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Chapter

Refractory Gastroesophageal Reflux Disease (GERD) Symptoms

Xia Chen and Fei Wang

Abstract

Gastroesophageal reflux disease (GERD) is a chronic condition in which patients suffer troublesome symptoms and/or complications as the reflux of stomach contents occurs. GERD is a common disease worldwide with the range of estimated prevalence 18.1–27.8% in North America, 8.8–25.9% in Europe, 2.5–7.8% in East Asia, 8.7–33.1% in the Middle East, 11.6% in Australia and 23.0% in South America. It causes significant morbidity, considerable decrease of quality of life and high costs of exams and treatment derived from repeated visit doctor. The patients with GERD suffer from typical symptoms such as heartburn and regurgitation, as well as other atypical symptoms including chest pain, cough, asthma, and hoarseness. With the usage of pump inhibitors (PPIs) in clinic, a dramatic improvement in symptom resolution and life quality, as well as in mucosal healing is expected. However, the treatment of GERD fails in a proportion of patients despite the high efficacy of PPIs. This situation is getting more and more common in clinical practices. In this chapter, we will discuss about this difficult situation, emphasizing diagnosis and treatment, combined with suggested management of these patients.

Keywords: gastroesophageal reflux disease (GERD), refractory proton pump inhibitor (PPI) symptoms, high-resolution manometry (HRM), impedance-pH monitoring, refractory reflux symptoms

1. Introduction

Gastroesophageal reflux disease (GERD) is a chronic condition in which patients suffer troublesome symptoms and/or complications as the reflux of stomach contents occurs. GERD is a common disease worldwide with the range of an estimated prevalence of 18.1–27.8% in North America, 8.8–25.9% in Europe, 2.5–7.8% in East Asia, 8.7–33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America [1]. It causes significant morbidity, considerable decrease of quality of life, and high costs of exams and treatment derived from repeated visits to the doctor.

The patients with GERD suffer from typical symptoms, such as heartburn and regurgitation, as well as other atypical symptoms including chest pain, cough, asthma, and hoarseness. With the usage of proton pump inhibitors (PPIs) in the clinic, a dramatic improvement in symptom resolution and life quality, as well as in mucosal healing, is expected.

However, the treatment of GERD fails in a proportion of patients despite the high efficacy of PPIs. This situation is referred as to refractory GERD symptoms. What is worse, it is getting more and more common in clinical practices. In this

chapter, we will discuss about this difficult situation, emphasizing on diagnosis and treatment, combined with suggested management of these patients.

2. Definition of refractory GERD symptom

The definition of "refractory GERD" has traditionally been described as a group of varying symptom presentations related to GERD, which persists even though the patients accepted the standard daily PPI therapy for at least 12 weeks. Some researchers referred to a failure to achieve satisfactory symptomatic response, for example, less than 50% improvement of relief of symptoms and life quality, to once-daily PPI to be classified as "refractory GERD" or "refractory reflux symptoms" [2]. The continued symptoms must be to a degree that impairs quality of life, and symptoms must be "reflux-related," which are supposed to be influenced by sex, age, ethnicity, social status, comorbidity, and cultural background. However, there is a controversy of the PPI dose for the definition of "refractory GERD." Some investigators prefer that inadequate response to twice-daily PPI treatment as refractory disease [3]. Moreover, the patient's remaining symptoms are subjective to and dependent on the patient's expectations of the therapy. It needs more clinical practice and further researches to supplement the definition in the future.

3. Causes of refractory GERD symptom

There are some underlying causes of refractory GERD. Firstly, poor compliance and adherence should be excluded before further evaluation is pursued. There are some key points of medication administration for patients, such as taking PPIs at the optimal 30–60 minutes prior to meal; avoiding discontinued PPIs without doctors' instruction even though the symptoms are relieved; receiving enough information about PPIs therapy. These points are initial important considerations for resolving the refractory GERD. Then, other disorders with GERD-like symptoms, such as esophageal disorders and functional gastrointestinal disorders, should be considered in the differential diagnosis of patients with persistent symptoms (**Figure 1**).

