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MINIREVIEWS

Refractory chronic cough due to gastroesophageal reflux: Definition, mechanism and management

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Abstract

Refractory chronic cough due to gastroesophageal reflux is a troublesome condition unresponsive to the standard medical anti-reflux therapy. Its underlying mechanisms may include incomplete acid suppression, non-acid reflux, transient lower esophageal sphincter relaxations and esophageal hypersensitivity. The diagnosis of this disorder depends on both the findings of multi-channel intraluminal impedance-pH monitoring and the subsequent intensified anti-reflux therapy. The strategies of pharmacological treatment for refractory chronic cough due to reflux include the optimization of proton pump inhibitors and add-on therapies with histamine H_2 receptor antagonists, baclofen and gabapentin. However, the further study is needed to satisfy its management.

Key words: Esophageal pH monitoring; Chronic cough; Anti-reflux therapy; Refractory cough; Gastroesophageal reflux

Core tip: Refractory cough due to reflux can be defined as a reflux-induced cough resistant to standard medical anti-reflux treatment but responsive to the subsequent intensified anti-reflux therapy. It may be associated with the residual acid or non-acid reflux, transient lower esophageal sphincter relaxations and esophageal hypersensitivity. The definite diagnosis of the disorder depends on the positive findings of multi-channel intraluminal impedance-pH monitoring as well as favorable response to the intensified anti-reflux therapy. The current therapeutic strategies include the complete acid suppression and add-on uses of baclofen or gabapentin.

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INTRODUCTION

Gastroesophageal reflux-induced chronic cough (GERC) is a special form of gastroesophageal reflux disease with predominant cough symptom[1] and along with cough variant asthma, upper airway cough syndrome or eosinophilic bronchitis, is considered as a common cause of chronic cough[2,3]. Like gastroesophageal reflux disease, proton pump inhibitors (PPIs) alone or in combination with prokinetic agents are a standard medical therapy for GERC and can resolve the cough in most patients[1]. However, a small percentage of patients with GERC are resistant to the standard anti-reflux treatment and this condition is also defined as refractory GERC[4]. This review summarizes our understanding about the definition, mechanism and management of refractory GERC.

DEFINITION OF REFRACTORY GERC

How to define refractory GERC remains to be controversial. There is no consensus on the refractory gastroesophageal reflux disease which GERC can refer to. The generally accepted definition of refractory gastroesophageal reflux disease is the persistent classical reflux-related symptoms such as regurgitation and heartburn despite the treatment with PPIs twice daily for at least 4-8 wk[5]. Recently, Sifrim *et al*[6] proposed that refractory gastroesophageal reflux disease should be defined as the condition in which symptoms (heartburn and/or regurgitation) are not responsive to a stable double dose of PPIs during a treatment period of at least 12 wk and patients continue to report troublesome symptoms while "on" PPIs at least thrice weekly for the last 3 mo[6]. As one of extraesophageal symptoms, cough can be caused by many diseases other than GERC. A cause-effect association between reflux and cough is more difficult to establish than regurgitation and heartburn, and too long-lasting trial with PPIs may delay the diagnosis and treatment of the other etiologies of chronic cough. Therefore, we have defined refractory GERC as a condition of chronic cough with the objective evidence of abnormal reflux as demonstrated by multichannel intraluminal impedance-pH monitoring (MII-pH), and resistant to a 8-wk standard medical anti-reflux treatment but responsive to the subsequent intensified anti-reflux therapy[4,7]. This definition is consistent with the principles recommended in several guidelines for the management of chronic cough[1,8] as well as the generally accepted definition of refractory gastroesophageal reflux disease[5].

The exact prevalence of refractory GERC is still unclear. It is estimated that 10%-40% patients with gastroesophageal reflux disease do not or only partially respond to the standard dose of PPIs[9]. Unlike erosive esophagitis, nonerosive reflux disease has basically normal esophageal mucosa under an endoscope and normal or slightly abnormal esophageal acid exposure as indicated by MII-pH, accounts for 70% of gastroesophageal reflux disease and is poorly responsive to PPIs treatment[10,11]. Therefore, nonerosive reflux disease is responsible for the majority of refractory gastroesophageal reflux disease. Our preliminary results have shown that refractory GERC accounts for about one third of GERC[12], and is comparable with the prevalence of refractory gastroesophageal reflux disease.

MECHANISMS OF REFRACTORY GERC

It is well known that GERC may be caused by microaspiration of the refluxate into the airways (reflux hypothesis) and esophageal-tracheobronchial reflexes mediated by the afferent nerves in the distal esophagus (reflex hypothesis)[1]. However, the mechanisms underlying the refractory GERC is poorly understood. It may be associated with the incomplete acid suppression, non-acid reflux, transient lower esophageal sphincter relaxations (TLESRs) and esophageal hypersensitivity.

