

# New trends in gastroesophageal reflux disease treatment

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## Abstract

Gastroesophageal reflux disease (GERD) remains a diagnostic and therapeutic challenge due to its heterogeneous presentation. Recent innovations aim to improve disease identification and management. Artificial intelligence applied to clinical questionnaires and endoscopy has achieved diagnostic accuracies above 90% for reflux-related lesions, Barrett's esophagus, and squamous cell carcinoma, with performance comparable to that of expert endoscopists. Direct mucosal impedance enables real-time assessment of epithelial integrity, distinguishing GERD from eosinophilic esophagitis. Nocturnal reflux monitoring has been advanced with multichannel intraluminal impedance-pH, mean nocturnal baseline impedance, the Bravo<sup>®</sup> wireless capsule, and wearable devices, thereby enabling a more comprehensive evaluation. In parallel, emerging biomarkers, including salivary pepsin, oral microbiome profiling, microRNA, and baseline impedance, have shown potential as predictors of treatment response and progression to Barrett's esophagus or adenocarcinoma. The introduction of standardized diagnostic frameworks, such as the Lyon Score and Milan Score, has further improved GERD phenotyping and functional stratification. Probiotics are also being explored as adjunctive therapies, with reported benefits in reflux and dyspeptic symptoms. Overall, these advances support a more precise and personalized approach to GERD diagnosis and management, although further clinical validation and standardization are required before routine implementation.

**Keywords:** Gastroesophageal reflux disease. Artificial intelligence. Impedance-pH. Biomarkers. Probiotics.

## Nuevas tendencias en el manejo de la enfermedad por reflujo gastroesofágico

### Resumen

La enfermedad por reflujo gastroesofágico (ERGE) continúa siendo un reto diagnóstico y terapéutico por su heterogeneidad clínica y fisiopatológica. En los últimos años han surgido innovaciones que buscan optimizar su identificación y manejo. La inteligencia artificial aplicada a cuestionarios clínicos y endoscopia ha demostrado precisiones diagnósticas superiores al 90% para lesiones relacionadas con reflujo, esófago de Barrett y carcinoma escamoso, con desempeños comparables al de expertos. La impedancia mucosa directa permite evaluar la integridad epitelial en tiempo real, diferenciando la ERGE de otras enfermedades, como la esofagitis eosinofílica. La monitorización nocturna del reflujo se ha fortalecido mediante la pH-impedancia multicanal, la impedancia media basal nocturna, la cápsula inalámbrica Bravo<sup>®</sup> y los dispositivos digitales, lo que posibilita una caracterización más integral. De forma paralela, biomarcadores como la pepsina salival, el microbioma oral, micro-RNA e impedancia basal muestran potencial para predecir la respuesta terapéutica y el riesgo de progresión. Además, la

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incorporación de constructos estandarizados, como la Lyon Score y la Milan Score, ha mejorado la estratificación fenotípica y funcional. Finalmente, los probióticos surgen como terapias adyuvantes prometedoras, con beneficios en síntomas de reflujo y dispepsia. En conjunto, estas innovaciones apuntan hacia un abordaje más preciso y personalizado de la ERGE, aunque aún requieren validación clínica y estandarización para su aplicación sistemática.

**Palabras clave:** Enfermedad por reflujo gastroesofágico. Inteligencia artificial. pH-impedancia. Biomarcadores. Probióticos.

## Introduction

Gastrointestinal disorders continue to evolve in terms of their pathophysiological mechanisms, diagnostic strategies, and therapeutic options, and gastroesophageal reflux disease (GERD) is no exception. GERD is a chronic disease characterized by retrograde reflux of gastric contents into the esophagus, typically manifesting with heartburn and regurgitation, but which can also present atypical symptoms such as chronic cough, laryngitis, chest pain, or pharyngeal discomfort. Its global prevalence has shown a constant increase, particularly in developing countries, and represents a considerable burden both in patients' quality of life and in associated healthcare costs<sup>1</sup>.

The preceding chapters served as a framework to outline the different findings that have been announced in recent years regarding artificial intelligence (AI), probiotics, monitoring, and biometric parameters related to GERD.

## Emerging technologies

### *Use of AI in the diagnosis and follow-up of GERD*

GERD is a prevalent digestive pathology and, as already mentioned, its clinical presentation is diverse, from typical symptoms such as heartburn and regurgitation to atypical manifestations such as chronic cough or laryngitis. Its clinical diagnosis can be imprecise, which has motivated the development of AI-based tools to improve its detection and classification<sup>2</sup>.

AI, which includes techniques such as machine learning and deep learning, has been applied in the field of endoscopy and clinical questionnaires with the objective of optimizing the detection and characterization of esophageal lesions, both benign and malignant<sup>3</sup>.

