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Non-Acid GERC: Pathogenesis, Diagnosis and Management

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Abstract:- Total Recent investigations have highlighted the pivotal influence of non-acid reflux in the etiology of chronic cough associated with gastroesophageal reflux disease (GERC). Differentiation between acid and non-acid GERC is effectively achieved through esophageal pH monitoring, with non-acid reflux drawing attention for its linkage to non-standard symptoms and the intricacies involved in its management.

The combination of multi-channel intraluminal impedance with pH monitoring (MII-PH) and its related metrics, including acid exposure time (AET), symptom association probability (SAP), and symptom index (SI), as well as the quantity, pH, nature of reflux, its spread, and acid clearance time, alongside innovative measures such as mean nocturnal baseline impedance (MNBI) and post-reflux induced peristaltic wave index (PSWPI), is pivotal in precisely delineating reflux patterns and identifying the temporal connection between non-acid reflux occurrences and episodes of coughing. The prevailing reliance on proton pump inhibitors (PPIs) for treatment has encountered constraints in effectively managing non-acid GERC, underscoring the necessity for personalized treatment modalities that confront the unique pathophysiology of non-acid GERC to ameliorate patient outcomes.

As research continues to deepen our understanding and enhance treatment methods for this multifaceted condition, the pursuit of effective treatment strategies becomes crucial. Our review aims to delineate the spectrum of therapeutic options, advancements in diagnostics, and an improved grasp of the pathogenesis of non-acid GERD. The focus of this review is to further the advancement of patient care management and to inspire continued research in this intriguing domain of gastroenterology.

Keywords:- *GERC, GERD, MII-pH Monitoring, Chronic Cough, MNBI*

I. INTRODUCTION

During Chronic cough induced by gastroesophageal reflux, or GERC, stands as a distinct subgroup of gastroesophageal reflux disease (GERD) related illnesses, primarily distinguished by persistent coughing and identified as one of the principal etiology of chronic cough(1). The categorization of GERC hinges on the pH level of the refluxate, which delineates between acidic reflux (with a pH of ≤ 4.0) and non-acid reflux (with a pH exceeding 4.0). Non-acid reflux comprises two subtypes: weak acidic reflux, characterized by a pH greater than 4.0 but less than 7.0, and weak alkaline reflux, with a pH equal to or higher than 7.0.(2).

In recent years, the role of non-acid reflux in causing GERC has gained increasing recognition(3). However, the complexity of nonacid GERC, encompassing its pathophysiology, diagnostic processes, and treatment options, remains less understood than its acid reflux-induced counterpart. The proposed mechanisms behind GERC include the potential aspiration of stomach contents into the airways or esophageal-triggered bronchial reflexes through sensory nerve pathways(4). Additionally, the occurrence of nonacid GERC may be associated with intermittent relaxation of the lower esophageal sphincter and an increased esophageal sensitivity(5). Modern techniques like Multichannel Intraluminal Impedance-pH (MII-pH) monitoring have significantly advanced our capability to identify and distinguish between acid and nonacid GERC. With MII-pH metrics, such as the DeMeester score, Acid Exposure Time(AET), Symptom Association Probability(SAP), symptom index(SI), number of reflux episodes, Post-reflux Swallow-induced Peristaltic Wave Index (PSWPI), and mean nocturnal baseline impedance (MNBI), healthcare professionals can now diagnose nonacid GERC with greater precision. The combined use of the PSWPI and AET along with MNBI has been particularly noted for its diagnostic effectiveness for nonacid GERC.

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Currently, managing GERC involves dietary and lifestyle modifications, a range of pharmacological treatments, and, when necessary, surgical interventions. Proton pump inhibitors (PPIs) are the most commonly used medications for this condition(6). However, their effectiveness is primarily observed in patients with acidic reflux confirmed by MII-pH monitoring. For patients who do not respond to standard treatments, the emerging role of neuromodulators like baclofen offers new hope. These agents are showing promise in treating nonacid GERC and are increasingly becoming a focus of interest among healthcare professionals.

Although there has been progress in researching nonacid GERC, a significant gap in our detailed understanding of its pathogenesis, diagnosis, and management still exists. The absence of standardized clinical treatment protocols continues to be a major challenge, adversely affecting the patient outcomes. To tackle these existing gaps in knowledge, we offer a thorough overview of the current and emerging diagnostic tools, treatment options, and potential future developments in diagnosing and treating patients with nonacid GERC.

II. THE ASSOCIATION OF CHRONIC COUGH WITH GERD

Many A persistent chronic cough, persisting beyond three weeks in patients who have normal CXR and are not undergoing treatment with ACE inhibitors, has been the subject of extensive studies, particularly in its relationship to GERD in cough pathogenesis. This type of cough is prevalent, affecting an estimated 9% to 33% of the population in both Europe and the United States(7), imposing a considerable socioeconomic burden(8). In contrast to Western nations, historically, chronic cough among Asians was seldom linked to GERD(9). However, there has been a noticeable rise in chronic cough linked with GERD in Japan (10)and China(11), paralleling the increased prevalence of GERD in these regions When investigating the causes of chronic cough and after excluding other factors like asthma and postnasal drip, GERD should be taken into account as a potential aetiology(12). Across several studies, GER has been identified as a contributor to chronic persistent cough in about 38–82% of patients, either independently or alongside bronchial asthma and postnasal drip(13-18). Over 90% of chronic persistent cough cases are attributed to GERD, bronchial asthma, or postnasal drip, either as separate conditions or in combination. Addressing this, the American College of Chest Physicians has endorsed a consensus statement, grounded in evidence-based practices, presenting an algorithm to guide the evaluation of chronic cough in immunocompetent adults.(19). At the core of this algorithm is the guidance that clinicians should first explore postnasal drip as a potential cause when assessing patients with a chronic persistent cough and normal chest X-rays, before considering bronchial asthma and GERD. This diagnostic progression is strategically aimed at isolating the primary etiology of the cough

