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Latin American consensus on diagnosis of gastroesophageal reflux disease

Jorge A. Olmos[1] | John E. Pandolfino[2] | María M. Piskorz[1] | Natalia Zamora[3] | Miguel A. Valdovinos Díaz[4,5] | José M. Remes Troche[6] | Mauricio Guzmán[7] | Albis Hani[8] | Luis R. Valdovinos García[9] | Hannah Pitanga Lukashok[10] | Gerson Domingues[11] | Eduardo Vesco[12,13] | Mariel Mejia Rivas[14] | Luis F. Pineda Ovalle[15] | Daniel Cisternas[16] | Marcelo F. Vela[17]

Correspondence
Jorge A. Olmos, Neurogastroenterology Sector, Hospital de Clinicas Jose de San Martin, Universidad de Buenos Aires, Buenos Aires, Argentina.
Email: jorge.a.olmos@gmail.com

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Medtronic

Abstract

Background: Diagnosing gastroesophageal reflux disease (GERD) can be challenging given varying symptom presentations, and complex multifactorial pathophysiology. The gold standard for GERD diagnosis is esophageal acid exposure time (AET) measured by pH-metry. A variety of additional diagnostic tools are available. The goal of this consensus was to assess the individual merits of GERD diagnostic tools based on current evidence, and provide consensus recommendations following discussion and voting by experts.

Methods: This consensus was developed by 15 experts from nine countries, based on a systematic search of the literature, using GRADE (grading of recommendations, assessment, development and evaluation) methodology to assess the quality and strength of the evidence, and provide recommendations regarding the diagnostic utility of different GERD diagnosis tools, using AET as the reference standard.

Key Results: A proton pump inhibitor (PPI) trial is appropriate for patients with heartburn and no alarm symptoms, but nor for patients with regurgitation, chest pain, or extraesophageal presentations. Severe erosive esophagitis and abnormal reflux monitoring off PPI are clearly indicative of GERD. Esophagram, esophageal biopsies, laryngoscopy, and pharyngeal pH monitoring are not recommended to diagnose GERD. Patients with PPI-refractory symptoms and normal endoscopy require reflux monitoring by pH or pH-impedance to confirm or exclude GERD, and identify treatment

Abbreviations: ACG, American College of Gastroenterology; AET, acid exposure time; AGA, American Gastroenterological Association; BID, twice a day; BP, basal pressure; CD, Crural diaphragm; CI, confidence interval; C-pH, catheter-based pH-metry; DIS, dilated intercellular spaces; EE, erosive esophagitis; EES, extraesophageal syndromes; EGD, esophagogastroduodenoscopy; EGJ, esophagogastric junction; ENT, ear, nose and throat; GB, gastric belching; GERD, gastroesophageal reflux disease; GIS, GERD impact scale; GSRS, gastrointestinal symptom rating scale; H2RA, H2 receptor antagonists; HRM, high resolution manometry; HRM-IMP, high resolution esophageal manometry with impedance; HS, histological scores; IEM, ineffective esophageal motility; LA, Los Angeles; LES, lower esophageal sphincter; LPR, laryngopharyngeal reflux; LR, likelihood ratio; MI, mucosal impedance; MII-pH, multichannel intraluminal impedance with pH-metry; MNBI, mean nocturnal basal impedance; NBI, narrow band imaging; NCCP, non-cardiac chest pain; NERD, non-erosive reflux disease; NPV, negative predictive value; PICO, population, intervention, comparison and outcome; PPIs, proton pump inhibitors; PPV, positive predictive value; PSPW, post-reflux swallow-induced peristaltic wave; PSPWI, PSPW Index; QD, once a day; RDQ, reflux disease questionnaire; RR, risk ratio; SAP, symptom association probability; SGB, supragastric belching; SI, symptom index; TLESR, transient lower esophageal sphincter relaxation; WC-pH, pH-metry with wireless capsule.

For Affiliation refer page on 12

failure mechanisms. GERD confounders need to be considered in some patients, pH-impedance can identify supragrastric belching, impedance-manometry can diagnose rumination.

Conclusions: Erosive esophagitis on endoscopy and abnormal pH or pH-impedance monitoring are the most appropriate methods to establish a diagnosis of GERD. Other tools may add useful complementary information.

