

The Clinical Spectrum of Gastroesophageal Reflux Disease: Facts and Fictions

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Keywords

Nonerosive reflux disease · Reflux hypersensitivity · Functional heartburn · Rome criteria

Abstract

Background: This review addresses the intricate spectrum of gastroesophageal reflux disease (GERD), a condition affecting 10–30% of the Western population. GERD is characterized by the backflow of gastric contents into the esophagus, causing typical and atypical symptoms. Its pathophysiology involves various factors such as hiatal hernia, esophageal motor disorders, and dietary triggers. The review explores the complexities of GERD spectrum, including nonerosive reflux disease (NERD), reflux hypersensitivity (RH), and functional heartburn (FH). **Summary:** The diagnostic process for GERD, based on the Lyon Consensus 2.0 criteria, encompasses clinical evaluation, endoscopy, and functional tests, including pH-impedance and wireless-pH monitoring. NERD, a significant subset of GERD, is defined by reflux symptoms and abnormal reflux burden without mucosal damage. RH, classified under functional esophageal disorders by Rome IV criteria, presents with typical esophageal symptoms associated with reflux but lacks of structural, inflammatory, or motor causes. FH is

identified by heartburn with normal endoscopy, reflux testing, and esophageal manometry results. The management of RH and FH, focusing on reducing esophageal hypersensitivity, varies from standard GERD treatments. **Key Messages:** The review emphasizes the necessity of personalized treatment strategies due to the complexity and overlap of GERD subtypes. It highlights the importance of a multidisciplinary approach, involving gastroenterologists, psychologists, and other specialists, to improve patient outcomes and quality of life. The article underscores that understanding the distinctions and overlaps among NERD, RH, and FH is crucial for effective management, and the need for innovative approaches in diagnosis and treatment to address the unique challenges of each subtype.

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Introduction

Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder that affects a significant part of the population, ranging from 10% to 30% according to different epidemiological studies, in particular in Western countries [1, 2]. This condition is characterized by the

reflux of gastric contents into the esophagus and can lead to troublesome symptoms, and less frequently, to esophageal mucosal injury [3].

GERD manifests with a spectrum of symptoms that are categorized into two groups: typical and atypical or extraesophageal. The typical symptoms include heartburn, regurgitation, and noncardiac chest pain, while the extraesophageal manifestations consist of asthma, chronic cough, laryngitis, hoarseness, persistent sore throat, and damage to dental enamel [4]. This disorder has a significant impact on the quality of life and can lead to sleep disturbances, reduced work productivity, and overall decreased life satisfaction. Moreover, the economic burden of GERD is substantial, considering both direct medical expenditure and indirect costs related to loss of productivity [5, 6].

The pathophysiology of GERD involves a complex interplay of factors including patient's specific characteristics, such as hiatal hernia and comorbidities (i.e., obesity), esophageal motor disorders, and impaired acid clearance [7–12]. Recent advances in the understanding of GERD pathophysiology have highlighted the role of the esophageal epithelial barrier and neuro-immune modulation in symptoms onset [13–15].

The diagnosis of GERD typically involves a combination of clinical evaluation, endoscopy, and functional tests, such as pH-impedance monitoring and esophageal manometry. The use of 24-h esophageal pH-impedance monitoring is considered the current reference standard for diagnosing GERD, in particular in patients with a negative endoscopy [4]. This evaluation is crucial in quantifying esophageal acid exposure and correlating symptoms with reflux events. The impedance analysis allows the detection of both acid and nonacid reflux events, providing a more comprehensive assessment [16]. Nowadays, the Lyon Consensus 2.0 provides updated guidelines and criteria, which further refine the diagnostic process by integrating clinical, endoscopic, and functional findings to improve the accuracy of GERD diagnosis [17].