Coughs linked to GER can stem from diverse disease conditions, each characterized by different underlying causes. Significant aspiration, known as gross or macro aspiration, has been observed in various disorders such as recurrent aspirational pneumonia, pulmonary abscesses & fibrosis, obliterative bronchiolitis, and bronchiectasis. Furthermore, micro aspiration has been noted in individuals with conditions leading to inflammation of larynx, such as laryngitis, bronchitis, and sinusitis. Nevertheless, some patients experience a chronic persistent cough without other symptoms related to reflux.(20) and those with bronchial asthma have been documented to exhibit vagally mediated distal esophageal-tracheo-bronchial reflex mechanisms(21).

The cough associated with GERD does not have specific features or timing that set it apart from coughs due to other causes(22). It can present either as a productive cough with phlegm, akin to the type seen in chronic bronchitis, or as a dry cough. Night-time occurrences of this cough are relatively rare, affecting only a minority of patients(22). Notably, in up to 75% of cases, the cough may arise without any accompanying gastrointestinal symptoms, thus acting as a covert sign of GERD(23). Alternatively, when assessing chronic cough, it is prudent to consider GERD as a likely cause, especially in instances where patients encounter typical gastrointestinal symptoms like heartburn and regurgitation on a regular basis. This consideration is further emphasized if chest imaging or the overall clinical presentation is suggestive of a condition that mirrors aspiration syndrome(24). Coughs linked to GERD can be related to various aspiration syndromes, encompassing conditions such as Mendelson syndrome, pneumonia, and lung abscess.

Although the features and timing of a cough may not consistently signal GERD as the root cause of chronic coughing, there is a clinical profile that can predict with considerable accuracy (around 91%) whether the patient's cough will respond positively to anti-reflux therapy. This remains valid even if the patient does not display any gastrointestinal symptoms. Numerous prospective studies with pre- and post-intervention comparisons indicate a probable association between chronic cough and GERD.(14, 15, 22, 25).

III. THE OVERVIEW OF NON-ACID GERC

A. Incidence:

Recent research recognises the substantial impact of non-acid reflux on the development of persistent cough(27). studies suggests that with discontinuation of proton pump inhibitor (PPI) therapy, a significant proportion (37%) of cases with GERD and a significant majority (80%) of cases with PPI-treated chronic cough show non-acid reflux(28). Among GERC patients who discontinued acid suppression therapy, the proportion of reflux types was as follows: 65% acid, 29% weak acid, and 6% weak alkaline(29). An analysis of 50 patients undergoing PPI therapy found that 26% exhibited a positive symptom index (SI) for non-acid-related chronic cough. The higher frequency of non-acid-related persistent cough after PPI treatment may be attributed to the

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inhibitory effect of PPIs and the elevated pH caused by the initial acid reflux. The absence of accurate diagnostic methods may greatly underestimate the actual occurrence of non-acid GERC.

B. Clinical Presentation:

The females are more commonly affected than males by either types (acid & non-acid) of GERC(30). Majority of the patient with non-acid GERC presents chronic day time dry cough while some of them present with associated postnasal drip and throat clearing(27, 30). However, the typical symptoms of acid reflux are less commonly presented in the case of non-acid GERC because of the chemical composition of refluxate which is less likely to cause esophageal injury(31). The difference between the symptomatic presentation among acidic and non-acidic GERC is due to different mechanism of occurrence. Where non-acid GERC is occurs due to stimulation of esophageal mechanical receptor, the acid GERC occurs due to stimulation of esophageal chemoreceptors(31). However , in the less than 60% of the cases both types present with typical GERD symptoms which makes it difficult to differentiate non-acid GERC from acid GERC.

C. Pathophysiology:

There are two major pathophysiological mechanism that contribute to explain the development of GERC(4). The first one is the reflex theory which encompasses acid and non-acid reflex. This theory presents a more accurate explanation for the majority of non-acid GERC instances and potentially underlines fundamental mechanism behind GERC because high reflux is less likely to occur in non-acid GERC. The second theory to explain the pathophysiology of GERC is the reflux theory which encompasses acid reflux, micro aspiration and airway reflux.