KEYWORDS
ambulatory reflux monitoring, gastroesophageal reflux disease

1 | INTRODUCTION

Gastroesophageal reflux disease (GERD) symptoms are very frequent in Latin America, with some regional variability. The prevalence of weekly typical GERD symptoms (heartburn, regurgitation) is 23% in Argentina[1] (among the highest in the world along with the United States and the United Kingdom[2]), but is only 12% in Colombia.[3]

Gastroesophageal reflux disease symptoms are diverse, including typical presentations like heartburn, but also non-cardiac chest pain (NCCP) and atypical manifestations such as cough, dysphonia, throat clearing, hoarseness, and globus.[4] Behavioral conditions like supragastric belching and rumination syndrome can act as GERD confounders.[5]

Gastroesophageal reflux disease pathophysiological mechanisms are also diverse and complex, including a component of hypersensitivity in some patients.[6–9] Therefore, diagnosing GERD can be challenging.[9]

Throughout this consensus process, acid exposure time (AET) measured during ambulatory pH-metry was used as the gold standard for diagnosing GERD.[10] AET has been consistently shown to predict response to medical[11–13] and surgical[14–16] treatment, independently of other diagnostic parameters.[12,15,16] Cut-off points for defining GERD based on AET have varied over time. The Lyon consensus suggests that GERD is confirmed if AET is >6.0%, excluded if AET is <4.0%, with a "gray area" of diagnostic uncertainty if AET is between 4% and 6%.[17]

The goal of this Latin American consensus was to critically assess, based on the best evidence available, the individual merits of different diagnostic methods for GERD. This was done through the formulation of population, intervention, comparison and outcome (PICO) questions (see Appendix S1; Figure 1) evaluated by GRADE methodology and software, with consensus recommendations issued (Table 1) after discussion and voting (zoom meetings) among a group of experts.[18-23] This document is intended to be a guide for the diagnostic management of GERD in Latin America, considering the local realities of this geographic region. This document is endorsed by the following scientific societies: Sociedad Argentina de Gastroenterología (SAGE), American Neurogastroenterology and Motility Society (ANMS), Asociación Colombiana de Gastroenterología, Asociación Mexicana de Gastroenterología (AMG), Federação Brasileira de Gastroenterologia (FBG), Sociedad Chilena de Gastroenterología (SChGE), Sociedad Ecuatoriana de Gastroenterología, Organización Panamericana de Gastroenterología (OPGE).

For each PICO question, we provide a recommendation based on GRADE, followed by relevance of the diagnostic method in the clinical practice context.

1. **Is the use of a clinical interview or a symptom questionnaire (GerdQ) recommended to diagnose GERD?**

   Quality of evidence: LOW ⊕ ⊕ ◯ ◯
   GRADE Recommendation: STRONGLY AGAINST
   Clinical relevance: Although a clinical interview or questionnaire alone cannot diagnose GERD, the importance of an adequate clinical history is undeniable.