Through this diagnostic process, the phenotypic presentation of GERD varies widely, ranging from nonerosive reflux disease (NERD) to erosive esophagitis (EE). NERD is characterized by reflux symptoms without mucosal damage at endoscopy, but with a conclusive diagnosis of GERD using pH-impedance monitoring, and accounts for the majority of patients suffering from GERD symptoms [18]. The histological finding of microscopic esophagitis may aid the clinician to improve the diagnosis of NERD, and a specific score in this field has been previously proposed and validated [19]. On the other hand, EE represents the presence of visible mucosal lesions at endoscopy [20]. According to the Los Angeles classification, reflux esophagitis severity is graded from A to D, based on the extent of mucosal breaks. This assessment uses the radial pattern with longitudinal

esophageal folds as landmarks [21]. In the new update of Lyon criteria, a conclusive diagnosis of GERD can be carried out in the presence of at least Los Angeles grade B esophagitis [17, 22].

The main complications of GERD include esophageal stricture, Barrett's esophagus (BE), and esophageal adenocarcinoma. BE is characterized by the replacement of the normal squamous epithelium of the esophagus with metaplastic columnar epithelium which has the potential to induce dysplasia and neoplasia. Thus, long-term surveillance and management strategies are essential for patients with BE who need to undergo regular endoscopic surveillance and, in cases with dysplasia, ablative therapies to prevent its progression to cancer [23].

The management of GERD involves lifestyle modifications, pharmacological therapy, and in some cases, surgical intervention. Lifestyle modifications include dietary intervention and weight loss in patients with overweight, while the pharmacological treatment primarily involves acid suppression therapy using proton pump inhibitors (PPIs) [24–27]. Unfortunately, GERD therapy is still challenging as PPIs provide symptom relief in approximately 60–70% of patients because acid is not responsible for symptoms in patients with heartburn due to esophageal functional disorders [28–31]. Several alternative therapeutic approaches have been proposed for managing PPI-refractory symptoms, and among these, alginate-based formulations, pain modulators and epithelial barrier protectors have been shown to control these symptoms [24, 32, 33]. The emergence of innovative antisecretory drugs, including the extensively researched vonoprazan, offers a promising solution to unmet needs in acid suppression, due to faster onset, prolonged effect, and improved control of nocturnal acidity [34].

Surgical options, such as Nissen fundoplication, are considered for patients with refractory GERD or those with large hiatal hernias. Additionally, Toupet fundoplication, a partial 270-degree posterior wrap, is an effective alternative, particularly suited for patients with impaired esophageal motility. This latter procedure offers comparable reflux control to Nissen fundoplication, with fewer postoperative complications such as dysphagia [35–37]. Endoscopic therapies, like transoral incisionless fundoplication, have emerged as less invasive alternatives to traditional surgery, but their long-term efficacy and safety are still under evaluation [38]. More recently, two novel surgical techniques have been proposed in order to reinforce the LES and prevent reflux: the magnetic sphincter augmentation, which involves the implantation of a ring of magnetic beads around LES to reinforce it, and the RefluxStop nonactive implantable device, a device implanted at the gastroesophageal junction that supports the natural valve mechanism without the need for significant anatomical alteration or external energy

sources [39, 40]. They have the potential of providing additional benefit for the management of GERD patients use in clinical practice, but data are still limited [39, 40].

In summary, GERD is a multifaceted disease with a wide spectrum of clinical presentations and varying degrees of severity. Its management requires a personalized approach, taking into account the patient's specific symptoms, disease severity, and response to therapy. Ongoing research and emerging treatments continue to enhance our understanding and management of this common and complex disorder.

The Diagnostic Challenge of True NERD

Diagnosing NERD poses a complex challenge due to the different clinical presentations and pathophysiological alterations among patients, demanding precise discrimination of GERD phenotypes through 24-h impedance-pH testing [18]. In this setting, the adoption of Lyon Consensus 2.0 criteria allows to define a conclusive diagnosis of GERD when acid exposure time (AET) is >6% [17]. When facing inconclusive evidence for GERD (acid exposure time between 4% and 6% and/or a total number of reflux episodes during 24 h test between 40 and 80), adjunctive evidence from histology, high-resolution manometry and new impedance metrics (mean nocturnal baseline impedance = MNBI and post-reflux swallow-induced peristaltic wave = PSPW index) could support the clinician to reach a diagnosis. Indicative evidence of GERD are suggestive histopathological scoring systems, hypotensive lower esophageal sphincter, ineffective or absent esophageal motility, positive symptom index and symptom association probability, a total number of refluxes over 24 h > 80 and a low MNBI (<1,500 Ω) [17]. In particular, the value of impedance metrics in confirming the diagnosis of GERD has been confirmed by recent investigation in patient studies off- and on-therapy [41–45], as well as in those reporting atypical symptoms [46, 47].