INCOMPLETE ACID SUPPRESSION

Incomplete acid suppression has been documented in patients with persistent symptoms despite the therapy with PPIs at a standard dose. Several studies have shown 4%-17% patients presented with abnormal acid reflux[13,14] and 7%-11% patients had a positive symptom index[15,16] as revealed by 24-h esophageal pH monitoring when they were "on" PPIs. The residual acid reflux can continue to elicit cough through microaspiration or esophageal-tracheobronchial reflex[1]. In addition to poor compliance such as not taking PPIs in time or at the suitable time, ineffective acid suppression may also be related to the difference in the responsiveness to therapy among patients. For example, the rapid metabolism of PPIs in some patients may result in that the high serum PPIs level can not be achieved for the adequate acid suppression[17]. Nocturnal acid breakthrough, a phenomenon of gastric pH below 4 for at least 1 h during the night, was also suggested as a cause of the failure to PPIs treatment by promoting gastroesophageal reflux during sleep[18]. However, accumulating evidence does not support a significant role of nocturnal acid breakthrough in the failure of PPIs treatment.

NON-ACID REFLUX

Non-acid reflux, an important constituent of reflux, includes weakly acidic (refluxate pH = 4-7) and weakly alkaline (refluxate pH > 7) reflux, with 95% belonging to weakly acidic reflux and only 5% belonging to weakly alkaline reflux[19]. Non-acid reflux accounts for 50% and 95% of reflux in the patients with gastroesophageal reflux disease "off" and "on" PPIs, respectively[20]. It is reported that cough-related reflux consists of acid (65%), weakly acidic (29%) and weakly alkaline (6%) reflux in the GERC patients "off" acid suppressive therapy[21]. In contrast, reflux-related cough is caused

by weakly acidic (74%), weakly alkaline (17%) and acid (4%) reflux in patients with refractory GERC[22]. The increase in weakly acidic reflux episode may derive from the relative increase in the percentage of original weakly acidic reflux due to the inhibition of acid reflux or in a considerable part, the transition of the original acid reflux due to pH value shift in the refluxates after PPIs treatment. The cough induced by weakly acidic reflux may be associated with esophageal distension due to increased reflux volume, persistent impaired mucosal integrity and esophageal hypersensitivity[23].

TLESRS

TLESRs refer to the spontaneous (not preceded by a swallow) relaxations of the lower esophageal sphincter lasting 10-60 s[24], which is a vagally mediated event induced by the volume distension of the stomach. Physiologically, it plays a role in venting air from the stomach after meals and also represents a main mechanism underlying all types of reflux[25]. In patients with established gastroesophageal reflux disease, TLESRs have a high prevalence and is two times more likely to be related to the reflux[26]. In general, PPIs can reduce the acidity and volume of refluxate in the esophagus, but have no ability to rectify the dysfunction of the lower esophageal sphincter and decrease reflux episodes.

ESOPHAGEAL HYPERSENSITIVITY

Esophageal hypersensitivity is defined as an exaggerated response of esophageal mucosa to normal or subthreshold stimuli and involved in the pathogenesis of GERC. It is unclear whether esophageal sensitivity in refractory GERC is higher than naive GERC. However, several lines of evidence have demonstrated that patients with nonerosive reflux disease are more sensitive to intraesophageal acid infusion, balloon distension and electrical stimulation than patients with erosive esophagitis[27,28].

The function of peripheral sensory terminals may be modified by inflammatory mediators released from the injured and inflammatory esophageal mocosa caused by reflux. Consequently, the transduction threshold is decreased in the primary sensory afferents, resulting in hypersensitivity at the site of injury or inflammation, and a heightened response to subthreshold or innocuous chemical, mechanical and electrical stimuli. It has been shown that the expression of acid-sensing receptors and transient receptor potential vanilloid 1 are up-regulated in the esophageal mucosa of patients with gastroesophageal reflux disease[28]. Patients with refractory GERC have the dilated intercellular spaces in the esophageal epithelium due to repeated exposure to acid and enzymes, which permits the penetration of some noxious or sensitizing substances through the epithelial barrier, exposes and activates subepithelial nerves, and prompts the transduction of acid signals from the peripheral afferents to cough center[29]. Once central sensitization is established, it can continue to potentiate cough even though the initial peripheral stimulus is discontinued.

DIAGNOSTIC APPROACH

According to the algorithms recommended in several guidelines for the management of chronic cough, a complete laboratory workup including sinus or chest imaging, pulmonary function test, bronchial provocation and induced sputum cytology should be performed in sequence or simultaneously to identify the common causes of chronic cough such as cough variant asthma, upper airway cough syndrome and eosinophilic bronchitis[1,8]. Possible GERC is considered when the patients have the concomitant typical reflux-related symptoms, the other common causes of chronic cough are excluded and the treatment specific to current etiologies fails to resolve cough completely[30]. If the laboratory findings reveal the abnormal reflux, the favorable response to the subsequent standard medical anti-reflux treatment will confirm the diagnosis of GERC. Otherwise, refractory GERC has to be assumed (Figure 1).