➢ *Reflex Theory:*

The reflex theory posits that GERC is associated with a heightened cough reflex and the emergence of neurogenic inflammation in the airways. This theory suggests that when reflux material stimulates the mucosal receptors beneath the esophagus, it activates a pathway to the cough center, triggering a bronchial cough response. The mechanism involves the discharge of neuropeptides like substance P from efferent nerves, leading to neurogenic inflammation or the activation of mast cell neuropeptide receptors. Consequently, inflammatory agents such as trypsin, histamine, and prostaglandin E2 are released, which then provoke the cough receptors and lead to the typical coughing symptoms.(32). Research suggests that nonacidic esophageal reflux induces cough by activating mechanical stretch receptors linked to Aδ fibers, whereas acid reflux prompts coughing by stimulating the vagus nerve via chemoreceptor transient receptor potential vanilloid type 1 (TRPV1), thereby triggering the esophago-tracheo-bronchial reflex.(33). Researchers have noted that the majority of non-acid reflux is weakly acidic and is associated with increased levels of mast cell tryptase (MCT) and substance P (SP), which are known to heighten cough sensitivity. (33). These results are consistent with the reflex theory, underscoring the role of the weak acid-induced esophago-tracheo-bronchial reflex in the emergence of non-acid GERC. They highlight its critical influence on cough hypersensitivity and the neurogenic inflammation of the airways that characterizes chronic cough due to non-acid reflux.

➢ *Reflux Theory:*

Reflux theory is alternatively also known as proximal reflux or micro/major aspiration theory and indicates that structural and functional abnormalities in lower esophagus leads to reflux of gastric content in throat as refluxate. There are four different mechanism by which reflux occurs: transient relaxations of the lower esophageal sphincter (TLESRs), reduced pressure in the LES, LES relaxation related to swallowing, and increased tension during periods of low LES pressure. Refluxate has the potential to activate cough receptors either by directly stimulating them or by inducing mucus hypersecretion in the lower respiratory tract to activate the cough receptors through stimulation of vagal reflex(34).

The association of acid reflux to chronic cough is strongly suggested by many studies as antacid therapy significantly improved the cough related symptoms in patient with acid GERC(35, 36). However, other studies found weakly acidic reflux as contributor to GERC pathogenesis as the acid suppressive therapy did not effectively improve the symptoms in many patients(29, 37, 38). Authors noticed that considerable non-acidic reflux in the proximal esophagus and larynx among the patients who diagnosed as non-acidic GERC, where non-acidic reflux constituted 73% of the total reflux in the proximal esophagus and 11% in the larynx. In addition, the cough receptors that were previously activated by the vagal reflex are also triggered by reflux. severe gastric acid reflux causes thicker lower oesophagus, structural and functional defects, and acid reflux into upper oesophagus which explains the reflux theory mechanism of pathogenesis of non-acid GERC(34, 39).In a multicenter study on 49 patients with reflux associated chronic cough, researchers found that largers volume of refluxate and longer period of time of exposure of refluxate to esophagus play a significant role in inducing cough than the acidity of refluxate which found to be less relevant(40). This also explaines the role of reflux in pathogenesis of Non acid GERC.

Moreover, Ravelli et al. demonstrated that pulmonary aspiration pulmonary aspiration of gastric content is common in those patient with unexplained and refractory pulmonary manifestation which suggests the GER could be underlying cause(41). They also found that a normal intraesophageal PH could not rule out GER in those patients. There is also an underlying hypothesis regarding GERC's mechanism which suggests that micro aspiration resulting from proximal as well as gastric reflux directly triggers coughing by irritating the respiratory tract which have been explained by Phua et al. They stated that patients with cough along with GERD have significantly reduced laryngopharyngeal sensitivity (LPS) as compared to healthy subjects which might elevate the risk of aspiration and cause pulmonary manifestation(42). There are several other studies which explains the proximal acid reflux and aspiration of gastric content as the cause of GERC(43-

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45). Moreover, persistent cough appears to protect lung by reducing the level of pepsin in pulmonary tract(46).

IV. RESPIRATORY TRACT INFLAMMATION AND HYPERSENSITIVITY

Both reflex and reflux theories are linked to pulmonary tract inflammation and hypersensitivity, with low regurgitation and sustained proximal reflux stimulation causing neurogenic inflammation and pharyngeal inflammation, respectively. This leads to pulmonary epithelial damage, exposure of cough receptors, and increased respiratory tract sensitivity, potentially play a significant role in coughing(47, 48). In a study Peterson and colleagues observed an elevated level of SP in sptum in those patients with the dual condition of asthma and acidic GERC, as well as those with chronic cough as compared to those with non-acidic GERC(49). In an another study researchers found that Patients with nonacidic and acidic GERC shown an increased cough sensitivity and release of Substance P and MCT in their airways, suggesting similar mechanisms of pathogenesis of both type of GERC(33). Non-acid GERC is seems to be influenced by sensory nerve stimulation, mast cell activation, and respiratory tract inflammation, with different molecular mechanisms affecting different clinical circumstances.

➢ *Diagnosis:*

Diagnosing GERC is challenging as over 70% of patients do not show typical GER symptoms(26, 50). Hence, The American College of Chest Physicians recommends ruling out other possible cause of chronic cough to predict the presence of GERC(26). However, symptoms alone cannot distinguish non acid reflux from acidic reflux, thus diagnostic testing require for proper diagnosis of the condition.

- *Monitoring Non-Acid Reflux:*

Traditional 24 hours pH monitoring and endoscopy fall short in identifying non-acid reflux associated chronic cough, especially in patients with normal esophageal lining epithelium. Therefore, these methods are not recommended as primary examinations for such cases. Instead, a range of alternative approaches and techniques are now employed to detect non-acid GERC which are explained below.