In true NERD patients, the symptomatic response to PPIs is less pronounced compared to those with EE. For instance, treatment with omeprazole 20 mg resulted in complete symptom relief in only 46% of true NERD patients over a 4-week period, with a 66% improvement rate. This contrasts with higher relief rates in ERD patients [48]. Further studies confirmed this trend, showing slightly better but still limited response rates in NERD patients compared to those with ERD. On the other hand, surgery may be a valuable therapy in patients with NERD. A retrospective analysis found that short-term outcomes of surgery for NERD patients were similar to those with ERD challenging the assumption that NERD is a less

severe condition and suggested that surgery could be equally beneficial for both NERD and ERD patients, especially those not responding well to acid suppressive drugs like PPIs [49].

Reflux Hypersensitivity

The definition of reflux hypersensitivity (RH) changed in the last decades following the various iterations of Rome criteria. In particular, the last Rome IV criteria proposed the inclusion of RH in the group of functional esophageal disorders [50]. RH has an important impact on patients' quality of life and on the health care system. It is characterized by chronic esophageal symptoms (heartburn or chest pain) without evidence of structural, inflammatory, or motor disorders. According to the Rome IV criteria, diagnosis requires symptoms for the past 3 months with symptom onset at least 6 months before diagnosis and the response to PPI therapy does not exclude the diagnosis since the overlap with other conditions is quite common [50–53].

More than 70% of patients with GERD symptoms present a normal upper endoscopy [54] and the recent use of pH-impedance monitoring allowed to demonstrate the high prevalence of esophageal functional disorders, within this large group of patients. Savarino et al. assessed pH-impedance monitoring off PPI treatment in 329 NERD patients demonstrating that 60% of the patients had functional disorders and RH was present in 36% of them [55]. The underlying mechanisms for esophageal hypersensitivity are not well known, but RH patients have a greater sensitivity than the functional heartburn (FH) ones and present an increased number of weakly acidic reflux events and a higher rate of proximal reflux that could be the main causes of symptoms [55].

An esophageal hypersensitivity due to peripheral and/or central sensitization appears to be the main triggering mechanism for symptom generation [56]. Stress, hypervigilance, and psychological disorders play an important role in aggravating the perception of esophageal stimulation [57]. The clinical presentation of RH does not differ from that of FH, but some authors have demonstrated that RH is more associated with female gender, irritable bowel syndrome (IBS), hiatal hernia, *H. pylori* status, and anxiety using multivariate logistic regression analysis [58].

The complex route to a correct diagnosis of RH, according to the Rome IV criteria, requires an upper endoscopy with biopsies to rule out a possible eosinophilic esophagitis. If this exam is negative, esophageal manometry and pH-impedance monitoring are needed to exclude a major esophageal motor disorder and to find a positive association between symptoms and reflux events [59].

Table 1. Characteristics and treatment of gastroesophageal reflux disease, RH and FH

	<u>GERD</u>		<u>Reflux hypersensitivity</u>	<u>Functional heartburn</u>
	<u>NERD</u>	<u>ERD</u>		
<u>Endoscopic findings</u>	●	●	●	●
<u>Histological findings</u>	●	●	●	●
<u>pH-impedance monitoring</u>				
<i>Conclusive diagnosis of GERD</i>	●	●	●	●
Symptom index or symptom association probability	●	●	●	●
<u>Impedance metrics</u>				
<i>MNBI</i>	●	●	●	●
<i>PSPW</i>	●	●	●	●
<i>AET > 6%</i>	●	●	●	●
<i>AET between 4 and 6% and positivity ancillary evaluations†</i>	●	●	●	●
<i>AET between 4 and 6% and negative ancillary evaluations†</i>	●	●	●	●
<i>AET <4%</i>	●	●	●	●
<u>Therapies</u>				
<i>Proton pump inhibitors</i>	●	●	●	●
<i>Acid lowering drugs (Alginate, Mucosal protectants)</i>	●	●	●	●
<i>Surgical therapies</i>	●	●	●	●
<i>Psychological counseling</i>	●	●	●	●
<i>Neuromodulators</i>	●	●	●	●