The difficulty in diagnosing refractory GERC is to confirm the cause-effect association between reflux and cough. The resistance to medical anti-reflux therapy may be refractory GERC or the ongoing cough is not related to any continuing reflux[4]. Of note, the false refractoriness to PPIs treatment due to poor compliance to treatment should be excluded. It is found that 40% of the patients with gastroesophageal reflux disease are not compliant to PPIs therapy in a large population based study[31]. Except for omeprazole sodium bicarbonate and dexlansoprazole, the traditional delayed release PPIs should be administered 30-60 min before meals to assure the maximal gastric acid inhibition[32]. When the factors are addressed, the possibility of refractory GERC may be increased.

As shown in Table 1, MII-pH is currently a major laboratory examination for the diagnosis of refractory GERC while barium radiographs and upper gastrointestinal endoscopy are not recommended or used only when MII-pH is unavailable because their overall sensitivity is extremely low[32]. With the impedance probes located at different sites of the esophagus, MII-pH can record the changes in the electric impedance induced by the movement of various types of bolus in the esophagus, recognize gas, liquid and mixed reflux based on the impedance value of bolus, and classify reflux as acid and non-acid according to the pH value of refluxate[19,33]. Theoretically, MII-pH has an ability to detect all types of reflux, identify the characters of refluxate and establish a temporal association between acid or non-acid reflux and cough. MII-pH is superior to the ambulatory 24-h esophageal pH monitoring for the diagnosis of GERC in that it provides additional information of non-acid reflux[30]. Recently, it has been reported that the presence of a pathological acid

Table 1 Diagnostic value of laboratory investigation for chronic cough due to gastroesophageal reflux

Diagnostic tests	Indications	Advantages	Drawbacks
Barium radiographs	Not recommended for diagnosis of GERC unless evaluating for dysphagia	High specificity	Extremely low sensitivity
Upper gastrointestinal endoscopy	Not recommended for diagnosis of GERC. Only useful for the detection of erosive esophagitis but not for non-erosive reflux disease	High specificity	Low sensitivity
Ambulatory 24-h esophageal pH monitoring	Able to detect acid reflux but not non-acid (weakly acidic and alkaline) reflux	Relatively high sensitivity	Modest specificity
Multi-channel intraluminal impedance-pH monitoring	Able to detect both acid and non-acid reflux	High sensitivity	Modest specificity

GERC: Gastroesophageal reflux-induced chronic cough.

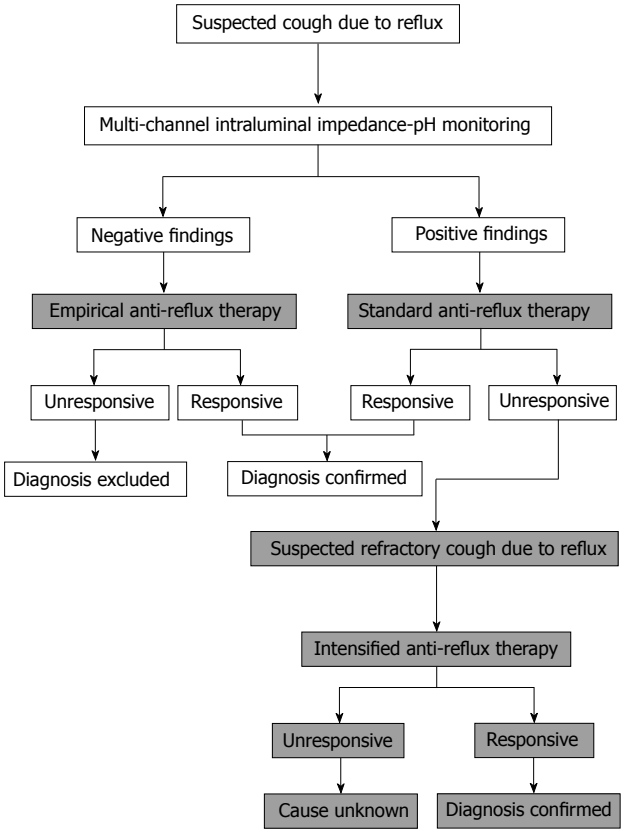

Figure 1 Diagnostic algorithm for refractory chronic cough due to reflux.

exposure time or pathological impedance baseline in MII-pH study may predict the better response to the treatment with PPIs in patients with chronic cough[34]. Therefore, MII-pH has been posited as a future standard for the reflux detection and monitoring[35].

MII-pH has the similar inherent limitations to ambulatory 24-h esophageal pH monitoring. For the estabishment of a temporal association between cough and reflux, the calculation of the symptom association probability (one of significant criteria in the diagnosis of GERC) still depends upon the counts and timing of cough reported by patients and the reflux recorded by MII-pH. Since patients usually underestimate the frequency of cough events or misreport their timing during MII-pH, the symptom association probability determined with above method is not adequately accurate. Several studies have demonstrated that only 40% of cough bursts are indicated by the patients, with a delay of around 30 s, and a positive symptom association probability is found in only 35% of GERC patients[21]. Even though with synchronized intraesophageal manometric monitoring or 24-h ambulatory cough sound recording for precise recognition of cough, the positive rate of the symptom association probability is only improved to 45%-48%[21,36]. Therefore, the sensitivity of MII-pH in the diagnosis of refractory GERC is not high enough to meet the need in clinical practice.