✓ Multichannel intraluminal impedance pH detection: MII-pH, a technique first documented by Silny in 1991, had been primarily used for monitoring the gas and liquid movements within the hollow structures. It works by measuring the electrical impedance of a catheter equipped with a ring electrode. In this method, a conductive electrode is inserted into the esophagus through the nasal passage, allowing the measurement of voltage variations between two electrodes. Latest studies have emphasized its effectiveness in detecting both acidic and non-acidic reflux, and also its advanced capability in evaluating the symptoms of gastroesophageal reflux disease (GERD)(51). It detects the characteristics of the refluxate that whether they are solid, liquid, gas or mixture. The voltage variations between electrodes also reflects the direction of movement of refluxate. For instance, when a liquid, which typically has low resistance, flows across an electrode, the impedance decreases. Additionally, during hiccups, the low ionic density of air creates a high resistance to electrical charges, resulting in a significant impedance to gas flow. A pH impedance probe use these information assess the direction of pill movement in the esophagus lumen and to document the occurrence of forward and backward motion during ingestion and regurgitation, respectively(52). The MII-pH system, when used in combination with pH monitorin g is not only useful to differentiate the type of reflux i.e. acid, weak acid & alkaline(53)but also for establishing the relationship between reflux occurrence and cough which are generally not possible with traditional monitoring method. Ambulatory pH-impedance-pressure monitoring, when combined with 24H dynamic manometry, facilitates the evaluation of the relational connection between different types of reflux(Acid & weak acid) cough. This technique has found a correlation between cough and mildly acidic reflux in patients suffering from chronic cough of unknown aetiology(54-56). There are a number of studies have shown that increasing esophageal impedance monitoring is how essential for effective and precise identification of non-acid GERC(27, 57, 58).However, the MII-pH method requires several adjustments to address the drawbacks such as limited normal reading range, low sensitivity, and false-negative results. A precise clinical symptoms diary is essential for assessing non-acid reflux but many patients fails to maintain a accurate record of their coughing episodes which leads to misdiagnosis. These factors emphasise the requirement for further research before adopting this method as standard non-acid GERC diagnostic tool.

✓ Associated metrics (MII-pH): pH and impedance monitoring are used to measure acid or non-acid exposure in the esophagus and determine the corelation between symptoms and occurrence of reflux. The two main tools for this purpose are the symptom index (SI) and symptom association probability (SAP) (59). The SI quantifies the proportion of reflux-related symptoms within the monitoring timeframe, yet it fails to account for the aggregate count of reflux incidents. Conversely, the SAP gauges the likelihood that the observed symptom-reflux correlation is not coincidental, remedying the SI's oversight by factoring in the overall quantity of reflux episodes in its assessment.

✓ Symptom associated probability (SAP): SAP is an effective method for identifying the association between cough and reflux. It involves creating a dynamic fourfold table, with each segment of 2 minutes serving as a separate calculation interval, to assess various combinations of symptoms and reflux represented by separate square. This approach accounts for both the frequency of reflux and cough symptoms, overcoming the limitations seen with other methods like the SI and Symptom Sensitivity Index (SSI). The SI and SSI are either focused on specific symptoms or constrained by the count of reflux episodes. This comprehensive approach of SAP makes it a frequent choice for diagnosis of non-acid reflux related chronic cough. SAP scores, calculated using pH measurements, can assess both acidic and nonacidic

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reflux. A score above 95% is typically considered positive, indicating a significant non-random correlation between reflux events and symptoms like cough(27). Nevertheless, the Patients suspected of suffering non-acid GERC often inaccurately record coughs & time during MII-pH monitoring, making it challenging to achieve a diagnostic SAP score over 95%. While combining a dynamic esophageal manometry with daily cough monitoring could improve accuracy(27, 60), this method is not widely yet used in China. Thus, current guidelines suggest considering an SAP score of 75% or higher as positive. To validate the effectiveness of such guideline, Xu et al. examined MII data from 103 patients suspected of having GERC, which revealed that an SAP of 80% or higher offers a better diagnostic precision for both acidic and non-acidic GERC(61). Non-acid GERC has slower nerve velocity and symptom onset compared to acid GERC. In a study authors observed that heartburn, cough and acid reflux after 2 min post reflux were 80%, 81%, 92% respectively in the patients with acid reflux while 54%, 56%, 79% respectively in those with non-acid reflux(31). Notably SAP calculation, which considers symptoms within a 2-minute window post-reflux, may not be suitable for non-acid GERC patients, suggesting the need to reassess the suitability of this time frame for calculating SAP in non-acid GERC cases.

- ✓ Symptom index (SI): The SI calculates the proportion of total coughs occurring within a certain timeframe after reflux. This period was initially set at 5 minutes but has recently been adjusted to 2 minutes. An SI value exceeding 50% is regarded as positive. In a study authors found that 13 out of 50 cases with non-acid related cough had positive SI(31). The SI has a key limitation: it heavily focuses on cough symptoms while ignoring the overall count of reflux events. This can result in misleadingly negative SI readings for patients with regularly frequent reflux but minimal cough symptoms during monitoring, potentially causing misdiagnoses. Moreover, Yang et al. suggested a diagnostic SI value of ≥45% for acid GERC & ≥30% for non-acid after evaluating 118 suspected case of GERC(62).
- ✓ Symptom sensitive index (SSI): The SSI measures the proportion of reflux incidents accompanied by cough. A SSI value of 10% or higher deemed positive. However, this method heavily relies on the count of reflux episodes, making it less suitable for diagnosing non-acid GERC.