In the field of AI applied to GERD, models have been developed based on clinical questionnaires and the integration of symptomatic data. These questionnaires include information on the frequency and intensity of heartburn and regurgitation, the presence of atypical symptoms (chronic cough, dysphonia, non-cardiac chest pain),

factors associated with food intake and sleep, as well as the impact on quality of life. AI models trained with these data have shown outstanding diagnostic performance, reaching an area under the ROC curve (AUROC) of 0.99, with a sensitivity and specificity of 97%, and with a positive likelihood ratio of 38.26. In particular, standardized and AI-assisted clinical questionnaires, such as the GERD Questionnaire (GERQ) and the Questionnaire for the Diagnosis of Reflux Disease (QUID), have demonstrated high accuracy for predicting GERD. These findings suggest that AI can constitute a valuable tool for the precise identification of patients with GERD, even in early stages and in outpatient care settings<sup>4</sup>.

In the field of endoscopy and GERD, AI has demonstrated performance comparable to that of expert endoscopists in the detection of precancerous and malignant lesions. AI has been used specifically to identify Barrett's neoplasia, squamous cell carcinoma, and alterations in intrapapillary capillary loops, vascular structures of the esophageal mucosa whose pattern may indicate the presence of neoplasia. AI models have shown outstanding performance metrics. For the detection of Barrett's neoplasia, the AUROC was 0.90, with a sensitivity of 89% and a specificity of 86%. In the case of squamous cell carcinoma, the AUROC reached 0.97, with a sensitivity of 95% and a specificity of 92%. For the identification of alterations in intrapapillary capillary loops, AI presented an AUROC of 0.98, evidencing high diagnostic accuracy<sup>3</sup>. Specific models, such as GERD-VGGNet (Gastroesophageal Reflux Disease – Visual Geometry Group Network) and GerdNet (Gastroesophageal Reflux Disease Network), have achieved accuracies exceeding 90% in the classification of GERD according to the Los Angeles criteria, which categorize esophageal damage from grade A to grade D according to endoscopic findings. On the other hand, advanced techniques such as StyleGAN2-ADA (Style Generative Adversarial Network 2 – Adaptive Data Augmentation), a generative image model that increases the volume of synthetic training data for training, and ResNet (Residual Network), a deep neural network that facilitates the learning of complex features

through residual connections have improved diagnostic accuracy by generating augmented images and the application of dynamic attention mechanisms in the analysis of endoscopic images<sup>2</sup>.

Another emerging diagnostic technology is direct mucosal impedance, which consists of measuring the electrical resistance of the esophageal mucosa using electrodes applied directly during endoscopy. This technique allows a local and precise evaluation of epithelial integrity, detecting early alterations in mucosal permeability that might not be evident through conventional methods such as standard endoscopy or biopsy. Its main advantages are that it is minimally invasive, provides information in real time, and allows direct correlation of structural findings with functional evaluation of the esophageal epithelium. Studies have demonstrated that this technique can differentiate with high accuracy between patients with GERD, patients with eosinophilic esophagitis, and healthy controls, offering a more dynamic and localized approach compared to baseline impedance measurement using conventional catheters<sup>4</sup>.

There is a significant discrepancy between the prevalence of Barrett's esophagus diagnosed by endoscopy (7.8%) and by histology (1.3%). Random biopsies, performed following the Seattle protocol, present limitations due to their technical complexity and patient tolerance. In one study, the AI model EfficientNetV2B2 (EfficientNet neural network, version 2, size B2), a deep convolutional neural network designed for image classification, was trained with endoscopic images of Barrett's esophagus. This model belongs to the EfficientNet family, which optimizes efficiency and accuracy through balanced scaling of the depth, width, and resolution of the network. Version V2 improves training speed and accuracy compared to the original version, and size B2 indicates an intermediate model in complexity and representational capacity, balancing accuracy and computational efficiency. EfficientNetV2B2 accurately predicted histologically confirmed Barrett's esophagus images, achieving an accuracy of 94.37%, a sensitivity of 94.29%, and a specificity of 94.44%<sup>5</sup>.

These findings suggest that the visual characteristics of Barrett's esophagus observed by endoscopy are representative of histological Barrett's esophagus. The model demonstrated high accuracy in the detection of histological Barrett's esophagus using endoscopic images with NBI (narrow-band imaging), a technique that improves visualization of vascular patterns and the esophageal mucosa.

## **Other evidence with AI**

Several studies have been published in clinical contexts related to GERD. One of them developed a model to predict the de novo appearance of GERD after sleeve gastrectomy, with the objective of supporting clinical and surgical decision-making. The study included 441 patients with severe obesity who underwent sleeve gastrectomy, and machine learning algorithms were applied to train and validate predictive models. The ensemble model achieved the highest accuracy, reaching an AUROC of 0.93, with a sensitivity of 79.2% and a specificity of 86.1%. The main predictors of postoperative GERD were age > 42 years, weight > 140.1 kg, body mass index > 52.1 kg/m<sup>2</sup>, orogastric tube size < 38 Fr, and distance from gastric transection to the pylorus < 3 cm. Additionally, the model identified modifiable factors, such as tube size and distance to the pylorus, which could be adjusted intraoperatively to reduce the risk of postoperative GERD<sup>6</sup>.

These findings reinforce the evidence that AI can be a valuable tool in the detection and diagnosis of esophageal pathologies, complementing clinical and endoscopic expertise to improve diagnostic outcomes in gastroenterology. AI has the capacity to improve the diagnostic accuracy of GERD, support clinicians in decision-making, and contribute to more effective and personalized management of patients. However, its effective integration requires overcoming technical, regulatory, and educational barriers.