The diagnostic criteria for the refractory GERC can be defined as follows[4,7,8]: (1) chronic cough, with or without the classical reflux-related symptoms such as regurgitation and heartburn; (2) MII-pH confirms the abnormal acid or non-acid reflux, defined as DeMeester score of $\geqslant$ 14.72 and/or the symptom association probability for acid or non-acid reflux of $\geqslant$ 95%. However, our study has shown that $\geqslant$ 80% may be an optimal cut-off value for the symptom association probability and can maintain the better balance between sensitivity and specificity in the diagnosis of GERC[37]; (3) cough fails to improve after 8-wk standard anti-reflux treatment with omeprazole (or equivalent PPIs) at 20 mg twice daily and domperidone at 10 mg thrice daily with life style modification, but responds to the subsequent intensified anti-reflux therapy; and (4) other causes of chronic cough are excluded. When a patient meets all the above criteria, refractory GERC can be definitely diagnosed.

THERAPEUTIC INTERVENTIONS

Refractory GERC can be treated pharmacologically and non-pharmacologically. Currently, the intensified medical anti-reflux treatment is the most common therapeutic option (Table 2).

OPTIMIZATION OF PPIS THERAPY

The modulation of brands and doses of PPIs is a useful strategy for the management of refractory GERC. When a PPI fails, switching to another PPI is possibly effective. Several clinical studies have demonstrated

Table 2 Evaluation of therapeutic options for refractory chronic cough due to gastroesophageal reflux

Therapeutic options	Evaluations
Pharmacologically	
Optimization of PPIs therapy	
Switch to another PPI	Useful for some refractory cough due to acid reflux
Doubling the current dose of PPI	Useful for refractory cough due to severe acid reflux
Add-on therapy	
Histamine H2 receptor antagonists	Useful for refractory cough due to severe acid reflux and night-time reflux
TLESRs inhibitors (baclofen)	Useful for refractory cough due to acid or non-acid reflux resistant to PPI therapy
Gabapentin	Useful for refractory cough due to acid or non-acid reflux resistant to PPI and baclofen therapy
Surgically	
Laparoscopic fundoplication	A treatment option for long-term therapy of refractory cough due to acid or non-acid reflux
Endoscopic therapy or transoral incisionless fundoplication	Not recommended for refractory cough due to reflux on the basis of lack of long-term efficacy
Radiofrequency augmentation	Not recommended for refractory cough due to reflux on the basis of lack of long-term efficacy

PPI: Proton pump inhibitor. TLESRs: transient lower esophageal sphincter relaxations.

that, when adequate symptom relief is not achieved with omeprazole, the switch to esomeprazole (40 mg once daily) for 8 wk may attenuate the symptoms and improve the health-related quality of life in 78% of the patients with gastroesophageal reflux disease[38,39]. This option is also cost-effective. When a single dose of lansoprazole (30 mg once daily) fails, switching to either omeprazole or esomeprazole (40 mg once daily) may achieve adequate symptom control in the patients with gastroesophageal reflux disease[40,41]. However, there is no study to demonstrate the efficacy of a switch to another PPI in patients with refractory GERC.

To increase the dose of PPIs may help to achieve complete acid suppression, and eliminate the residual acid reflux in patients with refractory GERC. Doubling the original dose of PPIs is a common selection. When the dose of lansoprazole is increased from 30 mg daily to 60 mg daily, adequate symptom control is achieved in approximately 20%-30% of patients who are unresponsive to the original low dose lansoprazole for 6-8 wk[40,41]. Our study has demonstrated that the cough in 38.9% of patients with refractory GERC was controlled after the treatment with a doubled-dose omeprazole (40 mg twice daily)[12]. These patients had a more severe esophageal acid exposure, as indicated by a mean 85-point DeMeester score, suggesting the standard dose PPIs were not enough to obviously reduce the acidity of refluxate. After treatment with doubled-dose omeprazole, the significant increase in the pH value of refluxate may markedly attenuate the acid-induced stimulation to the esophageal receptors, inhibit the esophageal-tracheobronchial reflex and finally resolve the cough[12].

ADD-ON THERAPY WITH HISTAMINE H_2 RECEPTOR ANTAGONISTS

Seventy-five percent of patients with refractory gastroesophageal reflux disease still present with abnormal nocturnal gastric acid secretion even after the treatment with PPIs twice daily[42]. The addition of a histamine H_2 receptor antagonist at bedtime may help to achieve complete acid suppression in these patients. Retrospective studies have shown that the combination of PPIs with histamine H_2 receptor antagonists may improve the overall symptoms in 72% of patients with refractory gastroesophageal reflux disease[43]. Since long-term use of histamine H_2 receptor antagonists may develop tachyphlaxis and decrease its therapeutic efficacy, its intermittent or on-demand use at bedtime is advocated. Our results showed the addition of ranitidine 150 mg twice daily attenuated the cough symptoms in 25% of patients with refractory GERC who were unresponsive to the therapy with high dose PPIs[12]. This combined therapy is not to eliminate the night-time reflux but to completely inhibit the day-time gastric secretion by acting on multiple targets in the parietal cells of the stomach. Surprisingly, refractory GERC responsive to the add-on therapy with ranitidine had lower severity of acid reflux (mean DeMeester score of only 36.3) than that responsive to treatment with doubled dose PPIs, suggesting that the esophageal hypersensitivity to acid is a major cause in these patients[12].

