REVIEW ARTICLE

Diagnosis and treatment of patients with nonacid gastroesophageal reflux-induced chronic cough

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Gastroesophageal reflux (GER) is one of the most common causes of chronic cough, and chronic cough due to GER represents a subtype of GER-related diseases. Gastroesophageal reflux-induced chronic cough (GERC) can be divided into two subgroups based on the pH of the GER. Nonacid GERC is less common than acid GERC, and its diagnosis and treatment strategy have not been standardized. However, nonacid GERC usually presents with its unique set of characteristics and features upon diagnosis and treatment in the clinic. Although the underlying molecular mechanism of nonacid GERC is not fully understood, it is considered to be associated with reflux theory, reflex theory and airway hypersensitivity. Multi-channel intraluminal impedance combined with pH monitoring is a promising new technique that can detect both acid and nonacid reflux, and our findings as well as those of others have shown its usefulness in diagnosing nonacid GERC. Development of new diagnostic techniques has led to an increased rate of nonacid GERC diagnosis. We summarize our experience in the diagnosis and treatment of nonacid GERC and provide a guide for future therapeutic approaches.

Key words: Chronic cough, multi-channel intraluminal impedance combined with pH monitoring, nonacid gastroesophageal reflux

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INTRODUCTION

Gastroesophageal reflux (GER) is one of the most common causes of chronic cough.[1] Based on its pH value, GER can be divided into two major subtypes, designated as acid and nonacid, which including weakly acid and weakly alkaline. Reflux with pH values ≤4, 4.1-7, and ≥7 is considered acid, weakly acid, and weakly alkaline reflux, respectively.[2] Prior to 2004, the cut-off pH value between acid and nonacid reflux was 6.5.[3] While most reported studies have focused on acid gastroesophageal reflux-induced chronic cough (GERC), several reports have mentioned that nonacid GER can also induce chronic cough.[4-8] However, compared to acid GERC, the diagnosis and treatment of patients with nonacid GERC have received little attention. The symptoms, diagnosis, and strategies for treating nonacid GERC have not been standardized, and this lack of standardization affects patient outcomes greatly. Conventional esophageal 24-h pH monitoring does not provide an accurate evaluation of nonacid reflux, resulting in difficulties in the diagnosis of nonacid GERC and even its misdiagnosis. Our group and others have shown that multi-channel intraluminal impedance (MII-pH) combined with pH monitoring is a useful technique to diagnose nonacid GERC.[9] Furthermore, we recently found that baclofen is useful but suboptimal treatment option for patients with nonacid GERC.[10] We also have substantial experience in the diagnosis and treatment of patients with nonacid GERC[6,9-12] and, therefore, have summarized our results and experience to provide a guide for future diagnosis and treatment of patients with this disorder.

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INCIDENCE AND CLINICAL FEATURES OF NONACID GASTROESOPHAGEAL REFLUX-INDUCED CHRONIC COUGH

Incidence

Acid reflux is a major cause of GERC, and diagnosis and treatment of this type of cough have received a great deal

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of attention. Our increased knowledge of acid GERC has been greatly appreciated. However, in recent years, nonacid reflux has also been recognized to play an important role and sometimes be a direct cause of reflux-induced chronic cough.[13] A meta-analysis showed that following withdrawal of protein pump inhibitor (PPI) treatment, 37% of the GERC cases were nonacid; additionally, 80% of PPI-treated chronic cough cases were nonacid.[14] Another study reported that among GERC patients removed from acid suppressive therapy, the percentages of acid, weakly acid, and weakly alkaline reflux were 65%, 29%, and 6%, respectively.[5] Also, among 50 patients who were monitored while receiving PPI therapy, 13 patients (26%) had a positive symptom index (SI) for nonacid-related cough. One reason for the increased incidence of nonacid-related chronic cough following PPI treatment may be related to the inhibitory function of PPIs; additionally, the increased pH value of the original acid reflux also contributes to the increased percentage of nonacid reflux. Due to a lack of proper diagnostic techniques, the actual incidence of nonacid GERC may be greatly underestimated.