- *Other Impedance Metrics:*

- ✓ DeMeester score & Acid Exposure Time: The DeMeester score (DMS) is a comprehensive metric used to assess acid exposure during extended pH monitoring, incorporating elements like acid exposure time (AET). AET, represents the total proportion of monitoring duration when esophageal pH remains <4. A suspicion of GERC arises with an AET of 4.8%, and acid GERC is considered likely when AET hits 6.2%(62, 63). Values that reside within these two limits are deemed as indeterminate. The DMS, initially a prevalent tool combining six different parameters to assess acid reflux, was widely used for identifying possible pathological exposure of the esophagus to acid and predicting the efficacy of PPI therapy. Nowadays, the preference has shifted towards using AET as a more reliable metric, owing to concerns about the DeMeester score's inconsistency in repeat assessments(64-66)
- ✓ Mucosal impedance: In severe reflux disease cases, dynamic impedance measurements can be unreliable because low baseline values that complicate interpretation. This indicates that GERD might cause long-term changes in the esophagus, difficult to track with standard impedance methods. To overcome this, the Mucosal Impedance (MI) technique was introduced. It utilizes a probe inserted through the working channel of an endoscope to directly assess the mucosal impedance(67).
- ✓ Baseline impedance is an accurate technique for detecting GERD and distinguishing its different types. Research by Naik et al. in 2019 demonstrated that baseline impedance had a positive predictive value (PPV) of 96% and a specificity of 95%.(68). However Further research is required to explore the role of Mucosal Impedance in GERC.
- ✓ Salivary pepsin: Pepsin, a key component of nonacidic gastric juice, is considered to be more damaging to the tissues of the upper respiratory tract than acid. In a comprehensive meta-analysis of research using immunoassay to detect pepsin in saliva and sputum, Samuels et al. concluded that pepsin testing offers a highly precise and noninvasive method for diagnosing GERD.(69). This method also proves effective for quick screening of the disorder.
- ✓ Bile reflux: Non-acid reflux includes components like recently consumed food and gas, nonacidic gastric and pancreatic secretions, with bile being a primary constituent. A study by Tack et al. revealed that in a group of 65 patients who were still experiencing GERC symptoms even after regular PPI therapy, 38% exhibited bile acid in their esophagus(70). This suggests a notable involvement of bile acid in nonacidic GERC cases. The 24-hour bile reflux monitoring technique is highly beneficial in evaluating GERD with precision. It records a range of data, including episodes of bile reflux, the duration of prolonged reflux events, the maximum length of a reflux episode, and the total time and proportion of reflux episodes with an absorption value equal to or exceeding 0.14. However, while this method excels in identifying and documenting bile acid, it is not capable of tracking reflux that is weakly acidic or detecting small amounts of acid in alkaline reflux.
- ✓ Post reflux swallow induced peristaltic wave: The PSPW in pH-impedance studies refers to the subsequent drop in impedance within a 30-second span after experiencing reflux. This occurrence is typically lower in GERD patients than in those without the condition. To determine the PSPW index, one must divide the total PSPW occurrences by the number of reflux episodes(71-73). The index is useful for assessing the effectiveness of the esophagus's primary peristaltic response to reflux, which is integral to its capability to perform successive contractions during rapid swallowing. Research has revealed that the PSPW index is indicative of diminished esophageal chemical clearance in GERD sufferers in

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comparison to individuals without GERD. Hence, the PSPW index has potential utility as a diagnostic indicator, especially in the absence of other impedance-pH assessment data(71, 74).

