

Phenotypes of gastroesophageal reflux disease: a vision based on its pathophysiology

Fenotipos de la enfermedad por reflujo gastroesofágico: una visión basada en su fisiopatología

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Abstract

The advancement of knowledge in pathophysiology and underlying etiologies of gastroesophageal reflux disease (GERD) has allowed the development of the concept of disease beyond the acidity of reflux. The variability in the symptom presentation and the response to treatment cannot be attributed only to reflux composition, since esophageal factors, such as structural, mechanical, biochemical, and physiological aspects, play an important role. The proposed personalized approach to GERD uses a stepwise approach that optimizes performance and phenotypic outcome while minimizing invasiveness, risk, and cost. Throughout the staggered approach to determine the GERD phenotype, clinicians may choose to stop further testing and continue treatment if available information identifies a different GERD phenotype. Since not all phenotypes GERD are the same and not all treatments are appropriate for all patients, therapeutic strategies must be personalized according to their phenotype.

Keywords: Gastroesophageal reflux disease. GERD phenotypes. GERD therapeutic strategies.

Resumen

El avance del conocimiento sobre la fisiopatología y la etiología subyacentes a la enfermedad por reflujo gastroesofágico (ERGE) ha permitido que el desarrollo de esta se extienda más allá de la acidez del reflujo. La variabilidad en la presentación de los síntomas y la respuesta al tratamiento no se puede atribuir solo a la composición del reflujo, ya que factores esofágicos, como aspectos estructurales, mecánicos, bioquímicos y fisiológicos, desempeñan un papel importante. El enfoque personalizado propuesto para la ERGE utiliza un método gradual que optimiza el rendimiento y el resultado fenotípico, y minimiza la invasividad, el riesgo y el costo. A lo largo del método escalonado para determinar el fenotipo de la ERGE, los médicos pueden optar por detener las pruebas adicionales y continuar con el tratamiento si la información disponible identifica un fenotipo de ERGE distinto. Dado que la ERGE no es la misma y no todos los tratamientos disponibles para controlarla son apropiados para todos los pacientes, las estrategias terapéuticas deben personalizarse de acuerdo con su fenotipo.

Palabras clave: Enfermedad por reflujo gastroesofágico. Fenotipos de la ERGE. Estrategias terapéuticas en la ERGE.

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Introduction

Gastroesophageal reflux disease (GERD) is defined as the presence of troublesome reflux, or erosive complications in the esophagus due to the retrograde reflux of gastric content. As more is learned on the underlying pathophysiology and etiology of GERD, the development of the disease extends beyond reflux acidity. The variability in symptom presentation and treatment response cannot be solely attributed to reflux composition, as esophageal factors such as structural, mechanical, biochemical, and physiological aspects play a significant role¹. The pathophysiology of GERD is multifactorial and complex, resulting from an imbalance between defensive factors that protect the esophagus (anti-reflux barriers, esophageal acid clearance, tissue resistance), and aggressive factors that reflux from the stomach (gastric acidity, volume, and duodenal content)². When harmful factors for the esophagus outweigh many of its protective mechanisms, such as the gastroesophageal junction barrier, acid clearance, and mucosal resistance, reflux composed of acid, pepsin, duodenal contents, and pancreatic enzymes cause direct damage to the mucosa, leading to GERD symptoms and complications. The mechanisms directly involved in GERD pathogenesis include: 1) motor abnormalities; 2) anatomical abnormalities; 3) impaired mucosal resistance³; 4) inverted gastroesophageal gradient.

The esophagus is located inside the thoracic cavity, so in normal esophageal physiology, intraesophageal pressure is equal to intrathoracic pressure and lower than intraabdominal pressure. To propel content towards the stomach (a compartment of higher pressure), the lower esophageal sphincter (LES) must maintain sustained basal contraction to counteract the gastroesophageal pressure gradient. However, when the LES fails to maintain tonicity, as in the case of a hypotonic LES, or the presence of a hiatal hernia, or under circumstances where intraabdominal pressure increases, reflux from the stomach to the esophagus can occur².