ADD-ON THERAPY WITH TLESRS INHIBITORS

Baclofen is a selective gamma-aminobutyric acid (GABA) B receptor agonist primarily used for the treatment of spasticity. It has been demonstrated baclofen can reduce the frequency of TLESRs, decrease the reflux episodes[44-46], and relieve the acid reflux related symptoms by 72% and non-acid reflux related symptoms by 21%[47]. In addition, baclofen has non-specific antitussive activity and has been used for the treatment of refractory chronic cough of unknown causes[48]. As an add-on therapy to PPIs, baclofen may significantly improve the cough symptoms and decrease the cough sensitivity to inhaled capsaicin in 56.3% of patients with refractory GERC[7]. Therefore, baclofen may be useful for treatment of refractory GERC unresponsive to other anti-reflux therapies.

However, baclofen can decrease but not completely abolish TLESRs. It has been documented that baclofen only reduces the frequency of TLESRs by 40%-60% and decrease the reflux episodes by 43%[44-46]. Therefore, the residual reflux may continue to produce cough through stimulating the receptors in the distal esophageal mucosa. This explains why baclofen is not always effective to relieve the refractory GERC. To develop more potent TLESRs inhibitors with few side effects may be a future direction. Furthermore, some refluxes may be secondary to the decreased pressure difference between stomach and esophagus because of the lower baseline pressure of lower esophageal sphincter, and thus be unrelated to TLESRs. Therefore, baclofen is not effective for these refluxes.

The main side effects of baclofen are related to the central nervous system since it can permeate the blood-brain barrier. This limits its clinical application. Nevertheless, the drug-related somnolence, drowsiness and fatigue are usually tolerable and may disappear within 3 wk in most patients. Only a few patients have to stop the baclofen treatment due to severe dizziness and drowsiness[7]. A gradual increase in the dose of baclofen from 5 mg to 20 mg per time may help to improve the patients' tolerance and avoid the severe adverse effects.

ADD-ON THERAPY WITH GABAPENTIN

Gabapentin is a lipophilic structural analogue of GABA, an important central neurotransmitter, and may prevent the synaptic release of neurotransmitters by binding selectively to the $Ca_{v}\alpha_{2}\beta$ subunit of the voltage gated calcium channels. It is primarily used to treat chronic neuropathic pain. Since patients with chronic cough have a similar central sensitization to those with chronic neuropathic pain, the possible inhibition of hypersensitized cough center with gabapentin may be a new therapy for the refractory chronic cough. Ryan *et al*[49] have demonstrated that gabapentin can improve the cough symptoms and cough-specific quality of life in the patients with refractory chronic cough with 8-wk treatment with gabapentin starting at 300 mg daily and titrating up to 1800 mg daily. Madanick *et al*[50] have reported that, after the add-on therapy with gabapentin, approximately 75% of GERC patients experienced at least 50% subjective improvement in cough, irrespective of findings from the esophageal pH monitoring. The dose of gabapentin they used was 300 mg daily in most patients and 900 mg daily or more in a few patients, obviously lower than that reported by Ryan *et al*[49]. At present, it remains unclear whether the cough attenuation after gabapentin therapy is associated with the inhibition of reflux. Further studies are needed to clarify this issue.

ANTI-REFLUX SURGERY

Anti-reflux surgery can treat GERC by artificially reestablishing the mechanical barrier between esophagus and stomach to block both acid and non-acid reflux. Currently, the most commonly used anti-reflux surgery is laparoscopic fundoplication, which can improve more in cough symptom and PPI elimination[51]. In contrast, the radiofrequency augmentation, silicone injection and endoscopic suturing of the lower esophageal sphincter as well as transoral incisionless fundoplication are not recommended due to the absence of evidence supporting their long-term efficacy[32]. The reported successful rate of laparoscopic fundoplication for refractory GERC was about 85%[52]. However, the efficacy of anti-reflux surgery reduces over time. The rate of cough resolution decreases post-operationally from 83% at 6 mo to 74% at 2 years, and 71% within 5 years[53]. Because of its invasiveness and uncertain efficacy, anti-reflux surgery is not a first-line treatment and not extensively used in clinical practice.

In conclusion, refractory GERC is a disorder difficult to manage. Its underlying mechanisms may be associated with incomplete acid suppression, non-acid reflux, TLESRs and esophageal hypersensitivity. MII-pH is a major laboratory examination and can establish the temporal association between reflux and cough, which, however, need to be confirmed by the subsequent intensified anti-reflux therapy. Refractory GERC can be treated pharmacologically and non-pharmacologically. The optimization of PPIs and add-on therapy with histamine H_2 receptor antagonists, TLESRs inhibitors baclofen and gabapentin are the selective pharmacological therapies for refractory GERC. However, the further study is needed to satisfy its management.