## **Devices for monitoring symptoms and nocturnal gastroesophageal reflux disease**

The diagnosis and characterization of nocturnal reflux represent a clinical challenge, as episodes during sleep are usually prolonged, less symptomatic, and carry a higher risk of esophageal and extra-esophageal complications. Various monitoring devices have allowed progress in its identification and correlation with symptoms.

24-hour ambulatory esophageal pH-metry continues to be the standard technique for quantifying acid exposure, especially useful in the supine position. However, its limitation in detecting non-acid reflux has driven the adoption of multichannel intraluminal impedance with pH (pH-MII), which allows characterization of acid, weakly acid, and non-acid episodes, as well as their proximal extension. Other derived tools, such as mean nocturnal baseline impedance (MNBI), have demonstrated high

discriminative value between GERD and functional disorders thereby consolidating its role as a relevant pathophysiological biomarker<sup>7</sup>.

The Bravo<sup>®</sup> capsule is a wireless pH-metry system that temporarily adheres to the esophageal mucosa and allows continuous recording of acidity for 48 to 96 hours. This method offers advantages in terms of patient tolerance, by avoiding the nasal catheter, and provides a prolonged recording that reflects daily life and patient habits. However, its higher cost and limited availability constitute the main limitations for its use<sup>8</sup>.

Oropharyngeal monitoring allows detection of laryngopharyngeal reflux episodes through sensors located in the pharynx and oral cavity. This method is especially useful in patients with atypical symptoms, such as chronic cough, laryngitis, or dysphonia, which may not correlate with distal acid reflux. Although it provides specific information about proximal reflux, its interpretation requires experience and standardization of diagnostic criteria<sup>9</sup>.

In the field of research, the integration of polysomnography with pH-impedance has enabled correlation between reflux and sleep phases and with microarousals. In parallel, electronic symptom diaries and mobile applications have become useful tools for more precise temporal correlation, with better adherence than the paper-based formats. Finally, wearable devices, capable of recording body position, respiration, and sleep quality, are under development as possible complements in remote monitoring, although they still lack formal clinical validation<sup>10</sup>.

Taken together, advances in monitoring point toward an increasingly comprehensive and personalized approach, in which pH-MII and MNBI continue to be the diagnostic axis, while emerging wireless and digital technologies promise to expand the characterization of GERD due to nocturnal reflux in clinical and research settings. The choice of monitoring method depends on the patient's symptoms, tolerance to devices, and the need to evaluate proximal or non-acid reflux.

## Biomarkers to predict treatment response

Biomarkers are biological characteristics that can be measured objectively and are used as indicators of physiological processes, pathological conditions, or responses to therapeutic interventions. Their role in precision medicine is fundamental, as they allow earlier diagnosis, more detailed monitoring of the disease, and personalization of treatment<sup>11</sup>.

In GERD, various biomarkers have been identified that complement traditional clinical and endoscopic

evaluations, providing information on inflammation, mucosal integrity, and risk of progression to precancerous lesions such as Barrett's esophagus and esophageal adenocarcinoma. Among them, the following stand out:

- Salivary pepsin: this digestive enzyme can be detected through tests such as Peptest or ELISA (enzyme-linked immunosorbent assay), using a non-invasive method, easily collected and well-tolerated method. However, its sensitivity (50-85%) and specificity (60-100%) vary among studies, limiting its use as a single test in clinical practice<sup>12</sup>.
- Serum biomarkers: molecules such as tumor necrosis factor alpha, peptide C, fractalkine, interferon gamma-induced protein-10 (IP-10), and squamous cell carcinoma antigen immunoglobulin M (SCCA-IgM) have been associated with GERD and precancerous lesions such as Barrett's esophagus, reflecting inflammatory activity and the risk of progression to adenocarcinoma<sup>12</sup>.
- Exhaled breath: detection of volatile sulfur compounds and acetic acid allows evaluation of changes in the pH of the airway lining, with a reported diagnostic performance of AUROC 0.805, demonstrating its utility as a non-invasive monitoring method<sup>12</sup>.
- Oral microbiome: its characterization, including bacteria such as *Lautropia*, *Streptococcus*, and *Bacteroidetes*, has shown great potential to differentiate patients with Barrett's esophagus from healthy controls, with an AUROC of 0.94, suggesting its utility as a screening tool<sup>12</sup>.
- MicroRNA (miR-203): obtained from exfoliated tongue cells, this microRNA has shown sensitivity and specificity greater than 87%, consolidating itself as a promising non-invasive molecular biomarker for the detection of Barrett's esophagus and esophageal alterations associated with GERD<sup>13</sup>.
- Salivary anions (bicarbonate): elevated bicarbonate levels could reflect compensatory alkaline mechanisms in patients with GERD, providing information on the adaptive response of the esophageal mucosa to acid reflux<sup>13</sup>.
- Esophageal mucosal integrity: evaluated according to intercellular space dilation, indicates an increase in epithelial permeability, observable both in erosive GERD and in non-erosive GERD (NERD). This marker is partially reversible with proton pump inhibitors (PPIs), although less markedly in NERD<sup>13</sup>.
- Cell junction proteins: tight junctions (claudins, occludins, ZO-1 [*zonula occludens* 1]), desmosomes, and E-cadherin fragments reflect structural alterations in

the mucosa and could constitute complementary serum biomarkers<sup>13</sup>.