Clinical features

The results of our study have shown that both nonacid GERC and acid GERC are more common in women than men.[15] Patients with nonacid GERC often present with a chronic dry cough or cough with a small amount of white phlegm that may be dominant during daytime or show no difference between day and night. Some patients also present with an accompanying postnasal drip or throat clearing;[13,15] however, symptoms of acid reflux and belching are greatly reduced in nonacid-related chronic cough. The burning sensation and other typical symptoms of acid reflux may be related to the chemical composition of the reflux. The chemical components of nonacid reflux produce less esophageal injury compared to the components of acid reflux.[16] Nonacid reflux usually occurs after meals and is caused by the rapidly increased food volume that stimulates esophageal mechanical stretch receptors, whereas acid reflux often stimulates chemoreceptors. The velocity of the nerve conduction produced by these two different types of receptors is different, which subsequently results in different types of reflux-related symptoms.[16] Although the clinical symptoms of nonacid and acid GERC are different, both types of GERC typically present with symptoms such as acid reflux, heartburn, and belching in <60% of the cases. Furthermore, many symptoms show overlap between the two different types of GERC, making it difficult to distinguish acid and nonacid GERC based only on clinical symptoms. Thus, the differential diagnosis between acid and nonacid GERC is still made by MII-pH monitoring.

Pathogenesis

The reflex and reflux theories are two major mechanisms that have been used to explain the cause of GERC.[1] The incidence of high reflux events is relatively low, and it is difficult to explain its occurrence in the majority of the nonacid GERC cases. The accumulated experimental and clinical evidence suggest that reflex theory provides a more accurate explanation for the cause of the majority of nonacid GERC cases and may also explain the underlying mechanism of GERC.

Reflex theory

Reflex theory, also known as distal reflex theory or esophago-tracheo-bronchial reflex theory, proposes that lower esophageal mucosal receptors are stimulated by reflux material and then activate the cough center through the esophagus, causing a bronchial cough reflex. Simultaneously, the corresponding efferent nerve endings release substance P (SP) CGRP, and other neuropeptides through exocytosis. These neuropeptides either induce neurogenic inflammation or indirectly activate neuropeptide receptors on the surface of mast cells to release tryptase, histamine, prostaglandin E2, and other inflammatory mediators, which finally stimulate cough receptors and result in cough.[17] Studies suggest that nonacidic esophageal reflux activates mechanical stretch receptors to cause cough through Aδ fibers, and acid reflux activates chemical receptors transient receptor potential vanilloid type 1 (TRPV1) to excite the vagus nerve and cause cough through the esophago-tracheo-bronchial reflex. Qiu *et al*.[6] reported that most nonacid reflux is weakly acidic, and accompanied by mast cell tryptase (MCT), SP, and increased cough sensitivity. These findings support the reflex theory which states that weak acid that causes esophago-tracheo-bronchial reflex plays an important role in the development of nonacid GERC.

Reflux theory

Reflux theory also called proximal reflux or micro/macro-aspiration theory, suggests that gastric contents back up into the throat due to structural and functional abnormalities in the lower esophagus. Reflux then either directly stimulates cough receptors or increases mucus secretion in the lower respiratory tract through vagal reflex to activate the cough receptors.[18] Several studies have also suggested that minute or numerous stomach contents can enter the lungs, resulting in aspiration inflammation.[1,19] It is true that patients with nonacid GERC can have proximal reflux at the proximal esophagus and throat, suggesting that reflux theory may provide a suitable explanation for some cases of nonacid GERC.[18,20] Patterson *et al*. found high accumulations of nonacid reflux in the proximal esophagus and throat among patients with nonacid GERC, with the incidence at these sites accounting for 73% and 11% of total reflux, respectively. This reflux can stimulate cough receptors that have been previously stimulated by vagal reflex. These investigators also believe that nonacid reflux is mainly comprised of

liquid reflux. Large amounts of reflux not only thicken the lower esophagus, resulting in localized structural and functional abnormalities but also facilitate movement of reflux into the upper esophagus. Although, reflux theory is not commonly used to explain the mechanism for nonacid reflux related cough, it does explain the reason for cough in a portion of nonacid GERC patients.