REFERENCES

1 **Irwin RS**. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129**: 80S-94S [PMID: 16428697 DOI: 10.1378/chest.129.1_suppl.80S]

2 **Lai K**, Chen R, Lin J, Huang K, Shen H, Kong L, Zhou X, Luo Z, Yang L, Wen F, Zhong N. A prospective, multicenter survey on causes of chronic cough in China. *Chest* 2013; **143**: 613-620 [PMID: 23238526 DOI: 10.1378/chest.12-0441]

3 **Wei W**, Yu L, Lu H, Wang L, Shi C, Ma W, Huang Y, Qiu Z. Comparison of cause distribution between elderly and non-elderly patients with chronic cough. *Respiration* 2009; **77**: 259-264 [PMID: 18596372 DOI: 10.1159/000142942]

4 **Xu X**, Chen Q, Liang S, Lü H, Qiu Z. Successful resolution of refractory chronic cough induced by gastroesophageal reflux with treatment of baclofen. *Cough* 2012; **8**: 8 [PMID: 23078809 DOI: 10.1186/1745-9974-8-8]

5 **Liu JJ**, Saltzman JR. Refractory gastro-oesophageal reflux disease: diagnosis and management. *Drugs* 2009; **69**: 1935-1944 [PMID: 19747009 DOI: 10.2165/11318520-000000000-00000]

6 **Sifrim D**, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut* 2012; **61**: 1340-1354 [PMID: 22684483 DOI: 10.1136/gutjnl-2011-301897]

7 **Xu XH**, Yang ZM, Chen Q, Yu L, Liang SW, Lv HJ, Qiu ZM. Therapeutic efficacy of baclofen in refractory gastroesophageal reflux-induced chronic cough. *World J Gastroenterol* 2013; **19**: 4386-4392 [PMID: 23885151 DOI: 10.3748/wjg.v19.i27.4386]

8 **Asthma Workgroup, Chinese Society of Respiratory Diseases (CSRD), Chinese Medical Association**. The Chinese national