- ✓ Number of reflux event: Standard metrics for MII-PH testing, such as AET, DMS, SAP, and SI, are widely recommended for the assessment of GERC(4, 26, 75). Despite their widespread use, these metrics are not without limitations. AET and DMS, for instance, merely gauge the severity of acid reflux events. Moreover, the effectiveness of SAP and SI may be reduced due to flaws in their algorithms and the possibility of inadequate patient compliance. To address these issues in diagnosis, a new objective benchmark has been introduced for more accurate identification of GERD. Under the guidance of The Lyon GERD Consensus, exceeding 80 reflux episodes in a 24-hour span is classified as abnormal, while a count below 40 is considered to be within the physiological norm for diagnosing GERD(66).
- ✓ The technique of impedance-pH monitoring stands as a dependable approach for quantifying reflux episodes, a variable that is notably stable and not significantly altered by the use of proton pump inhibitors (PPIs)(76). This makes it a valuable adjunctive assessment, especially when findings from AET are inconclusive. Contemporary studies underscore the diagnostic importance of quantifying reflux episodes for the assessment of both acid and non-acid GERC. Specifically, diagnosing non-acid GERC is effectively accomplished by recording upwards of 58 non-acid reflux episodes, whether as a stand-alone measure or combined with additional MII-PH indices(77). Crossing the threshold of 58 non-acidic reflux episodes and a rate of non-acid reflux higher than 68.18% provides clinicians with a robust indicator for the early identification of non-acid GERC. This criterion is emerging as one of the most definitive and objective measures within MII-PH evaluation, offering significant diagnostic merit for GERC, with increasing specificity for nonacidic variants. Nevertheless, there is a need for further investigative work to validate the exactness and consistency of this measure against traditional diagnostic modalities.
- ✓ Mean nocturnal base line impedance: The Acid Exposure Time (AET) is considered a critical measure for detecting abnormal reflux, yet it's noteworthy that nearly a third of reflux esophagitis patients may present with AET within normal limits(78). To overcome the limitations of AET, additional parameters such as Mean Nocturnal Baseline Impedance (MNBI) have been developed. These parameters are instrumental in examining chemical clearance processes and determining the health and function of the esophageal lining. They not only improve the accuracy of impedance-pH testing in distinguishing acid from non-acid GERC but also have the potential to identify those with non-acid GERC who could benefit from established anti-reflux therapies(71). In MII-pH monitoring, there are six impedance channels (Z1–Z6) strategically placed at intervals of 17, 15, 9, 7, 5, and 3cm above the LES. The established protocol for measuring MNBI in this procedure calculates the baseline impedance (BI) specifically at the channel situated 3cm above the LES, a method first proposed by Martinucci et al. To ensure precision, three 10-minute stable time frames around 1 a.m., 2 a.m., and 3 a.m. are chosen for measurement(79). During these periods, the patient is in a supine position, ideally without any swallowing, reflux events, artifacts, or significant pH changes. The average BI for each of these intervals is computed using specialized software. The average of these BI values then provides the MNBI, effectively reflecting the BI over a six-hour night-time duration. This methodology has gained widespread acceptance in many studies. However, variations exist in some research, such as using the impedance channel at 5cm above the LES or calculating an average MNBI value from the distal four channels (Z3–Z6) (80-83).
- ✓ Baseline impedance measurements serve as indicators of the esophageal mucosa's permeability, a phenomenon documented in animal studies and among healthy human subjects. Notably, lower impedance values have been observed in cases of both erosive and non-erosive GERD(84, 85). Decreased baseline esophageal mucosal impedance is linked to alterations in the intercellular spaces and tight junctions, and these changes are often associated with the manifestation of reflux symptoms(86-88).
- ✓ MNBI serves as an impedance-based diagnostic tool that records readings during sleep, thus avoiding the daytime interference of swallowing 108. Studies have demonstrated that low MNBI readings can effectively distinguish between several gastrointestinal conditions, such as different forms of esophagitis, cough-associated symptoms, non-erosive reflux disease (NERD), as well as discerning functional heartburn from GERD/NERD in comparison with healthy subjects(71-73). A reduced MNBI suggests a deterioration in the esophageal mucosal barrier and has proven to improve the diagnostic accuracy of impedance-pH tests for patients with uncertain GERD diagnoses. Furthermore, MNBI is valuable alongside Acid Exposure Time (AET) to monitor a patient's reaction to treatments for reflux(74).

➢ *Monitoring cough:*

Monitoring cough patterns plays a crucial role in diagnosing GERC since the assessment of SAP and SI relies on the documentation of cough incidents by the patient, typically noted in a diary or similar record-keeping tool. Such records are vital for identifying the correlation between reflux events and coughing, aiding in the effective diagnosis and management of GERC.

- ✓ Diary cough occurrence recording: A cough diary is a personal record in which individuals track occurrences of their coughs within a set timeframe, often over a 24-hour cycle. The data noted is based on personal observation, which can result in missing or incorrectly logged details. As a result, SAP determined from these diaries may not be entirely precise. Studies suggest that the frequency of coughs recorded by patients typically represents just 40% of the true number of episodes. Furthermore, recorded instances of coughing are typically noted to have an estimated duration of about 30 seconds. Additionally, the

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presence of a chronic cough might itself trigger GER, adding complexity to establishing a clear causal relationship between the two conditions. In a study by Wunderlich and Murray, it was found that only about one-third of cough episodes had a positive association with GER as determined by the symptom association probability metric(89). Despite these limitations, clinicians are still advised to recommend the keeping of a cough diary record for patients.

- ✓ 24H cough monitoring: Twenty-four-hour cough monitoring provides a more accurate assessment of cough severity compared to individual cough scores or quality of life evaluations. Currently, devices developed for cough monitoring, which continue to be refined, fall into two categories: single-element and multi-element. Devices with single-element design predominantly employ voice detection technology. (90-92). Conversely, multi-element devices not only record audio but also incorporate additional metrics like respiratory inductive plethysmography. (93). Currently, the application of cough monitoring in clinical setting within China is not yet a standard practice.

➢ *Diagnostic Standard:*

The updated 2021 Chinese cough guidelines set forth the diagnostic criteria for coughs linked to GERD (94). This encompasses: (I) a chronic cough that may present with or without classic reflux symptoms like heartburn and regurgitation; (II) the detection of abnormal acid or non-acid reflux through esophageal monitoring, indicated by an AET exceeding 6% or a SAP of 95% or higher; and (III) a significant reduction or complete resolution of cough symptoms following anti-reflux therapy. Yet, the application of these diagnostic criteria is confined to a select number of specialized cough research centers in China. This restriction stems mainly from the resource-intensive nature of esophageal impedance-pH monitoring, an essential element of the diagnostic procedure, which is costly and requires significant time to perform. At our cough clinic, we undertake esophageal impedance-pH monitoring for about 70% of patients presumed to have GERD-related cough to substantiate their diagnosis.(11, 95).