The process by which gastroesophageal reflux causes GERD involves a sequence of events that include the esophagogastric junction (EGJ) and the esophageal body, as well as mechanisms of visceral sensitivity regulation mediated by the central and peripheral nervous systems.

The primary protective factors include the LES, saliva, peristalsis, and the angle of esophageal passage through the hiatus (Hiss angle). Aggressive

factors are represented by transient lower esophageal sphincter relaxations (TLESRs), LES hypotension, gastric acidic reflux, increased LES distensibility, prolonged esophageal clearance, reduced gastric emptying velocity, and the presence of a hiatal hernia (Fig. 1)

The EGJ involves the overlap of the LES and the diaphragmatic crura formed by the diaphragmatic pillars, which represent the anti-reflux barrier and are the primary defensive factor. The LES keeps a high-pressure zone due to intrinsic muscle tone and excitatory cholinergic neuron stimulation. The diaphragmatic crura provide extrinsic compression to the LES, contributing to resting pressure (5 mmHg to 10 mmHg). The oblique entry of the esophagus into the stomach creates the Hiss angle, generating a valve effect that contributes to EGJ competence⁴.

Transient lower esophageal sphincter relaxations

TLESRs are the primary mechanism for the occurrence of gastroesophageal reflux and are twice as likely to be associated with acid reflux. Neurally mediated relaxation of the LES occurs during 3 prototypical motor events: 1) deglutitive relaxation of the LES, where pharyngeal stimulation can be the sensory trigger; 2) LES relaxation as part of secondary peristalsis, where esophageal distension provides the sensory trigger; 3) relaxations primarily triggered by gastric distension.

TLESRs differ from the other 2 forms of LES relaxation by having a sensory trigger site distal to the LES, concurrent inhibition of diaphragmatic crural activity, longer and more variable LES inhibition, and an unpredictable pattern of motor event termination in the esophagus, which can be primary peristalsis or spontaneous contractions⁵.

TLESRs are the primary mechanism for both acid and non-acid reflux, occurring in both healthy individuals and patients with GERD. Most reflux episodes occur mainly in the postprandial period (triggered by gastric distention to vent gas from the stomach) and are more frequent with delayed gastric emptying, high-fat meals, and diets rich in non-digestible carbohydrates due to colonic fermentation (glucagon-like peptide-1), in the upright position and they are rare at night⁶.

Acid pocket

Acid reflux and its associated symptoms most commonly occur after ingesting a meal that stimulates

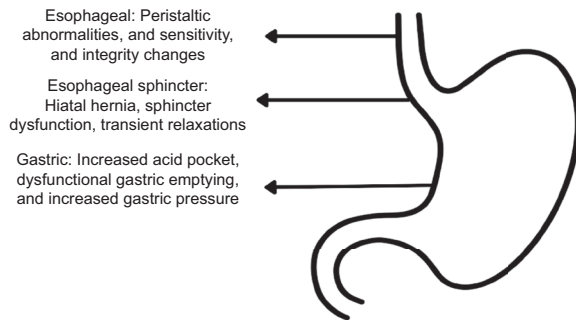


Figure 1. Main mechanisms for the development of gastroesophageal reflux disease.

acid secretion and stomach distension, reducing the density of gastric folds per surface area. Gastric folds in the proximal cardias region escape distension due to the restrictive effect of the diaphragmatic crura and the LES, preserving a high mucosal surface to luminal volume in the proximal stomach after a meal and a highly acidic luminal pH. The high acidity zone detected in the proximal stomach after a meal is referred to as the “acid pocket.” It serves to maintain an acidic barrier while eating at a time when ingestion of environmental pathogens is more likely and extends very close to or even through the EGJ after meals due to the opening of the distal segment of the LES. This short-segment reflux may be responsible for the high incidence rate of inflammation and metaplasia in the EGJ⁷. The proximal margin of the acid pocket can extend or cross the LES, and is significantly larger in patients with GERD, so its size and location correlate with the presence and size of a hiatal hernia⁶.