guidelines on diagnosis and management of cough (December 2010). *Chin Med J* (Engl) 2011; **124**: 3207-3219 [PMID: 22088510 DOI: 10.3760/cma.j.issn.0366-6999.2011.20.002]
9 **Hershcovici T**, Fass R. Management of gastroesophageal reflux disease that does not respond well to proton pump inhibitors. *Curr Opin Gastroenterol* 2010; **26**: 367-378 [PMID: 20571388 DOI: 10.1097/MOG.0b013e32833ae2be]
10 **Dean BB**, Gano AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004; **2**: 656-664 [PMID: 15290657 DOI: 10.1016/S1542-3565(04)00288-5]
11 **Lind T**, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, Junghard O, Lauritsen K, Lundell L, Pedersen SA, Stubberöd A. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997; **32**: 974-979 [PMID: 9361168 DOI: 10.3109/00365529709011212]
12 **Xu XH**, Chen Q, Yu L, Liang SW, Lü HJ, Qiu ZM. Efficacy of sequential stepwise anti-reflux therapy on refractory chronic cough due to gastroesophageal reflux (Abstract). *Lung* 2014; **192**: 1-2 [DOI: 10.1007/s00408-013-9552-7]
13 **Charbel S**, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. *Am J Gastroenterol* 2005; **100**: 283-289 [PMID: 15667483 DOI: 10.1111/j.1572-0241.2005.41210.x]
14 **Karamanolis G**, Vanuytsel T, Sifrim D, Bisschops R, Arts J, Caenepeel P, Dewulf D, Tack J. Yield of 24-hour esophageal pH and bilitec monitoring in patients with persisting symptoms on PPI therapy. *Dig Dis Sci* 2008; **53**: 2387-2393 [PMID: 18322797 DOI: 10.1007/s10620-007-0186-6]
15 **Mainie I**, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut* 2006; **55**: 1398-1402 [PMID: 16556669 DOI: 10.1136/gut.2005.087668]
16 **Sharma N**, Agrawal A, Freeman J, Vela MF, Castell D. An analysis of persistent symptoms in acid-suppressed patients undergoing impedance-pH monitoring. *Clin Gastroenterol Hepatol* 2008; **6**: 521-524 [PMID: 18356117 DOI: 10.1016/j.cgh.2008.01.006]
17 **Klotz U**. Impact of CYP2C19 polymorphisms on the clinical action of proton pump inhibitors (PPIs). *Eur J Clin Pharmacol* 2009; **65**: 1-2 [PMID: 18958459 DOI: 10.1007/s00228-008-0571-x]
18 **Peghini PL**, Katz PO, Bracy NA, Castell DO. Nocturnal recovery of gastric acid secretion with twice-daily dosing of proton pump inhibitors. *Am J Gastroenterol* 1998; **93**: 763-767 [PMID: 9625124 DOI: 10.1111/j.1572-0241.1998.221_a.x]
19 **Sifrim D**, Mittal R, Fass R, Smout A, Castell D, Tack J, Gregersen H. Review article: acidity and volume of the refluxate in the genesis of gastro-oesophageal reflux disease symptoms. *Aliment Pharmacol Ther* 2007; **25**: 1003-1017 [PMID: 17439501 DOI: 10.1111/j.1365-2036.2007.03281.x]
20 **Smout AJ**. Review article: The measurement of non-acid gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2007; **26** Suppl 2: 7-12 [PMID: 18081643 DOI: 10.1111/j.1365-2036.2007.03527.x]
21 **Sifrim D**, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut* 2005; **54**: 449-454 [PMID: 15753524 DOI: 10.1136/gut.2004.055418]
22 **Blondeau K**, Dupont LJ, Mertens V, Tack J, Sifrim D. Improved diagnosis of gastro-oesophageal reflux in patients with unexplained chronic cough. *Aliment Pharmacol Ther* 2007; **25**: 723-732 [PMID: 17311606 DOI: 10.1111/j.1365-2036.2007.03255.x]
23 **Tsoukali E**, Sifrim D. The role of weakly acidic reflux in proton pump inhibitor failure, has dust settled? *J Neurogastroenterol Motil* 2010; **16**: 258-264 [PMID: 20680164 DOI: 10.5056/jnm.2010.16.3.258]
24 **Dodds WJ**, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, Egide MS. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982; **307**: 1547-1552 [PMID: 7144836 DOI: 10.1056/NEJM198212163072503]
25 **Hershcovici T**, Mashimo H, Fass R. The lower esophageal sphincter. *Neurogastroenterol Motil* 2011; **23**: 819-830 [PMID: 21711416 DOI: 10.1111/j.1365-2982.2011.01738.x]
26 **Mittal RK**, Holloway RH, Penagini R, Blackshaw LA, Dent J. Transient lower esophageal sphincter relaxation. *Gastroenterology* 1995; **109**: 601-610 [PMID: 7615211 DOI: 10.1016/0016-5085(95)90351-8]
27 **Thoua NM**, Khoo D, Kalantzis C, Emmanuel AV. Acid-related oesophageal sensitivity, not dysmotility, differentiates subgroups of patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2008; **27**: 396-403 [PMID: 18081729 DOI: 10.1111/j.1365-2036.2007.03584.x]
28 **Knowles CH**, Aziz Q. Visceral hypersensitivity in non-erosive reflux disease. *Gut* 2008; **57**: 674-683 [PMID: 18079285 DOI: 10.1136/gut.2007.127886]
29 **Borrelli O**, Mancini V, Thapar N, Ribolsi M, Emerenziani S, de' Angelis G, Bizzarri B, Lindley KJ, Cicala M. Dilated intercellular space diameter as marker of reflux-related mucosal injury in children with chronic cough and gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2014; **39**: 733-742 [PMID: 24512625 DOI: 10.1111/apt.12652]
30 **Xu X**, Chen Q, Liang S, Lv H, Qiu Z. Comparison of gastroesophageal reflux disease questionnaire and multichannel intraluminal impedance pH monitoring in identifying patients with chronic cough responsive to antireflux therapy. *Chest* 2014; **145**: 1264-1270 [PMID: 24457470 DOI: 10.1378/chest.13-1634]
31 **El-Serag HB**, Fitzgerald S, Richardson P. The extent and determinants of prescribing and adherence with acid-reducing medications: a national claims database study. *Am J Gastroenterol* 2009; **104**: 2161-2167 [PMID: 19568229 DOI: 10.1038/ajg.2009.312]
32 **Katz PO**, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; **108**: 308-328; quiz 329 [PMID: 23419381 DOI: 10.1038/ajg.2012.444]
33 **Qiu Z**, Yu L, Xu S, Liu B, Zhao T, Lü H, Qiu Z. Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. *Respirology* 2011; **16**: 645-652 [PMID: 21342332 DOI: 10.1111/j.1440-1843.2011.01952.x]
34 **Ribolsi M**, Savarino E, De Bortoli N, Balestrieri P, Furnari M, Martinucci I, Casale M, Greco F, Salvinelli F, Savarino V, Marchi S, Cicala M. Reflux pattern and role of impedance-pH variables in predicting PPI response in patients with suspected GERD-related chronic cough. *Aliment Pharmacol Ther* 2014; **40**: 966-973 [PMID: 25109844 DOI: 10.1111/apt.12919]
35 **Bredenoord AJ**. Impedance-pH monitoring: new standard for measuring gastro-oesophageal reflux. *Neurogastroenterol Motil* 2008; **20**: 434-439 [PMID: 18416700 DOI: 10.1111/j.1365-2982.2008.01131.x]
36 **Smith JA**, Decalmer S, Kelsall A, McGuinness K, Jones H, Galloway S, Woodcock A, Houghton LA. Acoustic cough-reflux associations in chronic cough: potential triggers and mechanisms. *Gastroenterology* 2010; **139**: 754-762 [PMID: 20600028 DOI: 10.1053/j.gastro.2010.06.050]
37 **Chen Q**, Xu XH, Yu L, Liang SW, Lü HJ, Qiu ZM. [Optimal cut-off point of symptom association probability in the diagnosis of gastroesophageal reflux-induced chronic cough]. *Zhonghua Jie He He Hu Xi Za Zhi* 2013; **36**: 746-750 [PMID: 24433802 DOI: 10.3760/cma.j.issn.1001-0939.2013.10.010]
38 **Jones R**, Patrikios T. The effectiveness of esomeprazole 40 mg in patients with persistent symptoms of gastro-oesophageal reflux disease following treatment with a full dose proton pump inhibitor. *Int J Clin Pract* 2008; **62**: 1844-1850 [PMID: 19166433 DOI: 10.1111/j.1742-1241.2008.01923.x]
39 **Moayyedi P**, Armstrong D, Hunt RH, Lei Y, Bukoski M, White RJ. The gain in quality-adjusted life months by switching to esomeprazole in those with continued reflux symptoms in primary care: EncomPASS--a cluster-randomized trial. *Am J Gastroenterol* 2010; **105**: 2341-2346 [PMID: 20842110 DOI: 10.1038/ajg.2010.368]