Table 1: Diagnostic Standard of Non-Acid GERC

Diagnostic Criteria for Nonacid GERC	Description
Cough characteristics	Persistent chronic cough lasting for 8 weeks or longer, with possible accompanying symptoms such as acid reflux, heartburn, chest pain, etc.
MII-pH Monitoring	Abnormal nonacid reflux is determined by MII-pH monitoring when the DMS is below 14.72, the SAP for nonacid reflux is 95% or higher, the AET is 6% or less, and the total number of reflux episodes surpasses 58..
Response to Treatment	A complete resolution or substantial improvement in cough (indicated by a decrease in cough symptom score by more than 50%) following a structured anti-reflux therapy regimen.
Exclusion of Other Causes	Confirmation that other potential causes of chronic cough have been investigated and ruled out.

➢ *Management:*

- *Acid Suppression and Alginates Therapy:*

PPI are effective in reducing non-acid reflux and related damage, promoting mucosal healing, and lowering airway sensitivity (30). However, the medical consensus generally does not recommend PPIs as a primary treatment for non-acid GERC. Tutuian et al. conducted a study and found 26% of patients on PPI experienced non-acid GERC, a lower percentage than those without PPI(96). Studies in our department revealed that PPI in combination with prokinetics can achieve a satisfactory therapeutic goal in patients with non-acid GERC (30). Additionally, augmentation of acid suppression therapy might be effective in increasing the pH during reflux incidents, consequently decreasing the occurrence of acid reflux events. In a study with a small cohort of 12 patients suffering from nonacidic reflux, an improvement in symptoms was observed in half of the patients following a doubling of their proton pump inhibitor (PPI) dosage(97).

Alongside the option of increasing the dosage of PPI, treatments based on alginate serve as another method for controlling acid. Alginate compounds come with a range of potential benefits. They can thicken the stomach's fluid content, which may help prevent reflux. Additionally, they have the ability to neutralize substances that aren't acidic, such as pepsin and bile salts, and they can create a barrier above the layer of stomach acid(98, 99). In a study of 25 patients with non-acid reflux who were not responding to PPI alone, it was found that the addition of alginate to their treatment led to a median improvement of 75% in their symptoms. The overall efficacy of this combined treatment approach was 92%, underscoring the effectiveness of using both PPI and alginate in managing non-acid reflux(99). Nonetheless, in contrast to earlier reports, certain studies indicate that alginate compounds are more effective in reducing acidic reflux rather than nonacidic reflux. This was demonstrated in research involving a new alginate, which did not show a significant reduction in non-acid reflux incidents, yet proved to be effective in reducing acidic reflux episodes(100). Additionally, In a concise crossover research, the impact of a regular antacid and a combination of alginate-antacid on acid exposure after meals was compared and they found the alginate-antacid mix was more effective at reducing acid exposure following meals than the antacid alone. Despite this, the study noted no notable difference in the overall frequency of reflux incidents, which included both acid and non-acid reflux(101).

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One might contend that alginate therapy, by thickening the consistency of gastric contents, could potentially decrease the volume of reflux despite not lessening the number of reflux episodes. This hypothesis warrants further exploration for confirmation. Clinically, alginates are widely utilized, supported by patient-reported advantages and a well-documented safety profile. However, definitive proof substantiating the efficacy of alginates in managing non-acid reflux is currently insufficient.

- *Prokinetics:*

Prokinetics are drugs that augment gastrointestinal motility by increasing the affinity of M receptors to acetylcholine, resulting in enhanced gastric and esophageal motility. Additionally, they mitigate the effects of reflux material on the lower esophagus and decrease the amount and frequency of nonacidic reflux(102). In a meta-analysis of 12 RCTs involving over 2000 participants, Ren et al. investigated the supplementary effects of prokinetics on GERD patients unresponsive to PPI therapy. The analysis showed that prokinetic agents reduced the frequency of reflux events, yet the esophageal acid exposure time did not change. Patients experienced an improvement in overall quality of life; however, there was no significant enhancement in clinical symptoms or in the GERD-typical findings observed during endoscopy. As anticipated, side effects were more common among those treated with prokinetics.(103).

- *TLESR Inhibitors:*

The foremost medication being researched for its impact on the lower esophageal sphincter (LES) is baclofen, which activates gamma-aminobutyric B receptors. Its action reduces the occurrence of transient LES relaxations and strengthens its the basal tone, both key factors in the therapeutic approach to GERD(104). A meta-analysis of 9 RCTs evaluated baclofen's role as a GABAB receptor agonist in the management of GERD. The analysis determined that baclofen notably decreased AET, reduced the frequency of reflux episodes, and lowered the rate of transient LES relaxations (TLESRs), all without an uptick in adverse effects(105) . A RCT independently found that that baclofen was effective in reducing both acid as well as non-acid reflux, in addition to improving GERD-related symptoms(106). Furthermore, a crossover trial investigated the use of baclofen as a supplementary treatment to PPI in GERD patients and found a marked decrease in non-acid reflux occurrences, but no significant change was seen in acid reflux incidents, and there was no clear symptomatic improvement too, which may be attributed to the limited range of assessed symptoms(107). A new RCT has shown that baclofen, may be effective in managing rumination syndrome, presumably by affecting the LES(108). In light of this evidence, it appears reasonable to use baclofen as a treatment option for non-acid reflux. Nonetheless, additional research, particularly on its efficacy in symptom relief, is necessary.