† Findings suggestive for GERD are histopathological scoring systems, hypotensive lower esophageal sphincter ineffective or absent esophageal motility, positive symptom index and symptom association probability, a total number of refluxes over 24h > 80 and a low mean nocturnal baseline impedance (<1500 ohms)

From a therapeutic point of view, the role of diet and lifestyle modifications remains unknown [31, 56]. Histamine-2 receptor antagonists have been shown to reduce esophageal chemoreceptor sensitivity to acid and for this reason can be considered a possible therapy [60, 61]. PPI therapy is able to reduce esophageal acid exposure and seems to improve symptom perception, even though their correct dosing is not clear in RH patients [62]. Surgical therapy, in particular laparoscopic Nissen fundoplication, has proven to be a useful therapeutic approach in a proportion of these subjects [63]. Neu-

romodulators may have an important role, but the results are controversial in the few placebo-controlled trials so far published [31].

Functional Heartburn

The term FH has been introduced in medical literature at the end of the second millennium [64] in order to identify patients presenting primarily with the symptom heartburn in the setting of normal endoscopy, reflux

testing, and esophageal manometry. The advent of 24-h impedance-pH monitoring [4] has allowed us to narrowing down the number of patients with FH, by defining them as affected by FH in case of normal esophageal acid exposure and negative symptom-reflux association with acid and weakly acidic reflux [18].

The Rome IV criteria for functional esophageal disorders [65] stated that the diagnosis of FH must be made in patients with heartburn as frequent as twice a week for the past 3 months in the absence of structural, inflammatory, motility, and metabolic abnormalities. This means that the diagnostic process is quite complex and requires the use of several invasive techniques [66].

From an epidemiological point of view, FH can represent until 40% of patients with heartburn, and it can be considered as a chronic disorder with significant impact on the quality of life [67]. The mechanism sustaining the symptomatology of patients with FH is far from being understood, even though it has been demonstrated with esophageal balloon distension and electrical stimulation the existence of lower perception thresholds for pain responsible for increased esophageal pain sensitivity compared to patients with NERD [68].

The clinical presentation of FH is characterized by the presence of the symptom heartburn, whose frequency and intensity do not differ from those of the other GERD phenotypes [69], while the other typical reflux symptom, that is regurgitation, is generally lacking. Interestingly, concomitant functional disorders such as functional dyspepsia (FD) [70, 71] and IBS [58] are more frequently associated with FH than with the other phenotypes of NERD.

As to the diagnostic approach, esophageal endoscopy is negative and also the presence of microscopic esophagitis is similar to that of normal subjects and significantly lower than in NERD and RH patients [72]. Impedance-pH monitoring does not show abnormal functional parameters, including the results of the new remunerative impedance metrics (i.e., MNBI and PSPW index), which are normal and much higher than those found in patients with RH [73]. Also, the esophageal motility pattern evaluated with the modern high resolution manometry is usually reported as normal in FH [9, 74].

On the basis of the absence of any pathogenetic role of acid refluxing in excess from the stomach into the esophagus or any symptom-reflux association, FH is responsible for the majority of cases with heartburn refractory to acid-suppressant therapy, particularly PPIs [75]. On the contrary, many studies have demonstrated that patients with FH present altered psychological features, such as depression and anxiety, which are more frequent than those found in the other patients with NERD [75] and can be a relevant co-factor in increasing esophageal hypersensitivity.