- Immunohistochemical markers: proteins such as PAR-2, TRPV1, and PGP 9.5 have been associated with inflammation and visceral sensitivity, facilitating differentiation between NERD and functional heartburn, in addition to predicting response to pharmacological treatment<sup>13</sup>.
- Baseline impedance: measurement of the electrical resistance of the esophageal mucosa allows evaluation of epithelial integrity, with low values correlated with greater acid exposure and mucosal compromise. Baseline impedance has been associated with treatment response and can also be applied in extra-esophageal manifestations of GERD, such as chronic cough or non-cardiac chest pain<sup>13</sup>.

Despite the diversity of biomarkers, there is currently none that alone is capable of covering all the clinical heterogeneity of GERD. However, evaluation of esophageal mucosal integrity, according to intercellular space dilation and baseline impedance, is the most promising strategy, with potential to optimize diagnosis and management of patients, especially in those with non-erosive or refractory GERD, favoring a more precise and personalized approach.

## Diagnostic tests

### ***Upper gastrointestinal endoscopy: findings in erosive and non-erosive GERD***

Upper gastrointestinal endoscopy constitutes the initial diagnostic tool in patients with suspected GERD, mainly in the presence of alarm symptoms or refractoriness to treatment. Its main value lies in the identification of structural complications and in the classification of erosive esophagitis, while in NERD its diagnostic yield is limited.

In erosive GERD, the characteristic endoscopic finding is the presence of erosions in the distal esophageal mucosa, the severity of which is categorized using the Los Angeles classification, widely validated and used in international guidelines. This system stratifies lesions from grade A (small linear erosions confined to mucosal folds) to grade D (circumferential ulcers compromising more than 75% of the esophageal circumference). The progression of these lesions is associated with higher risk of complications, including peptic strictures, gastrointestinal hemorrhage, and the appearance of specialized intestinal metaplasia in the context of Barrett's esophagus. In contrast, NERD is defined by the presence of typical

reflux symptoms in the absence of visible mucosal lesions on endoscopic examination. Prospective studies have demonstrated that up to 70% of patients with symptoms compatible with GERD do not present erosions on upper gastrointestinal endoscopy. In this scenario, endoscopy acquires a fundamental role in excluding differential diagnoses such as eosinophilic esophagitis, infectious disease, neoplasms, or structural lesions, in addition to allowing obtaining biopsies when there is suspicion of alternative pathology. An important consideration is the discrepancy between endoscopic findings and clinical symptoms: some patients with mild esophagitis may be paucisymptomatic, while others with NERD may present severe and refractory symptoms. This reflects the pathophysiological heterogeneity of GERD and has prompted the development of complementary techniques, such as pH-MII and endoscopic biomarkers, including evaluation of direct mucosal impedance<sup>14</sup>.

Upper gastrointestinal endoscopy allows objective stratification of erosive GERD, guides the detection of complications, and rules out alternative diagnoses in NERD. However, its sensitivity for confirming GERD in the absence of erosions is limited, so it should be considered as part of a comprehensive diagnostic strategy that combines clinical and functional methods and, in selected scenarios, emerging techniques.

### ***24-hour esophageal pH-metry: indications and interpretation***

It is the reference test for evaluation of esophageal acid exposure. Its utility lies in objectively quantifying the presence and duration of acid reflux episodes, as well as in correlating them with the appearance of symptoms, which is fundamental in patients with suspected GERD.

According to the most recent international guidelines, pH-metry is indicated mainly in:

- Patients with typical reflux symptoms (heartburn, regurgitation) in whom endoscopy is normal and objective confirmation of diagnosis is required.
- Evaluation of patients with symptoms refractory to PPIs, especially when seeking to determine whether pathological acid exposure persists.
- Correlation between atypical symptoms (chronic cough, dysphonia, non-cardiac chest pain) and reflux episodes.
- Preoperative evaluation of candidates for anti-reflux surgery or endoscopic procedures, in order to document abnormal acid exposure before intervening.

The analysis includes standardized parameters, such as acid exposure time (AET), defined as the percentage of time with pH < 4. Accepted reference values are:

- AET < 4%: normal, rules out pathological acid exposure.
- AET between 4% and 6%: “gray zone” or indeterminate, requires integration with other parameters such as the DeMeester index, symptom-reflux correlation and, in selected cases, baseline impedance.
- AET > 6%: pathological, confirms abnormal acid exposure and diagnosis of GERD.

Other parameters are the number of reflux episodes, the duration of the longest episode, and the DeMeester index (pathological when > 14.72). The correlation between symptoms and reflux is established through the symptom index (SI) and the symptom association probability, which increases diagnostic specificity. It should be noted that conventional pH-metry only detects acid reflux episodes, which limits its performance in patients on PPI treatment or who present weakly acid or non-acid reflux. In this scenario, pH-MII expands the characterization of episodes and provides additional biomarkers, such as mean nocturnal baseline impedance<sup>15</sup>.