Airway inflammation and hyper-sensitivity

It is generally believed that both of the above-mentioned theories are associated with airway inflammation and hyper-sensitivity. Neurogenic inflammation caused by low regurgitation and pharyngeal airway inflammation caused by long-term proximal reflux stimulation can both cause airway epithelial damage and subsequent exposure of cough receptors. Such exposure results in both reconstruction and increased numbers of cough receptors, resulting in increased airway sensitivity which may directly contribute to the occurrence of cough.[21,22] Patterson *et al*.[23] found that compared to non-GERC subjects, patients with asthma combined with acidic GERC, as well as patients with chronic cough, both had higher levels of SP in their induced sputum. Qiu *et al*.[6] found that both nonacid and acid GERC patients had increased cough sensitivity, and showed release of SP and MCT in their airways, suggesting that these two types of coughs may be stimulated by similar mechanisms. Sensory nerve excitation, airway inflammation caused by activation of mast cells, and increased cough sensitivity all contribute to nonacid GERC, and different mechanistic theories may be suitable for different clinical cases. Therefore, elucidation of the mechanism involved in individual cases of nonacid GERC will definitely benefit the selection of an optional therapeutic strategy.

MONITORING OF NONACID REFLUX AND COUGH

Monitoring of nonacid reflux

Conventional 24 h-esophageal pH monitoring does not detect nonacid reflux and is difficult to use for detection of nonacid GERC. Additionally, endoscopy does not detect nonacid GERC in patients with normal esophageal mucosa, and also cannot be used for the first-line examination. However, several other methods and techniques are currently used to detect nonacid GERC.

Multi-channel intraluminal impedance combined with pH monitoring

MII-pH was first reported by Silny in 1991 and was mainly used to monitor the flows of gas and liquid inside of hollow organs by recording the electrical impedance of a composed ring electrode catheter. When using this method, a conductive electrode is inserted into the esophagus through the nose to record the voltage change between two electrodes. This voltage change reflects the reflux characteristics (gas, solid, liquid or mixture) and direction of movement. When combined with pH monitoring, the MII-pH system not only distinguishes nonacid and acid reflux but can also analyze the correlation between cough and reflux events. These features are not available when using conventional monitoring methods; therefore, MII-pH will no doubt be widely used to determine the characteristics of reflux. Several reports, including ours, have described how MII-pH can be utilized to efficiently and accurately identify nonacid GERC,[3,4,6,7] as well as the range of reflux.[24] These capabilities can be exploited to monitor effectively the change in reflux before or after treatment, which is tremendously beneficial for clinical diagnosis or modification of treatment strategies. However, MII-pH requires further modifications to avoid several disadvantages. For example, the range of normal readings needs further examination, and problems of low sensitivity and false-negative signals need to be addressed. One reason for these limitations is that to calculate the probability that symptoms are due to nonacid reflux, a patient must maintain an accurate diary of clinical symptoms. However, some patients fail to record or inaccurately record the durations of coughing episodes, which artificially lowers the symptom associated probability (SAP). Therefore, the MII-pH system has not been perfected and requires further modifications before being adopted as a standard method for diagnosing GERC.

Twenty-four-hour bile reflux monitoring

Nonacid reflux contains the food and gas consumed prior to reflux, nonacid gastric secretions, pancreatic secretions, and is mainly composed of bile. Tack *et al*. found that 38% of 65 patients exhibiting GERC reflux symptoms after regular PPI therapy had bile acid in the esophagus,[25] suggesting that bile acid might play important role in nonacid GERC. Therefore, 24-h bile reflux monitoring is useful for making a correct evaluation of GER disease, because it records several different events and parameters, including bile reflux episodes, prolonged reflux episodes, the longest reflux time, and the total duration and percentage of reflux with an absorption value ≥0.14. However, although 24-h bile reflux monitoring can accurately detect and record bile acid, it cannot monitor weakly acid reflux and small amounts of acid that may be contained in alkaline reflux.

Pepsin

Pepsin is the main component of nonacid gastric secretions, and many investigators believe that pepsin is more injurious to the mucosa of the upper respiratory tract than acid. Samuels *et al*. conducted a comprehensive meta-analysis of reported studies that have used an immunoassay to detect pepsin in saliva and sputum. The results showed that examination for pepsin is a highly reliable and noninvasive method for diagnosing GER, and can also be used in rapid screening for the disorder.

Twenty-four hour intraluminal pressure monitoring

Although 24-h monitoring of intraluminal pressure cannot directly reflect the presence or status of GERC, it can reflect the barrier function of the gastroesophageal junction. In addition to helping position the esophageal impedance and pH electrode, and assist in assessing esophageal function and predicting surgical outcomes, this method can also be used to predict the efficacy of anti-reflux therapy and determine the need for long-term maintenance therapy. Results reported by Blondeau *et al*. suggest that MII-pH combined with intraluminal pressure monitoring is better for diagnosing GERC than the use of either method alone.