Overall, the absence of both macroscopic and microscopic alterations of esophageal mucosa, the normal values of esophageal impedance-pH monitoring, and the lack of association between the appearance of the symptom heartburn and the occurrence of reflux episodes visible in impedance-pH tracings have led to consider FH as a clinical entity separated from GERD and therefore not pertaining to the realm of reflux disease [17, 55].

Finally, the treatment of FH does not require any PPI therapy or other anti-reflux modalities, as it is the most frequent underlying cause of PPI failure [76]. Instead, the use of medications aimed at reducing esophageal hypersensitivity should be more indicated in these patients [69]. However, the few placebo-controlled clinical trials available in the literature have provided conflicting results as likely consequence of our poor knowledge of the mechanisms sustaining the development of this condition [31]. Obviously, anti-reflux surgery has no role in the treatment of FH because of the lack of any evidence of abnormal reflux and the absolutely poor outcomes following this kind of therapy [77].

Overlap between GERD and Functional Symptoms

Several studies underlined the frequent overlap between GERD and gastrointestinal symptoms expression of functional disorders. Indeed, it has been observed that GERD often overlaps with FH, and this can also explain some cases of PPI refractoriness [78, 79]. Moreover, critical studies have shed light on the intricate relationship between GERD and other functional gastrointestinal disorders, such as IBS and FD [80]. This co-occurrence not only complicates the process of accurate diagnosis but also presents an important issue in developing effective treatment strategies.

Patients who exhibit symptoms of both GERD and IBS often present more severe gastroesophageal reflux symptoms and report a lower quality of life as compared to those who suffer from GERD alone [70]. This overlap suggests common pathophysiological mechanisms, possibly involving visceral hypersensitivity, altered motility, and psychosocial factors [51]. On the other hand, several epidemiological studies included patients with concomitant IBS and GERD without distinguish FH from GERD via pathophysiological investigations, introducing a potential selection bias in their conclusions [80].

A significant overlap between GERD and FD has been also reported. A systematic review published in 2011 highlighted that dyspeptic symptoms like epigastric pain and bloating were more prevalent in GERD patients [81]. Moreover, a significant finding from a large-scale survey indicated that among individuals with GERD, FD, and IBS, nearly 31% met the criteria for at least two of these conditions [82]. This intersection of GERD and FD

symptoms, often leading to diagnostic challenges, underlines the complexity of these gastrointestinal disorders and their impact on patient quality of life and disease management [83, 84].

Conclusion

In brief, GERD is a complex condition with several manifestations and significant impact on patients' quality of life. It encompasses a wide clinical spectrum from NERD to EE, each with unique diagnostic and management challenges. Recent advancements, particularly in diagnostic methods like 24-h pH-impedance monitoring and the Lyon Consensus 2.0, have improved the accuracy of GERD diagnosis and highlighted the importance of personalized treatment approaches [4, 17].

RH and FH are distinct, yet related entities. RH is characterized by esophageal symptoms without evident structural, inflammatory, or motor disorders, can overlap with GERD, and requires careful assessment to manage its impact on quality of life. Its treatment may include a range of options from lifestyle modifications to pharmacotherapy and neuromodulators [73]. FH challenges the traditional understanding of acid reflux role in symptom development and requires a peculiar approach to treatment, often focused on reducing esophageal hypersensitivity rather than traditional anti-reflux therapies (Table 1).

The complexity of these conditions and the need for tailored treatment strategies highlight the evolving understanding of esophageal disorders. A multidisci-

plinary approach involving gastroenterologists, psychologists, and other specialists is pivotal to improve patient outcomes and quality of life. This comprehensive understanding underscores the multifaceted nature of esophageal disorders and the need for personalized patient care.

Conflict of Interest Statement

E.M., A.P., F.C., M.R., A.M., and V.S. declared no conflict of interest. E.V.S. has served as speaker for Abbvie, Agave, AG-Pharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr. Falk, E.G. Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, J.B. Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, and Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, and Zeta Farmaceutici.

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Author Contributions

E.M., A.P., F.C., M.R., A.M., V.S., and E.V.S. design of the study, data collection and analysis, writing of the manuscript, and improving the final version.

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