsatisfactory response” in previous studies, so the prevalence of non-responsive GERD to practical PPI dose are similar to that in previous studies (13.2% to 28.5%).<sup>14,15</sup>

We focused the ordinary practice of treatment for GERD. In Korea, the National Health Insurance support the medical cost of half-dose PPIs for 4 weeks in patients with NERD and standard-dose PPIs for 8 weeks in patients with ERD. So, we defined the non-responsive GERD as the non-responsive GERD which does not respond to practical dose of PPI in Korea.

To determine whether GERD is responsive to PPIs or not, an objective and easily available symptom assessment tool should be needed. There have been many symptomatic as-



**Fig. 2.** Composite scores between intractable gastroesophageal reflux disease (GERD) and non-intractable GERD. (A) Initial score. (B) Final score.

assessment tools for GERD, however, most of them were complicated and were not readily available to physicians in ordinary medical practice.<sup>16</sup> Thus, the members of the Korean GERD research group joined in this study have adopted the CS for GERD that was previously validated and uses a scoring system.<sup>11</sup>

GERD is classified into ERD and NERD. In contrast with NERD which can be diagnosed based on typical symptoms such as heartburn and acid reflux, the diagnosis for ERD requires endoscopy regardless of symptoms. In order to evaluate symptomatic improvement with the CS, we indeed enrolled patients with NERD and patients with symptomatic ERD.

Symptomatic ERD has been reported to show different features from asymptomatic ERD which symptomatic ERD is frequently associated with epigastric pain syndrome and postprandial distress syndrome.<sup>17</sup> Correspondingly, this study showed that subjects with symptomatic ERD suffered from high rates of epigastric pain and fullness (71% and 54%, respectively).

We assessed the total CS for typical symptoms as well as the CSs for atypical symptoms. Among several atypical symptoms, bloating and epigastric pain were reported to be common in Asians countries.<sup>18</sup> Of course, bloating, which are similar with abdominal fullness, is one of the dyspeptic symptoms rather than a symptom of GERD. However, some studies showed that dyspeptic symptoms might accompany GERD symptoms.<sup>19,20</sup>

There was symptom discrepancy between NERD and symptomatic ERD. Among atypical symptoms of GERD, epigastric pain was frequent in patients with symptomatic ERD and fullness was frequent in patients with NERD.

Compared with the patients with responsive GERD to practical PPI dose, the patients with non-responsive GERD to practical PPI dose had lower symptom score for heartburn than responder to PPI. On the contrary symptom scores of atypical symptoms such as epigastric pain and fullness were higher in the patients with non-responsive GERD to practical PPI dose. So, we guess that the patients with non-responsive GERD in Korea have symptoms indicating functional dyspepsia frequently.

This study has some limitations. First, this study was designed as a retrospective study. However, as noted above, we enrolled subjects during the same period who were assessed

with the same symptom assessment tool at the different hospitals, so, in that regard, it is reasonable to view this study as a kind of prospective multicenter study. Second, the study period was short (5 months), so there were not many subjects enrolled in this observational study. In addition, almost no subjects with GERD symptoms underwent esophageal manometry or 24-hour esophageal pH monitoring. Thus, we did not evaluate the extent of acid reflux or the relationship with symptoms in intractable GERD. Nevertheless, we believe that this study provided important information regarding the prevalence of and diagnostic approach to non-responsive GERD. A larger sized prospective multicenter study with esophageal manometry or 24-hour esophageal pH monitoring would be needed to show the cause and more accurate prevalence of non-responsive GERD, as well as, study on the issues of dose and duration of PPI would be needed to overcome the high proportion of GERD which did not respond to practical dose of PPI recently used in Korea.

In conclusion, this multicenter Korean study showed that the rate of non-responsive GERD to practical PPI dose was substantially high, up to 26%. In addition, the patients with the non-responsive GERD to practical PPI dose frequently showed dyspeptic symptoms such as epigastric pain and fullness.

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