40 **Fass R**, Murthy U, Hayden CW, Malagon IB, Pulliam G, Wendel C, Kovacs TO. Omeprazole 40 mg once a day is equally effective as lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease (GERD) who are resistant to conventional-dose lansoprazole therapy-a prospective, randomized, multi-centre study. *Aliment Pharmacol Ther* 2000; **14**: 1595-1603 [PMID: 11121907 DOI: 10.1046/j.1365-2036.2000.00882.x]

41 **Fass R**, Sontag SJ, Traxler B, Sostek M. Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. *Clin Gastroenterol Hepatol* 2006; **4**: 50-56 [PMID: 16431305 DOI: 10.1016/S1542-3565(05)00860-8]

42 **Xue S**, Katz PO, Banerjee P, Tutuian R, Castell DO. Bedtime H2 blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. *Aliment Pharmacol Ther* 2001; **15**: 1351-1356 [PMID: 11552905 DOI: 10.1046/j.1365-2036.2001.01050.x]

43 **Rackoff A**, Agrawal A, Hila A, Mainie I, Tutuian R, Castell DO. Histamine-2 receptor antagonists at night improve gastroesophageal reflux disease symptoms for patients on proton pump inhibitor therapy. *Dis Esophagus* 2005; **18**: 370-373 [PMID: 16336606 DOI: 10.1111/j.1442-2050.2005.00518.x]

44 **Beaumont H**, Boeckxstaens GE. Does the presence of a hiatal hernia affect the efficacy of the reflux inhibitor baclofen during add-on therapy? *Am J Gastroenterol* 2009; **104**: 1764-1771 [PMID: 19491837 DOI: 10.1038/ajg.2009.247]

45 **Zhang Q**, Lehmann A, Rigda R, Dent J, Holloway RH. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. *Gut* 2002; **50**: 19-24 [PMID: 11772961 DOI: 10.1136/gut.50.1.19]

46 **Lidums I**, Lehmann A, Checklin H, Dent J, Holloway RH. Control of transient lower esophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in normal subjects. *Gastroenterology* 2000; **118**: 7-13 [PMID: 10611148 DOI: 10.1016/S0016-5085(00)70408-2]

47 **Vela MF**, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. *Aliment Pharmacol Ther* 2003; **17**: 243-251 [PMID: 12534409 DOI: 10.1046/j.1365-2036.2003.01394.x]

48 **Dicpinigaitis PV**, Rauf K. Treatment of chronic, refractory cough with baclofen. *Respiration* 1998; **65**: 86-88 [PMID: 9523374 DOI: 10.1159/000029232]

49 **Ryan NM**, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; **380**: 1583-1589 [PMID: 22951084 DOI: 10.1016/S0140-6736(12)60776-4]

50 **Madanick RD**. Management of GERD-Related Chronic Cough. *Gastroenterol Hepatol* (N Y) 2013; **9**: 311-313 [PMID: 23943667]

51 **Liang WT**, Wu JM, Hu ZW, Wang ZG, Zhu GC, Zhang C. Laparoscopic Nissen fundoplication is more effective in treating patients with GERD-related chronic cough than Stretta radiofrequency. *Minerva Chir* 2014; **69**: 121-127 [PMID: 24970301]

52 **Chandra KM**, Harding SM. Therapy Insight: treatment of gastroesophageal reflux in adults with chronic cough. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 604-613 [PMID: 17978817 DOI: 10.1038/ncpgasthep0955]

53 **Allen CJ**, Anvari M. Does laparoscopic fundoplication provide long-term control of gastroesophageal reflux related cough? *Surg Endosc* 2004; **18**: 633-637 [PMID: 15026893 DOI: 10.1007/s00464-003-8821-6]

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