The research on the effects of baclofen on extra-esophageal symptoms remains limited. A recent open-label study examined the efficacy of combining baclofen with PPI, finding improvements in various symptoms and cumulative reflux symptom scores over three months periods. Initially, the majority of the patients mainly had non-acidic reflux, but the study didn't conduct any follow-up to determine long-term results. Further investigations are required to better understand the role of baclofen in treating extra-esophageal symptoms and to verify its sustained effectiveness in alleviating symptoms(109). In a randomized trial with 234 participants, the effectiveness of baclofen and gabapentin in treating GERC, particularly those resistant to PPI and domperidone, was assessed. The study found that both medications had comparable effectiveness, with success rates of 53.0% for baclofen and 57.3% for gabapentin. The role of non-acid reflux in these outcomes is unclear, as the study did not specifically focus on this aspect. However, given the lack of response to PPIs in all patients, non-acid reflux might have been a contributing factor. Additional research is required to more precisely understand the effects of baclofen and gabapentin on GERD-related coughs and to clarify the role of non-acid reflux in these treatments(110).

In clinical practice, the prescribing of baclofen is frequently limited due to its potential side effects. Common adverse reactions includes dizziness, tiredness, headaches, and gastrointestinal issues. Informing patients about these potential side effects is a regular part of the prescribing process. Attempts to create other GABA-B agonists with fewer side effects have mostly ceased because of their insufficient effectiveness.

Buspirone, a serotonin receptor agonist specifically on the 5-HT1A receptor in the fundus and esophagus, demonstrates promise in enhancing the tone of the lower esophageal sphincter (LES) and in improving fundic accommodation, which might raise the reflex threshold(111). Notably, in a study with scleroderma patients, buspirone increased LES pressure and reduced heartburn and regurgitation symptoms(112). Similar outcomes were seen in healthy individuals(113). However, these effects were not replicated in a randomized trial involving patients with ineffective esophageal motility. Further investigations are necessary to better understand buspirone's impact and its possible role in treating esophageal disorders.

- *Surgical Therapy to Reduce Reflux Burden:*

Surgical procedures are meticulously crafted to fortify the lower esophageal sphincter for individuals grappling with GERD, with the objective of reinstating a robust barrier between the stomach and the lower esophagus, thereby reducing or eradicating reflux occurrences. Conventional surgical methods include Nissen fundoplication, a thorough wrapping technique suitable for patients with regular esophageal motility, and partial fundoplication for those with compromised esophageal motility. Another option is endoscopic radiofrequency ablation, a procedure utilizing heat generated by electrodes to alter esophageal tissues, aiming to alleviate symptoms.(114).

Numerous investigations have delved into non-acidic reflux, particularly in patients who exhibit resistance to proton pump inhibitors. In a noteworthy study, 19 individuals who remained unresponsive to PPIs underwent fundoplication. Among them, 14 exhibited a positive

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symptom index for nonacidic reflux, four for acidic reflux, and one displayed a negative SI. The researchers noted that patients with a positive SI typically displayed a favorable response to treatment, in contrast to the sole patient lacking a positive SI, who showed no improvement.(115). Another study with a smaller sample size achieved a 100% success rate in five patients with an atypical GERD symptoms and positive SI for nonacidic reflux(116). In a distinct investigation involving 33 patients experiencing persistent GERD symptoms and subjected to pH testing while on a twice-daily PPI regimen, most displayed primarily non-acid reflux. Interestingly, the extent of non-acid reflux didn't align with treatment effectiveness, despite an overall success rate of 79%. Surprisingly, the presence of a positive SAP emerged as the only predictor for favorable treatment outcomes(117). Finally, a supplementary study, currently accessible solely in abstract format, concluded that there were no significant variances in treatment outcomes among patients undergoing fundoplication for either acid or non-acid reflux. (118).

Fundoplication and similar mechanical treatments can be effective in managing both esophageal and extraesophageal symptoms associated with non-acid reflux, particularly when there's a definite connection between symptoms and reflux. Nevertheless, it's important to exercise caution when considering these interventions for patients with non-acid reflux, unless there's strong evidence suggesting a direct association between their symptoms and reflux. Additionally, the lack of extensive data on the long-term success of such surgical methods necessitates a high level of proof before recommending these irreversible procedures to patients primarily suffering from non-acid reflux.

V. CONCLUSION

The uncommon nature of nonacid reflux among patients with GERC presents challenges in both diagnosis and effective treatment, due to less developed diagnostic methods for these cases. However, the introduction of MII-pH monitoring has improved our ability to detect the specific characteristics of reflux, enhancing the detection of nonacid GERC. Moreover, the MNBI not only improve the accuracy of impedance-pH testing in distinguishing acid from non-acid GERC but also have the potential to identify those with non-acid GERC who could benefit from established anti-reflux therapies. Despite these advancements, the conventional approach of treating with PPIs has shown limited effectiveness in nonacid GERC patients. This has led to an increased interest in investigating neuromodulators as an alternative treatment option for those unresponsive to PPIs, with drugs like Gabapentin and Baclofen being considered promising options. However, the side effects linked to these medications have raised concerns among patients. Clearly, there is an urgent need for further research to develop new pharmacological treatments that not only address symptoms such as chronic cough but also reduce the adverse effects linked to the current medications.

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