The position of the acid pocket is more important than its length. When it is located above the diaphragm, between 74% and 85% of all TLESRs result in acid reflux. Conversely, when it is found below the diaphragm, only between 7% and 20% of TLESRs involve acid reflux⁶.

Hiatal hernia

Hiatal hernia is defined as a cephalic migration of the EGJ, or other abdominal contents into the mediastinum through the diaphragmatic hiatus. Its clinical significance lies in its association with GERD. The natural anti-reflux mechanism is disrupted, and LES competence is affected. Between 50% and 94% of the patients with GERD are diagnosed with hiatal hernia

by endoscopy or radiology, whereas the prevalence of hiatal hernia in control subjects ranges from 13% to 59%. Although the presence of a hiatal hernia is not considered indispensable for the diagnosis of GERD, it is supportive evidence for the diagnosis according to the Lyon Consensus guidelines. Hiatal hernia is a clinically relevant diagnosis in patients with GERD-like symptoms refractory to standard medical treatment and in those suffering from GERD due to TLESRs⁸.

Patients with hiatal hernia have a high incidence of GERD. This is because the proximal stomach displaces through the diaphragm, compromising the effect of the LES by reducing its pressure and altering its responsiveness³.

The increased proximal acid pocket favors a larger reservoir of highly acidic juice available to reflux into the esophagus whenever the LES relaxes spontaneously or decreases its pressure⁷.

The process through which gastroesophageal reflux causes GERD involves a sequence of events that encompass the EGJ and the esophageal body, as well as mechanisms regulating visceral sensitivity mediated by the central and peripheral nervous systems. The perception of symptoms in GERD is related to increased esophageal sensitivity to various stimuli. This visceral hypersensitivity can be a consequence of positive regulation of peripheral afferent nerve receptors by acid-induced inflammation. Both peripheral sensitization and central sensitization play a crucial role in esophageal hypersensitivity. The hypothesis is that acid stimulation in the esophagus promotes sensitization of the cingulate and insular cortices, which are part of the limbic system that processes and modulates sensory signals from the gastrointestinal tract. As a result, there is a reduction in the pain threshold, which begins to occur with non-painful stimuli⁹.

Personalization theory in gastroesophageal reflux disease

Patients with GERD symptoms can be classified based on multiple factors, including their medical history (predominant symptom and response to proton pump inhibitors [PPIs]), endoscopic findings (gastroesophageal flap valve, hiatal hernia, esophagitis), ambulatory reflux testing (acid exposure, reflux events), and esophageal functional testing (reflux clearance). Different combinations of these factors can result in more than 50 classifications of GERD.

Table 1. Major phenotypes of gastroesophageal reflux disease: important clinical modulating factors

Symptomatology	Clinical modifiers
Non-erosive reflux disease, and/or without endoscopic evidence	– Physiological tests with results similar to low-grade esophagitis – Overlapping symptoms with reflux hypersensitivity and heartburn
– Reflux hypersensitivity	– Conceptual differentiation based on association of positive or negative symptoms in diagnostic tests
– Functional heartburn	– Similarity, almost indistinguishable in clinical practice
– Low-grade erosive esophagitis (Grade A or B)	– Low-grade erosive esophagitis (Grade A or B) is a finding in 6% of asymptomatic controls, mostly nonspecific
– High-grade erosive esophagitis (Grade C or D)	– Function of the esophagogastric junction and esophageal clearance are altered in the supine position – The presence of hiatal hernia should be ruled out
Barrett's esophagus	– Endoscopic findings ranging from intestinal metaplasia in the EGJ to short-segment or long-segment Barrett's esophagus >3 cm – Biological spectrum ranging from metaplasia without dysplasia to high/low-grade dysplasia
Reflux chest pain syndrome	– Non-cardiac chest pain with physiological signs of GERD, or typical reflux symptoms – Higher susceptibility to GERD therapy compared to other causes of chest pain
Reflux disease with dominant regurgitation	– Very incompetent EGJ with large reflux volumes – Differential diagnosis with rumination and achalasia
– Laryngopharyngeal reflux	– Significant influence by neuronal hypersensitivity
– Chronic cough	– More responsive to GERD therapy when accompanied by typical reflux symptoms

EGJ: esophagogastric junction; GERD: gastroesophageal reflux disease.