Cough monitoring

Cough monitoring is an important method for diagnosing GERC, because the evaluation of SAP and SI are based on the patient's cough symptoms as recorded in a diary or other type of document.

Diary cough record

A diary cough record is a record of coughs that occur during a certain time span, usually of 24 h. The information recorded is very subjective, and relevant information is often omitted or mis-recorded by the patient. Therefore, an SAP value based on a cough diary may not be entirely accurate. Studies have shown that the number of coughs recorded by a patient is only 40% of the actual number. Additionally, coughs are typically recorded as lasting ~30 s. Finally, a chronic cough by itself can lead to GER, which makes it difficult to judge the causal relationship between the two events. A study performed by Wunderlich and Murray showed that only 35% of cough cases showed a positive relationship between cough and GER as judged by SAP.[26] However, maintenance of a diary cough record should still be recommended by clinicians.

Twenty-four hour cough monitoring

An objective measurement of cough severity by 24-h cough monitoring can more accurately gauge the severity of a cough than the use of indirect methods such as subjective cough scores and quality of life assessments. While the devices used for cough monitoring are still in development, they can be divided into two types, consisting of single and multi-element. The single element cough monitoring device is based on voice recognition,[27] and represented by the Helsinki Monitor[28] and Laisaisite cough frequency monitor,[24] while multi-element devices record not only sound but also other such as respiratory inductive plethysmography readings.[29] At present, cough monitoring has not been conducted in a clinic in China.

DIAGNOSTIC CRITERIA AND STANDARDS

Diagnostic criteria

Diagnostic criteria are developed to determine the causal relationship between nonacid reflux and cough. Some useful parameters for such criteria are listed below.

Symptom associated probability

SAP has a high statistical accuracy for showing the correlation between cough and reflux. When calculating SAP, a continuous fourfold table is constructed, in which every 2 min is considered a calculation interval. Each square includes a combination of different symptoms and reflux. The possibility of an association between reflux and symptoms is calculated using Fisher's exact test. This method not only considers the number of reflux and cough symptoms, but also overcomes the symptoms of the SI and SSI which rely solely on cough or the limitations of the number of reflux, and is therefore frequently used in the diagnosis of nonacid GERC. SAP scores can be calculated for both acid and nonacid reflux based on pH values. A positive SAP score signifies that occurrence of reflux and cough are not random,[13] and an SAP >95% is usually considered positive. However, patients who are suspected to have nonacid GERC and are undergoing MII-pH monitoring often fail to record a cough, or incorrectly record the timing of a cough, making it difficult to achieve a diagnostic criterion with an SAP >95%. While a combination of continuous esophageal manometry and cough monitoring may improve the positive SAP rate,[13,30] such combination monitoring is not yet commonly used in China, and current cough guidelines recommend that an SAP ≥75% should be considered as positive. To confirm the accuracy of this guideline, we analyzed the MII results obtained from 103 patients with suspicious GERC and showed that an SAP ≥80% provided greater diagnostic value and accuracy for both acid and nonacid GERC. However, this result should be confirmed by studies conducted at multiple centers. As mentioned above, nerve velocity in nonacid GERC is slow, and GERC symptoms also tend to be slow. Agrawal *et al*.[16] reported that in cases of acid GERC, the incidences of cough, acid reflux, and heartburn occurring within 2 min after acid reflux were 81%, 92%, and 80%, respectively. However, in nonacid GERC patients, the incidences of the same symptoms were significantly reduced and reported to be 56%, 79%, and 54% respectively. However, it should be noted that only symptoms that occur within 2 min after reflux are considered when calculating SAP. Therefore, the 2 min time window may be not very suitable when calculating an SAP for nonacid GERC patients, and should be re-evaluated.