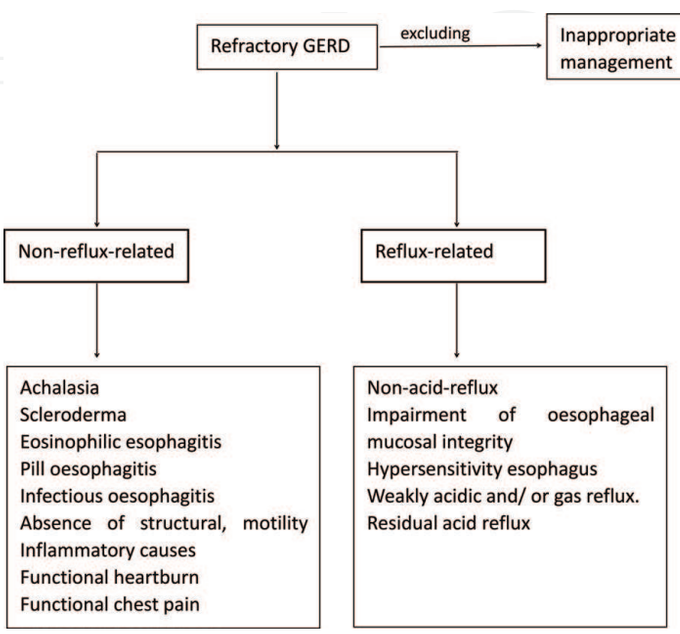


Figure 1.
Causes of refractory GERD symptom.

Additionally, obesity and overeating are other common factors associated with PPI failure in patients initially diagnosed with GERD.

4. Diagnosis of refractory GERD symptom

4.1 Symptom evaluation

The first important step is to identify the actual nature of the persisting symptoms. It can help a physician to choose the correct equipment for the next step of diagnosis. The typical symptoms of GERD are heartburn and regurgitation, which can be recognized by the GerdQ questionnaire. It is a revision of the Reflux Disease Questionnaire (RDQ) with positive predictor questions about heartburn and regurgitation as well as negative predictors about epigastric pain and nausea. It is reported that there is a sensitivity of 65% and specificity of 71% with GerdQ, which is close to the efficiency done by the clinical judgment of gastroenterologists [4]. However, presenting regurgitation should also be differentiated to gastroparesis or rumination syndrome. Except that, the physician should be aware of the proportion of patients with the atypical symptoms, such as retrosternal discomfort and pain, cough, asthma, hoarseness, throat discomfort, foreign body sensation in throat, globus sensation, belching, dysphagia, and epigastric pain and epigastric discomfort.

A recent study shows that there is about half of patients with atypical symptom, combined or uncombined with typical symptom [5]. In short, it is essential to figure out which symptoms respond and which do not respond to PPI therapy. More detailed questioning about symptom often help clarify the cause for a patient's persistent symptoms. Especially, the patients with atypical symptom might have poor response to PPI therapy because there are probably other causes or diseases that overlapped GERD.

4.2 Endoscopy

Upper endoscopy should be taken principally to exclude non-reflux esophageal disorders and other gastric diseases and to check whether erosive esophagitis exists, which can provide evidence of ongoing acid reflux. However, endoscopy is of limited value for diagnosis of refractory GERD symptom. It is because that most patients have normal endoscopy. The potential reasons are that most patients with refractory GERD symptom have other esophageal motility problem; they have non-erosive reflux disease (NERD); or PPIs they taken has healed the mucosal injury.

4.3 Esophageal manometry

All patients with refractory GERD symptom are strongly recommended to undergo esophageal manometry. The purpose mainly is to find esophageal motor disorders, for example, achalasia, weak peristalsis, hypertensive esophageal dysmotility, diffuse esophageal spasm (DES), hiatus hernias (HH), high UES pressure, and abnormal lower esophageal sphincter (LES) pressure. Secondly, but more important, esophageal manometry is applied for identifying the accurate location of LES in order to place reflux monitoring pH sensors.