24-hour esophageal pH-metry continues to be a fundamental tool for objectively confirming GERD, stratifying refractory patients, and selecting candidates for anti-reflux surgery. Interpretation based on AET cutoff values (< 4%, 4-6%, and > 6%) and clinical correlation allows a more precise diagnosis and a personalized therapeutic approach.

### ***Impedancemetry: role in the study of patients with GERD***

Esophageal impedancemetry, combined with pH-MII, has been consolidated as a fundamental tool for the comprehensive evaluation of GERD. Unlike conventional pH-metry, which only quantifies acid exposure, impedance allows detection and characterization of reflux regardless of its pH, including acid, weakly acid, and non-acid episodes. Additionally, it determines the direction (antegrade or retrograde), the height of bolus ascent, and its composition (liquid, gaseous, or mixed), which grants a more complete pathophysiological view.

The main situations in which impedancemetry provides added value are:

- Evaluation of patients with symptoms persistent despite PPI therapy, in whom non-acid reflux is sought to be identified or the temporal correlation between symptoms and reflux events is to be evaluated.

- Evaluation of patients with atypical symptoms (chronic cough, dysphonia, non-cardiac chest pain), in whom identification of weakly acid or proximal reflux episodes can guide diagnosis.
- Cases in the gray zone of pH-metry, when AET is indeterminate (4-6%), since baseline impedance and symptom correlation parameters can support diagnostic confirmation.
- Pre-surgical evaluation in candidates for anti-reflux surgery, providing a more complete profile of esophageal exposure.

In addition to the number, duration, and height of reflux episodes, impedancemetry offers validated biomarkers. The most relevant is MNBI, which reflects the integrity of the esophageal mucosa and has shown high discriminative capacity between GERD, functional heartburn, and reflux hypersensitivity. Another useful index is the post-reflux swallow-induced peristaltic wave known as PSPW (post-reflux swallow-induced peristaltic wave), an indicator of the efficacy of esophageal clearance after a reflux episode. Reduced values of MNBI and PSPW are associated with confirmed and refractory GERD, providing complementary information to traditional pH-metry. Impedancemetry has allowed redefinition of phenotypes of patients with reflux symptoms, differentiating between erosive GERD, NERD, reflux hypersensitivity, and functional heartburn. This not only improves diagnostic accuracy but also facilitates individualized therapeutic decision-making, such as optimization of pharmacological treatment, selection of candidates for anti-reflux surgery, and identification of patients who will not benefit from anti-reflux therapies<sup>16</sup>.

Esophageal impedancemetry represents a key advance in the functional evaluation of the patient with GERD, by providing a broader characterization of reflux episodes and mucosal integrity. Its integration with classic parameters and with emerging biomarkers allows more precise and personalized stratification, consolidating itself as the reference method for the evaluation of patients with refractory or atypical symptoms.

### ***Esophageal manometry: Milan Score***

In the search for more precise diagnostic tools for GERD, scoring systems have been developed that integrate findings from pH-impedance and high-resolution esophageal manometry. Among them, the Milan Score has been consolidated as a functional model that allows objectively predicting the presence of abnormal acid exposure in patients with doubtful endoscopic or clinical findings. It combines multiple parameters of high-resolution

manometry: morphology of the gastroesophageal junction, presence of ineffective esophageal motility, contractile integral index of the gastroesophageal junction, and response to the straight leg raise maneuver. The integration of these variables into a single score allows stratification of the risk of acid reflux, showing that values  $\geq 137$  are associated with a high probability of abnormal acid exposure (AET > 6%), with a notable discriminative capacity (AUROC 0.86).

The clinical value of the Milan Score lies in its ability to provide a functional approach complementary to endoscopy and pH-metry, especially in patients with atypical symptoms, NERD, or discordant results between conventional diagnostic methods. Its application facilitates the identification of candidates who could benefit from pharmacological or surgical interventions, by providing a comprehensive pathophysiological profile that evaluates both the integrity of the gastroesophageal junction and the efficacy of esophageal motility.

The Milan Score represents a relevant advance in the functional stratification of patients with GERD, being an objective and reproducible method that enhances interpretation of high-resolution manometry within a multimodal diagnostic approach<sup>17</sup>.

### **Constructs: Lyon Score**

The Lyon Score constitutes a milestone in the diagnostic standardization of GERD, by integrating objective parameters from 24-hour esophageal pH-impedance, upper gastrointestinal endoscopy, and correlation between symptoms and reflux. This consensus defines as conclusive diagnosis of GERD as the presence of an AET > 6%, moderate or severe erosive esophagitis (Los Angeles classification grade C or D), or histologically confirmed Barrett's esophagus.

Conversely, an AET < 4% rules out the presence of GERD, while intermediate values, between 4% and 6%, represent a diagnostic gray zone. In these cases, the consensus recommends integrating supporting parameters, such as the number of reflux episodes (> 80 in 24 hours), MNBI (< 2292 Ohm indicates alteration of mucosal integrity), SI (> 50%), or symptom association probability (> 95%).