Symptom index

The SI represents the percentage of total coughs which occur in a specified period following reflux; the previously specified period was 5 min but has now been revised to 2 min. A value >50%, is considered positive. Agrawal *et al*.[16] reported that 13 of 50 patients with nonacid GERC were SI

positive. A limitation of the SI is its over-reliance on cough symptoms and exclusion of the total number of reflux incidents. Patients who experience frequent reflux, but little or no cough symptoms during monitoring may show an artificially negative SI that can lead to misdiagnosis. Based on our results from 118 patients with suspicious GERC, we suggest that SI values ≥45% and ≥30% are more appropriate for diagnosing acid and nonacid GERC, respectively.[31]

Symptom sensitive index

The SSI refers to the percentage of the total number of reflux events that are associated with cough, and an SSI ≥10% is considered positive. This method is largely dependent on the number of reflux events, and it not very suitable for diagnosing nonacid GERC.

Diagnostic standards for nonacid gastroesophageal reflux-induced chronic cough

The diagnostic standards for nonacid GERC include the following:

1. Chronic cough with a duration ≥8 weeks, and with or without acid reflux, heartburn, chest pain, and other symptoms.
2. MII-pH shows abnormal nonacid reflux, a DeMeester score <14.72, and an SAP for nonacid reflux ≥95%.
3. Cough is significantly reduced or disappears after anti-reflux therapy.

The national standards for diagnosing cough in China can be found in the publication "Cough Diagnosis and Treatment Guidelines (2010)" written by the Committee for the Chinese Respiratory Society Guidelines for Management of Cough.[32] Currently, an SAP ≥75% is considered positive for nonacid GERC;[32] however, due to the increased application of continuous esophageal manometry and cough monitoring, the SAP cut-off point will soon be increased.[30]

The definition of refractory nonacid GERC requires further discussion. While the current definition of refractory GER disease can be used for reference purposes, no consensus has been reached on the exact definition of refractory GERC.[33] Unlike nonrefractory GERC, it is not easy to establish the causal relationship between GER and nonacid reflux related symptoms in cases of refractory GERC.[34] Furthermore, symptoms in nonacid GERC patients may be greatly reduced, which makes it more difficult to diagnose properly refractory nonacid GERC. Given the current lack of a common definition for refractory GERC, patients with abnormal nonacid reflux that is not relieved by an 8 week course of standard anti-reflux treatment consisting of omeprazole (or equivalent PPIs) 20 mg twice daily and domperidone 10 mg three times per day, should be suspected of having refractory GERC. However, patients who experience cough relief after receiving enhanced anti-reflux therapy should be diagnosed as refractory nonacid GERC.[10] This definition is not only in agreement with ACCP cough guidelines and the definition promulgated by the Chinese Medical Association concerning principles for diagnosis and treatment of GERC,[1] but is also in agreement with the generally accepted definition of refractory GER disease.[35]

Therapy

Proton pump inhibitors

PPIs can greatly reduce nonacid reflux and the damage caused by bile and other digestive agents.[15] It has also been reported that PPIs can repair mucosal injury and reduce airway sensitivity by reducing TRPV1-induced acid stimulation of the esophagus, and inhibiting vacuolar H^+-K^+ ATP enzymes in afferent neurons located on airways.[36] PPIs are not generally recommended for treatment of nonacid GERC.[5] Tutuian *et al*. reported that 26% of patients being treated with a PPI had been diagnosed as nonacid GERC, which was lower than the percentage of patients treated without a PPI. The results also showed that nonacid reflux was reduced or disappeared in some patients receiving PPI therapy. Recent studies in our laboratory have shown that combined therapy with a PPI and a prokinetic drug can achieve a satisfactory result in nonacid GERC patients.[15]

Prokinetic agents

Prokinetic agents can enhance M receptor sensitivity to acetylcholine, activate gastrointestinal smooth muscle to enhance motility of the stomach and esophagus, reduce the time which reflux material stimulates the lower esophagus and decrease the volume and frequency of nonacid reflux.[37] Although the full effects of prokinetic agents have not been defined, it seems logical that they may relieve symptoms of nonacid GERC.