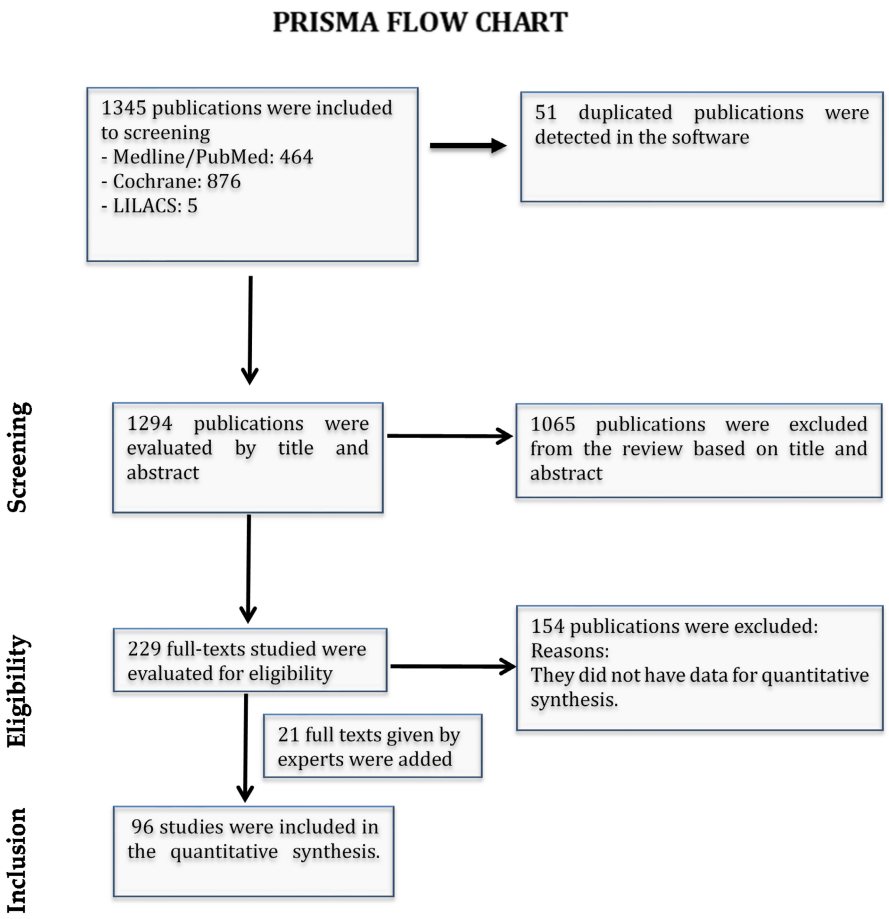
Although heartburn and regurgitation are considered typical GERD symptoms, their diagnostic yield is limited. In a systematic review, compared to esophagogastroduodenoscopy (EGD) sensitivity and specificity were suboptimal: 30% and 62% for heartburn, 76% and 96% for regurgitation.[24]

Standardized questionnaires have been developed to diagnose GERD. GerdQ, a widely used questionnaire developed for use in primary care settings, was found to have diagnostic efficiency for GERD similar to a clinical interview by a gastroenterologist, with specificity of 71% and sensitivity of 64%.[25,26]

The quantitative analysis was based on 10 observational studies evaluating GerdQ to discriminate GERD based on pathologic AET (Table S1). Sensitivity and specificity ranges were wide (43%–79% and 41%–93%, respectively). Patients with proven GERD tend to have higher scores but many patients with esophagitis have low scores.[25,27–33]

Thus, GERD cannot be diagnosed based on symptoms or questionnaires like the GerdQ alone. Patients with typical symptoms may not have the disease, some patients with proven GERD may be asymptomatic, and functional as well as esophageal motility disorders share similar clinical manifestations to GERD.

FIGURE 1 Flow diagram.



The expert panel recommended that clinical interview and questionnaires are not adequate to establish a GERD diagnosis. Level of agreement: 73%.

2. **Is a proton pump inhibitor trial recommended to diagnose GERD in patients with heartburn as the dominant symptom?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: WEAKLY IN FAVOR
Clinical relevance: Although based on low quality evidence the PPI test is inadequate to confidently diagnose GERD, a PPI trial is a reasonable and pragmatic first step in patients with heartburn without alarm features.

An empirical therapeutic test with proton pump inhibitors (PPIs), initially considered an alternative to reflux monitoring to diagnose GERD in patients with heartburn and no alarm symptoms, was subsequently extrapolated to patients with regurgitation, NCCP, and extraesophageal symptoms.[34–36]

The quantitative analysis (Table S2) was based on one study,[37] yielding a sensitivity of 86% (95% CI 70–93) and specificity of 29% (95% CI 8–58) for the PPI test compared to AET.

The expert panel could not achieve >70% agreement, but the majority concluded that a PPI test is inadequate to confidently diagnose GERD, while recognizing that this may be reasonable and useful in a primary care setting and for young patients with heartburn and no alarm features. A recent AGA practice update suggests a PPI trial for typical symptoms, followed by further investigation if there is no response. Agreement level: 67%.

3. **Is a proton pump inhibitor trial recommended to diagnose GERD in patients with regurgitation as the dominant symptom?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: A PPI trial is not a reasonable first step in patients with regurgitation as the dominant symptom, given the possibility of non-GERD confounders and the poor response of regurgitation with PPI therapy.