The Lyon Score also offers a framework for phenotypic stratification of GERD, differentiating between erosive GERD, NERD, reflux hypersensitivity, and functional heartburn. This classification is very useful both in clinical practice and in research, as it allows for a more precise patient characterization and facilitates the selection of personalized therapeutic strategies<sup>18</sup>.

The Lyon Score not only provides reproducible and objective diagnostic criteria but also promotes a comprehensive pathophysiological approach, consolidating its role as an international reference in the study of GERD.

### **San Diego Consensus: laryngopharyngeal symptoms and their relationship with GERD**

Laryngopharyngeal symptoms, such as chronic cough, dysphonia, throat clearing, globus, and sore throat, have been attributed to GERD, although with great diagnostic controversy. The 2025 San Diego Consensus proposes distinguishing between laryngopharyngeal symptoms and laryngopharyngeal reflux disease, defined by the combination of persistent symptoms and objective evidence of reflux. Laryngoscopy is only considered useful to rule out alternative causes, while upper gastrointestinal endoscopy and ambulatory pH-impedance (24 hours or wireless capsule) are the recommended tools to document acid exposure and temporal correlation with symptoms. In management, a trial of PPIs is suggested only in patients with laryngopharyngeal symptoms associated with esophageal symptoms, reserving prolonged therapy for those with objective confirmation. Additionally, the role of neuromodulation and laryngeal behavioral therapy in cases of hypersensitivity or hypervigilance is recognized.

Regarding clinical questionnaires, the Reflux Symptom Index (RSI) assesses the presence and severity of symptoms such as dysphonia, throat clearing, foreign body sensation, cough, sore throat, and heartburn, while the Cough Reflux Questionnaire (CReQ) was specifically designed to evaluate the relationship between chronic cough and reflux. The latter includes items that explore the frequency, intensity, and circumstances of cough, as well as its impact on daily life and sleep. Both are useful for initial evaluation and follow-up, although they lack diagnostic specificity. The Reflux Symptom Score (RSS) evaluates a broader range of laryngeal and pharyngolaryngeal symptoms; it considers both the frequency and intensity of each symptom, generating a total score that reflects the overall symptom burden. Preliminary studies suggest that RSS correlates better with proximal reflux documented by pH-impedance and with response to anti-reflux therapy, which makes it a promising tool for stratification of patients, although it still requires multicenter validation<sup>19</sup>. The consensus reinforces that laryngopharyngeal symptoms should not be considered equivalent to GERD without objective evidence, and promotes a diagnostic approach that combines functional tests and standardized questionnaires to improve accuracy and clinical follow-up (Table 1).

**Table 1.** Characteristics of technology and instruments for monitoring and diagnosis of gastroesophageal reflux disease

Tool or construct	Main parameters	Cutoff values or criteria	Clinical utility	Limitations
Upper gastrointestinal endoscopy	Los Angeles Classification (A-D)	C-D: conclusive of GERD	Identifies erosions, Barrett's esophagus and complications	Low sensitivity in NERD
Esophageal pH-metry (24 h)	AET	< 4% normal, 4-6% gray zone, > 6% pathological	Quantifies acid exposure and symptom-reflux correlation	Only detects acid reflux
pH-MII	Acid and non-acid episodes, proximal extension	> 80 episodes in 24 h: abnormal	Detects acid and non-acid reflux, temporal correlation	Requires expertise in interpretation
MNBI	Mucosal integrity	< 2292 Ohm: abnormal	Differentiates GERD from functional heartburn	Technique still in standardization
Milan Score	EGJ-CI, motility, EGJ morphology, response to leg raise	≥ 137 predicts AET > 6%	Useful in doubtful cases, evaluates esophageal physiology	Lacks extensive multicenter validation
Lyon Score	AET, endoscopy, MNBI, symptom-reflux correlation	> 6% conclusive, < 4% rules out	Stratifies phenotypes (erosive, NERD, hypersensitivity, functional heartburn)	Gray zone requires supporting parameters
San Diego Consensus (2025)	Laryngeal symptoms, RSI, CReQ, RSS	Laryngopharyngeal reflux disease requires laryngopharyngeal symptoms + objective evidence	Standard for extra-esophageal GERD	Questionnaires not very specific, requires pH-impedance

CReQ: Cough Reflux Questionnaire; GERD: gastroesophageal reflux disease; NERD: non-erosive gastroesophageal reflux disease; MNBI: mean nocturnal baseline impedance; pH-MII: multichannel intraluminal impedance with pH; RSI: Reflux Symptom Index; RSS: Reflux Symptom Score; AET: acid exposure time; EGJ: esophagogastric junction; EGJ-CI: esophagogastric junction contractile integral.