Therefore, the unique combination of factors gives rise to different GERD phenotypes. Therefore, the approach to personalize and decide GERD treatment is based on the expected outcome for the specific disease phenotype¹⁰.

Given the heterogeneity of what falls under the umbrella of GERD, it is reasonable that clinical treatment should focus on the unique pathophysiological characteristics of each syndrome. One strategy does not fit all patients, as not all benefit from potent acid inhibition, and many may be harmed by surgical intervention. From this perspective, precision medicine is being applied to GERD. Table 1 lists some of the main GERD syndromes that are commonly encountered, along with some important differentiating clinical characteristics. Their pathophysiology is focused on severe incompetence of the EGJ, manifested by a hypotensive LES, the presence of a hiatal hernia, supine reflux, and poor acid clearance (Fig. 2). The combination of reflux while lying down, poor acid clearance, and acid from the acid pocket migrating through the EGJ leads to prolonged acid exposure of the distal esophagus. This is particularly problematic during sleep when primary peristalsis decreases,

there is a lack of salivation, and relative insensitivity to esophageal acid exposure¹¹.

The association of reflux symptoms such as heartburn is higher in high-grade esophagitis compared to non-erosive reflux disease (NERD). However, some of these patients show a relative insensitivity to intraesophageal acid exposure, as 11% to 47% of the patients with erosive esophagitis do not report heartburn or regurgitation. The pathophysiology of low-grade esophagitis (Los Angeles classification A and B) involves less severe impairment of the EGJ compared to high-grade disease. The Lyon Consensus defines different GERD phenotypes that predict abnormal reflux burden based on clinical evaluation and esophageal testing (Table 2).

Heartburn and regurgitation are defined as bothersome symptoms, yet we should mention that what is bothersome to one patient may not be so for another, and none of the symptoms are specific to GERD. This is particularly true for the symptom of heartburn and subsequent analysis, as NERD has been subdivided into true NERD, reflux hypersensitivity, and functional heartburn based on the normal/abnormal dichotomous interpretation of acid exposure within the