4.4 Ambulatory monitoring for reflux

There are two methods for esophageal reflux monitoring, called as On-PPI and Off-PPI. In off-PPI (7 days after cessation of PPI), the presence of abnormal acid reflux and/or positive symptom-reflux relationship can be confirmed. The relevant

Nonerosive reflux disease (NERD)	No mucosal break Normal esophageal acid exposure
Hypersensitive esophagus (HE)	No mucosal break Normal esophageal acid exposure SI > 50%, SAP > 95%
Functional heartburn (FH)	Heartburn refractory to PPIs, no mucosal break, normal esophageal acid exposure SI < 50%, SAP < 95%

Table 1.
Diagnosis based on endoscopy, esophageal manometry, and ambulatory monitoring for reflux.

parameter to be observed is esophageal acid exposure, which is the proportion of time (in minutes or percentage of time) spent below pH 4, as well as correlation between symptoms and reflux events (symptom index (SI) and/or symptom association probability (SAP)). Positive symptom association with normal esophageal acid exposure is considered hypersensitive esophagus (HE), reflecting an underlying visceral hypersensitivity. For on-PPI reflux monitoring, impedance-pH monitoring should reasonably be proposed as the preferred investigation. It can detect nonacid reflux during the PPI therapy period, which is one of causes for persistent GERD symptom. It also can figure out whether acid reflux is controlled or not by the treatment (**Table 1**).

4.5 Assessment and evaluation for psychological status

Psychological disorders such as hysteria, anxiety, and distress should also be evaluated in patients with refractory symptoms. Weak correlation of symptoms with acid reflux events might indicate a high level of anxiety and hysteria as compared with patients who demonstrate a close correlation between symptoms and acid reflux event [6]. Anxiety and depression have been shown to increase reflux symptoms reported in population-based studies. A study has reported that patients who did not respond to PPI treatment were suffered from more psychosocial problem [7].

5. Management of refractory GERD symptom

5.1 Lifestyle modifications

Weight loss, head of bed elevation, and avoiding late-night meals, which have been shown as effective interventions for GERD, have not been demonstrated yet equally useful in patients with refractory reflux symptoms. The value of lifestyle modifications in patients with refractory symptoms lies in avoidance of specific lifestyle activities that have been identified by patients or physicians to trigger symptoms. A low-bulk and low-fat diet along with small but more frequent meals should surely be recommended.

5.2 Medicine

Increasing the PPI dose or to change to an alternative PPI improved the symptom in some patients [8]. However, this dosing strategy should be used for a short time period (2–3 months) and should be tapered if it does not result in improvement of symptoms. The addition of an H2RA at bedtime was shown to significantly reduce the duration of nocturnal acid breakthrough (NAB) pain modulators. Transient lower esophageal sphincter relaxation (TLESR) reducers can be considered for patients with abnormal frequency of nonacid reflux. The drugs that can reduce the number of reflux events regardless of their acidity are theoretically desirable

because of the potential for weakly acidic or bile reflux to cause symptoms. Nevertheless, high-quality controlled trials are needed to demonstrate its efficacy in patients with refractory symptoms.

Visceral pain modulator therapy has been another option for patients with an acid-hypersensitive esophagus or functional heartburn. A randomized, placebo-controlled trial has demonstrated citalopram 20 mg/day to be of symptomatic benefit in patients with acid-hypersensitive esophagus and refractory GERD symptoms [9].

5.3 Endoscopic therapy

Stretta procedure and EsophyX transoral incisionless fundoplication are two antireflux endoscopic devices which are clinically available. The Stretta procedure showed clinical improvement of esophageal symptoms and a decrease in PPI use but no significant effect on esophageal acid exposure [10]. EsophyX offers a less invasive alternative to laparoscopic fundoplication for PPI-dependent GERD patients, which still needs further studies to demonstrate its efficiency.

5.4 Antireflux surgery

Comparing with patients with adequate PPI symptom control, antireflux surgery might have a less favorable clinical outcome for the patients with refractory GERD symptom. Normal acid exposure and the presence of atypical reflux symptoms and persisting symptoms despite PPI therapy are predictors of a poor postoperative outcome. It is important to confirm pathological reflux before considering antireflux surgery if there is no proven esophagitis. Summarily, surgery can be a valuable option in patients with typical reflux symptoms with inadequate response to PPIs, provided abnormal esophageal acid exposure and/or positive symptom association analysis in off-PPI test [11].