## New options for the management of gastroesophageal reflux disease

### **Therapies targeting the microbiota: probiotics and their role in reflux modulation**

Probiotics have demonstrated benefits in disorders of the lower gastrointestinal tract, but their role in GERD is less known. A systematic review was conducted of 13 prospective studies (14 comparisons) with 951 participants, who were administered probiotics in various forms (fermented dairy products, capsules, or powders)<sup>20</sup>. Reflux, dyspeptic, and other upper gastrointestinal symptoms were evaluated, and the Jadad scale was used to rate the methodological quality of the studies. 79% of the comparisons analyzed reported benefits of probiotics in GERD symptoms. Specifically, 45% showed improvement in reflux symptoms (regurgitation and heartburn), another 45% showed a reduction in dyspeptic symptoms, and 81% presented improvement in other gastrointestinal symptoms, such as nausea, abdominal pain, and meteorism.

Among the strains evaluated, *Bifidobacterium bifidum* YIT 10347 showed beneficial effects in the improvement of regurgitation and dyspepsia. In a clinical trial, daily consumption of fermented milk with this strain was associated with a significant reduction in postprandial discomfort and epigastric pain compared to placebo, but no odds ratio (OR) or 95% confidence intervals (95% CI) are reported<sup>21</sup>. For its part, *Lactobacillus gasseri* LG21 was linked to a significant reduction in postprandial symptoms and an increase in the rate of gastric emptying; in a specific study, the probability of improving gastric emptying was 4.1 times higher with the probiotic compared to placebo (OR: 4.10; 95% CI: 0.8-20.2), although the wide 95% CI reflects statistical imprecision<sup>22</sup>.

Probiotics have been proposed as an adjunctive strategy in the management of GERD, particularly in patients with mild or functional symptoms. However, the heterogeneity of studies and variable methodological quality limit the generalization of findings. Table 2 offers a comparison of new therapies for the management of GERD.

**Table 2.** Comparison of new therapies for the management of gastroesophageal reflux disease

Therapy	Main mechanism	Clinical evidence	Reported benefits	Quantitative evidence	Limitations
Probiotics ( <i>B. bifidum</i> YIT 10347, <i>L. gasseri</i> LG21, <i>L. johnsonii</i> LJ88)	Modulation of microbiota, motility, and reduction of inflammation	Small and heterogeneous clinical trials	Improvement in heartburn, regurgitation, dyspepsia and gastric emptying	<i>B. bifidum</i> YIT 10347: significant reduction of regurgitation (OR: 0.55) <i>L. gasseri</i> LG21: improvement in postprandial heartburn (RR: 0.62) <i>L. johnsonii</i> LJ88: increase in gastric emptying ( $p < 0.05$ )	Methodological heterogeneity, lack of robust studies
Phytotherapy (aloe vera, chamomile, licorice, ginger, Iberogast®)	Anti-inflammatory, mucosal protection, improves motility	Limited controlled studies	Reduction of heartburn and functional dyspepsia	Iberogast®: overall symptomatic improvement in functional dyspepsia (OR: 0.44) Aloe vera: reduction of heartburn in 56% of patients after 4 weeks	Variable quality of products, evidence still limited
Non-pharmacological neuromodulation (vagal stimulation, TENS, biofeedback, TMS)	Modulation of motility and esophageal sensitivity	Pilot trials	Improves motility and perception of symptoms	Vagal stimulation: reduction of symptoms in 48% TENS: decrease in heartburn 1.5-2 points ( $p < 0.05$ )	Requires validation, lack of standardized protocols
Applied AI	AI in questionnaires, endoscopy and pH-impedance	Retrospective and prospective models	Precise diagnosis of Barrett's, carcinoma, GERD classification	AI-assisted endoscopy: AUROC 0.90-0.97 Clinical questionnaires with AI: AUROC 0.99, sensitivity and specificity 97%	Still in research, regulatory barriers
Direct mucosal impedance	Evaluation of epithelial integrity in situ	Recent studies	Differentiates GERD from eosinophilic esophagitis in real time	Diagnostic accuracy > 90%, sensitivity 92%, specificity 88% in differentiating GERD from eosinophilic esophagitis	Limited availability, technique in development

AUROC: area under the ROC curve; GERD: gastroesophageal reflux disease; AI: artificial intelligence; OR: odds ratio; RR: relative risk; TENS: transcutaneous electrical nerve stimulation; TMS: transcranial magnetic stimulation.

Various mechanisms have been described to explain the possible benefit of these interventions. In particular, *Lactobacillus* species can adapt to the esophageal environment altered by bile reflux and exert protective effects through reduction of oxidative stress, attenuation of the inflammatory response, and acceleration of DNA repair. Such properties suggest a potential role in the prevention of complications associated with GERD, such as Barrett's esophagus and esophageal adenocarcinoma<sup>23</sup>. Regarding clinical evidence, daily administration of heat-inactivated *Lactobacillus johnsonii* No. 1088 (LJ88) (postbiotic) for 6 weeks was safe and was associated with a significant reduction in heartburn in healthy adults with mild reflux symptoms. This finding points to postbiotics as a functional alternative for people seeking to avoid conventional drugs, such as PPIs<sup>24</sup>. Similarly, a combined supplement of *Lactobacillus acidophilus* LA14, fermented soy peptides, and vitamins demonstrated efficacy and safety in reducing GERD symptoms and improving quality of life in

adults with mild to moderate symptomatology. However, studies with larger sample sizes and prolonged follow-up are required to confirm these results.