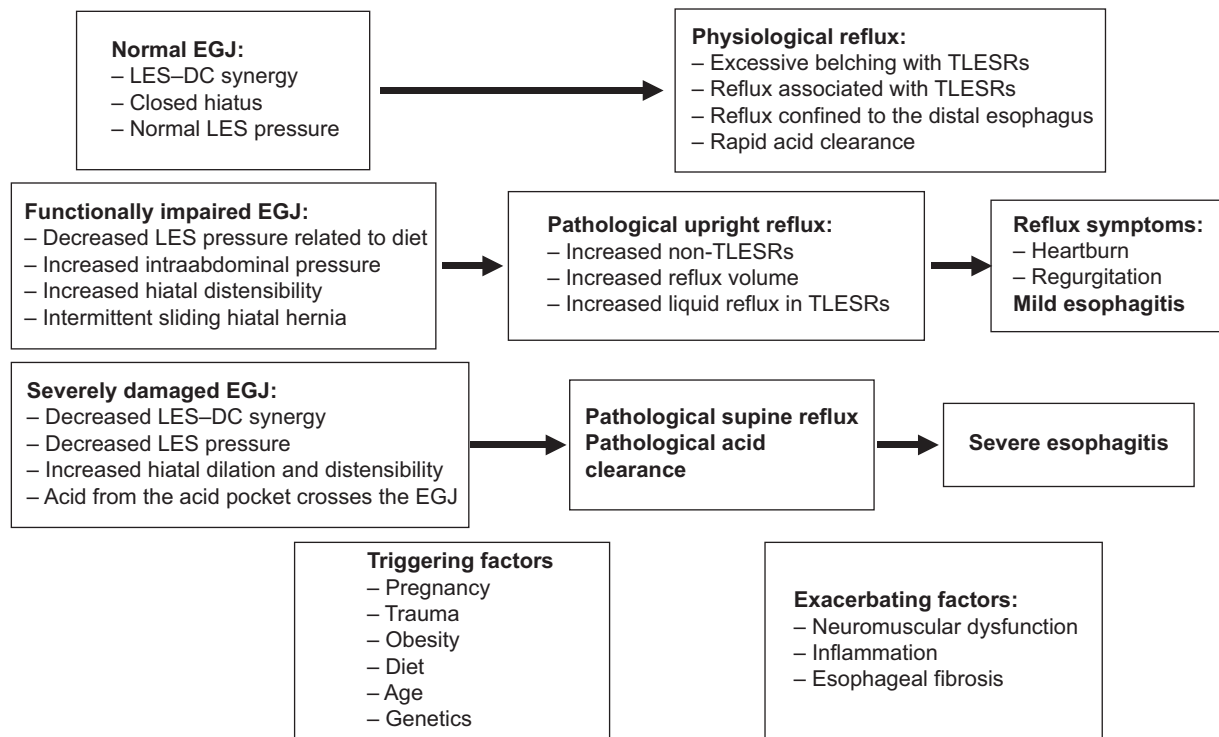


Figure 2. Gastroesophageal reflux disease and impact on the esophagogastric junction as an anti-reflux barrier. DC: diaphragmatic crura; EGJ: esophagogastric junction; LES: lower esophageal sphincter; TLESRs: transient lower esophageal sphincter relaxations.

esophagus and whether reflux symptoms correlate with pH-metry or pH-impedance studies. The physiological determinants of esophageal sensitivity have been extensively investigated, focusing on both mucosal structural integrity and neural pathways modulating pain, under the hypothesis that increased mucosal permeability facilitates the exposure of sub-epithelial sensory nerves to reflux since sensory nerves are more superficial and, therefore, more vulnerable to chemo-stimulation, especially in the proximal esophagus. Therefore, patients with NERD phenotypes develop symptoms not only from esophageal acid exposure but also from increased perception of pain through both peripheral and central mechanisms¹¹.

Dominant regurgitation

Disease with dominant regurgitation is a distinct phenotype of GERD due to its reduced response to therapy compared to disease with dominant heartburn. The mechanisms that cause it are somewhat different; specifically, severe EGJ failure with or without hiatal hernia facilitates the flow of gastric content into the esophagus in sufficient volume to be

perceived as liquid within the esophagus or regurgitation entering the hypopharynx. Problematic regurgitation (occurring 3 to 7 days a week) is common in GERD and is reported in 13% of the patients in multicenter studies, and it can disrupt sleep in up to 60% of the patients. PPI therapy is 10% to 20% less effective in relieving regurgitation compared to improving heartburn¹¹.

Extraesophageal signs of gastroesophageal reflux disease

The critical questions that should be addressed in these patients are:

- Does the patient have abnormal reflux, and how can it be detected?
- Is reflux causing the extraesophageal symptom?
- By what mechanism is this happening?

Conventional physiological tests for reflux investigate the distal esophagus, but this may be insensitive to extraesophageal syndromes due to the increased vulnerability of pharyngeal structures and the airway.

GERD comprises multiple facets of variable proportions with interactions between them and different pathophysiologies¹¹.

Table 2. Phenotypes of gastroesophageal reflux disease predicting abnormal reflux burden from clinical assessment and esophageal testing

Phenotype type	Indicator	High probability	Medium probability	Low probability	Modifying factors
Clinical	Symptomatology	Acid regurgitation, Heartburn	Chest pain	Chronic cough and laryngeal symptoms	Hypervigilance, low symptom tolerance
	Endoscopy	Severe esophagitis, Barrett's esophagus, peptic esophagitis	Mild esophagitis, normal + PPI therapy		Hiatal hernia, continuous PPI use
	Rome IV criteria	Non-erosive reflux	Symptom response to PPI therapy	Heartburn due to hypersensitivity and functional thoracic pain	Hypervigilance, low symptom tolerance
	Lyon Consensus	Definitive evidence of GERD	Borderline evidence	Reflow physiological parameters	Motor classification, new measurements
Mechanistic	Reflow pattern	Increased acid exposure and/or increased no. of events	Borderline acid exposure and/or increased no. of events	Normal measurements	pH of reflux, basal impedance, decrease in acid secretion
	Pathophysiological mechanism	Hypotense TLESRs, abnormal EGJ	Supragastric belching and rumination	Normal morphology and function	Obesity, increased circumferences, and intra-abdominal pressure
	Clearance	Lack of contractility and hiatal hernia	Minor motor disorder and/or contraction reserve	Normal peristalsis	Xerostomia, basal impedance, PSPW index, motor calcification
	Cognition/Sensations	Adequate perception of symptoms, symptom-reflux association	Increased perception	Visceral hypersensitivity and hypervigilance	Anxiety, depression, panic attack