5.5 Psychological treatment

According to a recent research, perceptions of reflux symptoms are associated with psychosocial distress in these patients with refractory GERD symptom who

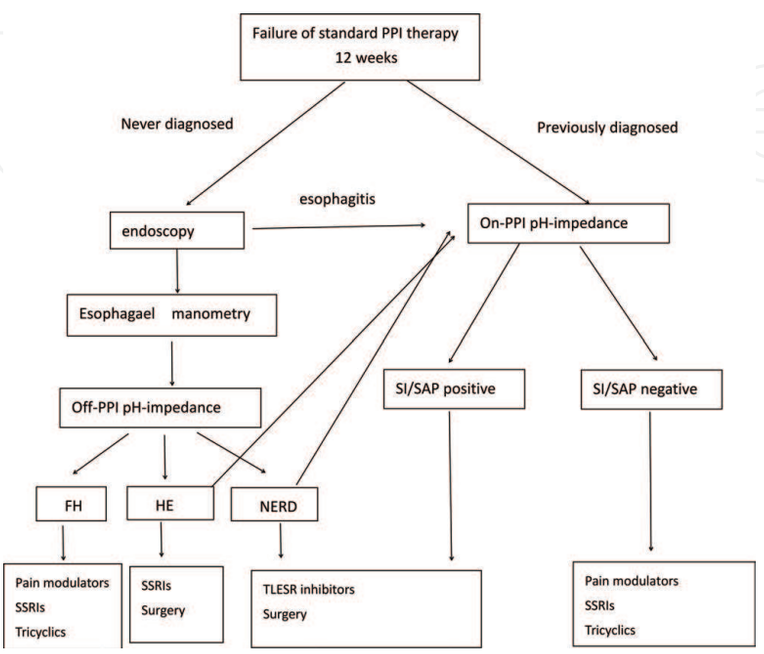


Figure 2.
Diagnostic and treatment algorithm for patients with refractory GERD symptom.

have normal impedance-pH results. Furthermore, patient-reported symptom severity is associated with physiological differences, as opposed to psychosocial factors [11]. In these patients with psychological disorders, treatment-targeted psychosocial abnormality may improve patient response to PPI therapy [2]. Psychological treatment should be a potential consideration in the case of the patients without other identifiable causes. In many clinical experiences, psychological disorders may be an underlying etiology in many patients with refractory symptoms (**Figure 2**).

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References

[1] El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut. 2014;**63**:871-880

[2] Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut. 2012;**61**:1340-1354

[3] Martinez SD, Malagon IB, Garewal HS, Cui H, Fass R. Nonerosive reflux disease (NERD)—Acid reflux and symptom patterns. Alimentary Pharmacology & Therapeutics. 2003;**17**:537-545

[4] Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Alimentary Pharmacology & Therapeutics. 2009;**30**:1030-1038

[5] Wang F, Li P, Ji GZ, Miao L, Fan Z, You S, et al. An analysis of 342 patients with refractory gastroesophageal reflux disease symptoms using questionnaires, high-resolution manometry, and impedance-pH monitoring. Medicine. 2017;**96**(5):e5906

[6] Becher A, El-Serag H. Systematic review: The association between symptomatic response to proton pump inhibitors and health-related quality of life in patients with gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. 2011;**34**:618-627

[7] Chen X, Li P, Wang F, Ji G, Miao L, You S. Psychological results of 438 patients with persisting gastroesophageal reflux disease symptoms by symptom checklist 90-revised questionnaire. Euroasian Journal of Hepato-Gastroenterology. 2017;**7**:117-121

[8] Fass R, Sontag SJ, Traxler B, Sostek M. Treatment of patients with persistent heartburn symptoms: A double-blind, randomized trial. Clinical Gastroenterology and Hepatology. 2006;**4**:50-56

[9] Viazis N, Keyoglou A, Kanellopoulos AK, Karamanolis G, Vlachogiannakos J, Triantafyllou K, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: A randomized, double-blind, placebo-controlled study. The American Journal of Gastroenterology. 2012;**107**:1662-1667

[10] Arts J, Sifrim D, Rutgeerts P, Lerut A, Janssens J, Tack J. Influence of radiofrequency energy delivery at the gastroesophageal junction (the Stretta procedure) on symptoms, acid exposure, and esophageal sensitivity to acid perfusion in gastroesophageal reflux disease. Digestive Diseases and Sciences. 2007;**52**:2170-2177

[11] Yadlapati R, Tye M, Keefer L, Kahrilas PJ, Pandolfino JE. Psychosocial distress and quality of life impairment are associated with symptom severity in PPI non-responders with normal impedance-pH profiles. The American Journal of Gastroenterology. 2018;**113**:31-38