Transient lower esophageal sphincter relaxation inhibitors

GER is defined as a series of 10~60 s spontaneous relaxations of the lower esophageal sphincter that are unrelated to swallowing.[37] Based on current studies of both acid and nonacid GER, transient lower esophageal sphincter relaxations (TLESRs) are considered the most important mechanism for GER Baclofen is a selective gamma-aminobutyric acid B receptor agonist, which is primarily used for treatment of spasticity.[38-40] Baclofen inhibits TLESRs and is often considered for use in combination therapy for nonacid GERC. Baclofen can reduce TLESRs by 40-60%, and GER by 43%.[41] Additionally, Vela *et al*. reported that baclofen inhibited both acid and nonacid reflux in patients with GER and reduced acid reflux-related symptoms and nonacid reflux-related symptoms by 72% and 21%, respectively.[42] Baclofen also demonstrates a nonspecific antitussive effect that has been beneficial in treating refractory chronic unexplained cough in the

clinic.[43] Our studies showed that baclofen not only relieved intractable cough associated with acid or nonacid GERC but also reduced sensitivity to capsaicin-induced cough. Baclofen was effective for cough reduction in 56.3% of patients, indicating it could be used as an alternative strategy for treating refractory GERC.[10,44] Regardless of its effectiveness, the side effects of baclofen have largely limited its clinical use. The central nervous system is the target of major baclofen-related side effects, and other side effects include dry mouth, nausea, vomiting, diarrhea, and constipation. In our clinical experience, the most common side effects were lethargy, drowsiness, and fatigue; however, these symptoms gradually lessened or disappeared within 3 weeks after treatment, with no residual effects. Only a minority of patients who experienced severe dizziness and drowsiness required an interruption in their treatment.[10] When treating patients with baclofen, it is recommended that treatment be initiated using small doses, which are then gradually increased in increments of 5-20 mg. This strategy can help improve patient tolerability and reduce the incidence and intensity of any serious side effects that may occur. In addition, new and more potent inhibitors of lower esophageal sphincter relaxation are being developed which require high concentrations to affect the central nervous system; such new drugs may show improved efficacy and safety margins when used for treatment of GER.[45,46]

Gabapentin

Gabapentin is a structurally homologous gamma-aminobutyric acid (GABA) which functions as an important central neurotransmitter and is primarily used to treat chronic neuropathic pain. Madanick *et al*. reported that ~75% of GERC patients experienced a ≥50% subjective improvement in cough symptoms after receiving gabapentin as add-on therapy at daily doses of 300 or 900 mg.[47] However, it remains unclear whether the cough attenuation experienced after gabapentin therapy was associated with inhibition of acid or nonacid reflux.

Surgery

Surgery can be performed which will enhance sphincter contraction of the lower esophagus in GERC patients, and thus recover the barrier between the stomach and lower esophagus to reduce or eliminate the occurrence of reflux. Traditional open surgical methods include Nissen complete fundoplication for patients with normal esophageal motility, partial fundoplication for patients with poor esophageal motility, and endoscopic radiofrequency ablation.[48] Tutuian *et al*. performed Nissen fundoplication for six patients with nonacid GERC, and five of the patients showed no recurrence of cough symptoms during a 5 years follow-up period.[4] Allen *et al*. reported that 70% of reflux and cough symptoms were improved in nonacid GERC patients during a 5 years period following fundoplication surgery;[49] however, higher rates of complication were found after anti-reflux surgery. Finally it was reported that while cough symptoms improved in 80% of GERC patients followed-up for 2 years, the symptoms were eradicated in <50% of patients.[50,51]

Although anti-reflux surgery such as fundoplication may be an option and benefit for some patients in this situation, its role has not been clearly defined and its application is limited.[4]

CONCLUSION

Taken together, the available evidence shows that the incidence of acid reflux and belching symptoms in nonacid GERC patients is significantly lower than in acid GERC patients. Additionally, the symptoms associated with both acid and nonacid GERC probably arise from the joint action of multiple factors, including those involved in reflex theory, reflux theory, and airway hyper-sensitivity. Due to the limited number of methods available to test for nonacid GERC, it is easy to fail to diagnose this disorder. However, with the development of diagnostic techniques such as MII-pH monitoring, which can distinguish between acid and nonacid reflux, the rate of diagnosis has tended to increase. The proper selection of treatments for nonacid GERC and the efficacy of such treatments deserve further study. Combination treatment of non-GERC with acid-suppressing agents and a prokinetic medicine has shown some benefits. Baclofen can be used for the treatment of nonacid GERC after failure of PPI therapy.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

XX contributed in the conception of the work, conducting the study, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. LY contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. QC contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HL contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and

agreed for all aspects of the work. ZQ contributed in the conception and design of the work, drafting and revising the draft,approval of the final version of the manuscript, and agreed for all aspects of the work.

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