EGJ: esophagogastric junction; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitors; PSPW: post-reflux swallow-induced peristaltic wave; TLESRs: transient lower esophageal sphincter relaxations.

Four phenotype steps in a personalized approach to gastroesophageal reflux disease

The proposed personalized approach to GERD uses a stepwise method that optimizes phenotypic performance and outcome while minimizing invasiveness, risk, and cost (Fig. 3).

Throughout the stepwise method for determining the GERD phenotype, physicians can, at any time, choose to stop further testing and proceed with treatment if the available information identifies a distinct GERD phenotype.

A thorough medical history is crucial in step 1 of GERD evaluation. The history typically focuses on symptom presentation, response to PPI treatment, and other key factors that may imply and modulate the severity of reflux, such as obesity and underlying

comorbidity (eg, scleroderma, or sleep apnea). When there is no esophagitis, therapeutic efficacy is higher for heartburn symptoms and lower for regurgitation, chest pain, and extraesophageal syndromes.

Performing an upper GI endoscopy is step 2 for patients with typical reflux symptoms without an adequate response to PPI therapy, atypical reflux symptoms, signs or warning symptoms such as dysphagia, GI bleeding, weight loss, or anemia, as it determines the presence and severity of erosive reflux disease¹⁰.

Endoscopic evaluation of the anti-reflux barrier integrity determines the likelihood of success of medical treatment as it can lead to increased reflux burden and acid exposure. The axial separation between the diaphragmatic crura and the LES results in decreased LES tone, so endoscopic evaluation of the anti-reflux barrier through hiatal hernia characterization (if present), measuring the separation between the EGJ and