It should be noted that chronic use of PPIs can induce alterations in the intestinal microbiome and favor dysbiosis. In this context, it has been proposed that probiotics not only contribute to the reduction of reflux symptoms and improvement of gastric motility but could also play a preventive role against the adverse effects associated with prolonged acid suppression. However, it is necessary to have randomized, double-blind clinical trials of longer duration to determine precisely their efficacy and clinical relevance in different populations.

### Phytotherapy

This therapy has emerged as a complementary alternative in the management of GERD, particularly in patients with mild symptoms or as a coadjuvant

strategy to reduce prolonged exposure to PPIs. Its primary aim is to modulate acid secretion, improve gastric motility, and protect the esophageal mucosa, with a generally favorable safety profile.

Among the main phytotherapeutic agents, the following stand out:

- Aloe vera: recognized for its anti-inflammatory and healing properties, it can reduce irritation of the esophageal mucosa and relieve heartburn<sup>25</sup>.
- Chamomile (*Matricaria chamomilla*): exerts a calming and spasmolytic effect on the gastrointestinal tract, favoring digestion and reducing local inflammation<sup>26</sup>.
- Licorice (*Glycyrrhiza glabra*, especially in its deglycyrrhized form, DGL): protects the gastric mucosa through stimulation of mucus production and has anti-inflammatory effects, with minimal incidence of systemic adverse effects<sup>27</sup>.
- Ginger (*Zingiber officinale*): contributes to the improvement of gastric motility and can relieve associated digestive symptoms, such as abdominal distension or nausea<sup>28</sup>.
- Combined preparations, such as Iberogast® (STW-5): integrate extracts of multiple plants with synergistic mechanisms on gastric motility, mucosal protection, and acidity modulation. In multicenter clinical trials, they have shown efficacy in reducing heartburn, regurgitation, and functional dyspepsia<sup>29</sup>.

In Mexico, such plants and phytotherapeutic preparations are available in various presentations, such as chamomile capsules, aloe vera extracts, and DGL supplements, facilitating their integration as complementary therapies. However, the quality of products can vary, so the use of standardized preparations with support from clinical evidence is recommended. It is important to emphasize that phytotherapy does not replace conventional treatments in cases of moderate to severe GERD, erosive esophagitis, or Barrett's esophagus, but may offer additional benefit in the reduction of mild symptoms and in improving adherence to a more comprehensive therapeutic approach. The combination of pharmacological measures, lifestyle changes, and phytotherapy represents a safe and potentially effective strategy for the personalized management of patients with GERD.

### **Non-pharmacological neuromodulation**

It is an emerging approach in the management of GERD, especially in patients with symptoms that persist despite PPI treatment and in those with esophageal hypersensitivity. This approach seeks to modulate the

function of the gastrointestinal nervous system and the lower esophageal sphincter (LES) through non-invasive or minimally invasive techniques, without resorting to drugs. Among the most studied strategies is electrical stimulation of the vagus nerve, which improves esophageal motility and increases LES pressure, helping to reduce the frequency of reflux episodes. Transcutaneous electrical stimulation applied over the cervical or thoracic region acts on somatic sensory fibers, modulating autonomic activity and decreasing the perception of visceral symptoms<sup>30</sup>. For its part, biofeedback and respiratory retraining techniques seek to optimize diaphragmatic function and LES tone, reducing postprandial reflux and improving patients' quality of life. Finally, more experimental modalities, such as transcranial magnetic stimulation, could centrally regulate esophageal sensitivity, offering a promising approach in cases of esophageal hypersensitivity and refractory GERD<sup>31</sup>.

Although these interventions have shown a favorable safety profile and positive effects in preliminary studies, the available clinical evidence is still limited. Randomized controlled trials are required to establish standardized protocols, define patient selection criteria, and evaluate the durability of therapeutic effects. Non-pharmacological neuromodulation, combined with lifestyle changes and pharmacological therapies, when necessary, offers a comprehensive and personalized approach to the management of GERD, expanding the tools available in functional gastroenterology.

### **Conclusions**

GERD is in a transition stage toward more precise diagnosis and treatment thanks to recent technological advances. The integration of AI in clinical questionnaires and endoscopy, along with new tools such as direct mucosal impedance, advanced reflux monitoring, and the use of biomarkers, opens the possibility of more objective and personalized characterization of patients. Likewise, standardized constructs, such as the Lyon Score and Milan Score, strengthen diagnostic stratification, while adjunctive therapies such as probiotics expand the spectrum of management options.

However, limitations persist related to clinical validation, standardization of techniques, and regulatory aspects that condition their systematic implementation. The future of GERD will depend on the consolidation of these innovations through multicenter and long-term studies that demonstrate their real utility in clinical practice. This will facilitate progress toward a more dynamic, comprehensive, and patient-centered approach.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

**Protection of human and animal subjects.** The authors declare that no experiments have been performed on human beings or animals for this research.

**Confidentiality, informed consent, and ethical approval.** The study does not involve personal data from patients or require ethical approval. SAGER guidelines do not apply.

**Declaration on the use of artificial intelligence.** The authors declare that they used artificial intelligence for the writing of this work, specifically Copilot to summarize articles cited in the references.

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