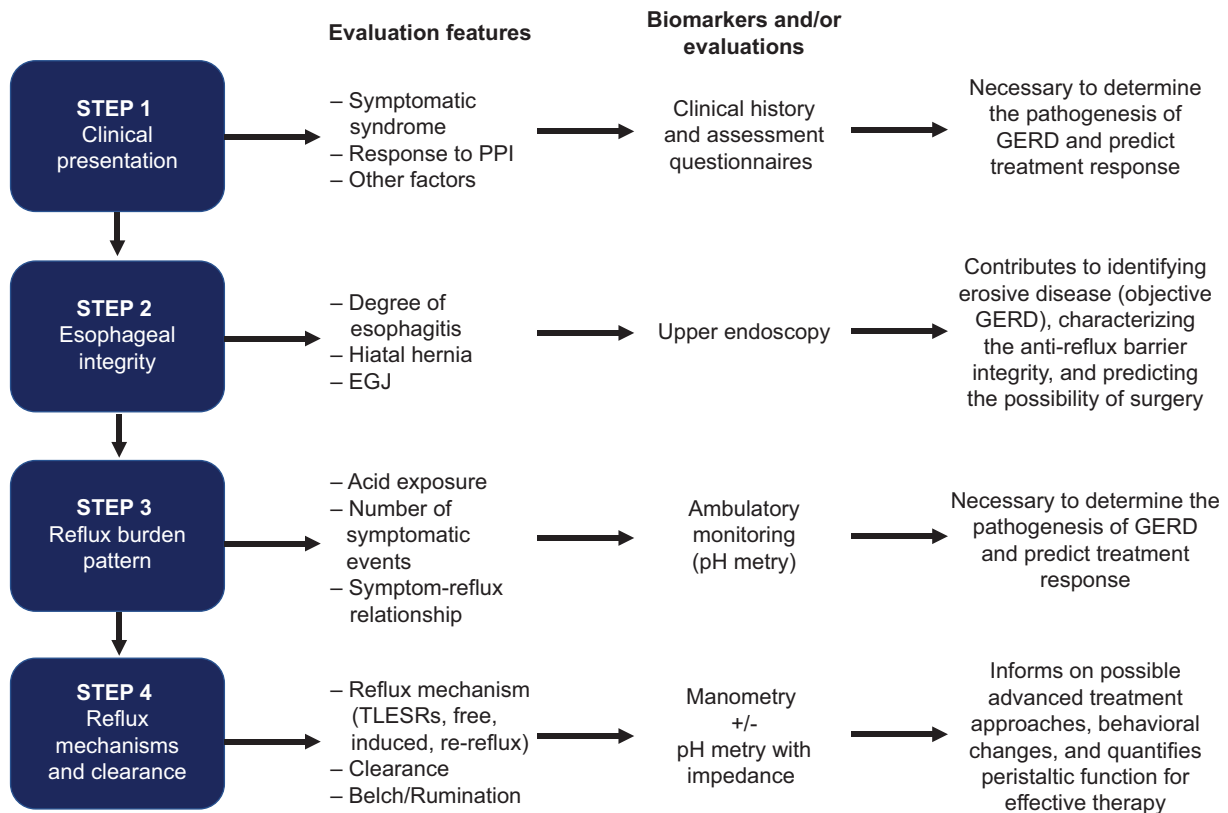


Figure 3. Steps for phenotypic diagnosis. GERD: gastroesophageal reflux disease; PPI: proton pump inhibitors.

the diaphragmatic crura, as well as the proximal spread of gastric folds and hiatal hernia classification are important steps in determining the GERD phenotype.

In the presence of NERD, step 3 is to characterize reflux burden with monitoring to assess acid exposure, reflux events, and the association between symptom perception and reflux events. When the pre-test probability of GERD is low, defined by the Lyon Consensus as the absence of erosive reflux disease, ambulatory reflux monitoring without acid suppression therapy is performed to establish the presence of GERD. Conversely, if the pre-test probability of GERD is high, defined by objective evidence of reflux from erosive disease on endoscopy or a prior positive reflux monitoring, ambulatory reflux monitoring with acid suppression therapy is performed to evaluate refractory GERD. For patients with unproven GERD, reflux monitoring can classify reflux burden as NERD with acid burden, reflux hypersensitivity, acid, or non-acid reflux regurgitation, or absence of GERD¹⁰.

Step 4 is the performance of esophageal manometry as another method to assess the anti-reflux

barrier and further characterize the mechanism of gastroesophageal reflux, as it can identify TLESRs associated with crural diaphragmatic inhibition that occur in response to gastric distension in the absence of swallowing. When the anti-reflux barrier is impaired, it can identify pathological reflux based on tension-induced reflux, free reflux, or re-reflux of the content of an irreducible hiatal hernia; it can also assess postprandial behavioral conditions such as rumination or supragastric belching. It also provides valuable evaluation of esophageal peristaltic function and clearance properties, helping to predict treatment response and the risk of post-treatment symptoms¹⁰.

To understand the syndromes and different phenotypes of GERD, it is important to consider acid reflux, weakly acid or bile reflux, visceral hypersensitivity, motor function, and the role of hiatal hernia as well as non-esophageal factors. Clearly, it is a family of syndromes with a complex matrix of contributing pathophysiology. Recognizing the modulating effects of anxiety, hypervigilance, and central and visceral hypersensitivity on the severity of

symptoms has greatly simplified the problem. Dr. Katzka and Dr. Pandolfino developed a conceptual matrix of physiology contributing to the major syndromes of GERD¹¹.

Since GERD is not the always same, and therefore, not all available treatments to control GERD are appropriate for all patients, therapeutic strategies must be personalized based on the GERD phenotype¹⁰.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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