When regurgitation is the dominant symptom, PPIs offer limited symptomatic benefit (improvement in 26%–64%) according to meta-analyses.[38-40]

The quantitative analysis was based on a single small study[41] (Table S3) that yielded sensitivity of 83% (95% CI 70–92) and specificity of 41% (95% CI 21–64) for the PPI test in patients with regurgitation.

The expert panel felt that in addition to low response to PPI, non-GERD confounders like achalasia and rumination need to be considered in patients with regurgitation as primary symptom, concluding that an empirical PPI test is inadequate to diagnose GERD and guide treatment in these patients. Agreement level: 80%.

TABLE 1 Summary of all recommendations.

Question	Quality of evidence	Strength of recommendation
(1) Is the use of a clinical interview or a symptom questionnaire (GERDQ) recommended to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(2) Is a proton pump inhibitor trial recommended to diagnose GERD in patients with heartburn as the dominant symptom?	LOW ⊕⊕◯◯	WEAKLY IN FAVOR
(3) Is a proton pump inhibitor trial recommended to diagnose GERD in patients with regurgitation as the dominant symptom?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(4) Is a proton pump inhibitor trial recommended to diagnose GERD in patients with chest pain as the dominant symptom?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(5) Is a proton pump inhibitor trial recommended to diagnose extraesophageal GERD in patients with concomitant typical GERD symptoms (heartburn, regurgitation)?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(6) Is a proton pump inhibitor trial recommended to diagnose extraesophageal GERD in patients without concomitant typical GERD symptoms (heartburn, regurgitation)?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(7) Is esophagram recommended to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(8a) Are anatomical endoscopic findings (hiatal hernia, flap valve) recommended to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(8b) Is the endoscopic finding of erosive esophagitis (Los Angeles grade C or D), recommended to diagnose GERD?	VERY LOW ⊕◯◯◯	STRONGLY IN FAVOR
(9) Is laryngoscopy recommended to diagnose extraesophageal GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(10) Is the use of electronic chromoendoscopy with magnification (for minimal change esophagitis) recommended to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(11) Are esophageal biopsies recommended to diagnose GERD in patients with normal endoscopy?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(12) Is >48-h wireless pH-metry recommended over 24-h catheter-based pH-metry to diagnose GERD?	LOW ⊕⊕◯◯	WEAKLY IN FAVOR
(13) Is the use of the number of reflux episodes measured by intraluminal impedance recommended to diagnose GERD?	MODERATE ⊕⊕⊕◯	WEAKLY IN FAVOR
(14a) Is PSPW measured by intraluminal impedance recommended as an adjunct parameter to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(14b) Is nocturnal basal impedance recommended as an adjunct parameter to diagnose GERD?	LOW ⊕⊕◯◯	WEAKLY IN FAVOR
(15a) Are symptom association tools (symptom index, symptom association probability) recommended to diagnose GERD in patients with esophageal symptoms?	VERY LOW ⊕◯◯◯	WEAKLY IN FAVOR
(15b) Are symptom association tools (symptom index, symptom association probability) recommended to diagnose GERD in patients with extraesophageal symptoms?	VERY LOW ⊕◯◯◯	STRONGLY AGAINST
(16) Is salivary pepsin recommended to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(17) Is RESTECH recommended to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(18) Is mucosal impedance recommended to diagnose GERD?	LOW ⊕⊕◯◯	WEAKLY AGAINST
(19) Are HRM findings recommended to diagnose GERD?	LOW ⊕⊕◯◯	STRONGLY AGAINST
(20) In patients with confirmed GERD who are refractory to PPI, is pH-impedance on PPI recommended over pH-metry to inform treatment changes?	LOW ⊕⊕◯◯	STRONGLY IN FAVOR
(21) In patients with uncomfirmed GERD and heartburn refractory to PPI, is pH-impedance off PPI recommended over pH-metry to inform treatment changesheartburn?	LOW ⊕⊕◯◯	WEAKLY IN FAVOR
(22) In patients with PPI-refractory symptoms in whom rumination is suspected as a counfounder, is pH-impedance recommended (vs. not doing it and vs. HRM with impedance)?	LOW ⊕⊕◯◯	WEAKLY AGAINST
(23) In patients with PPI-refractory symptoms in whom supragastric belching is suspected as a confounder, is pH-impedance recommended?	LOW ⊕⊕◯◯	STRONGLY IN FAVOR

Note: Recommendation reference chart: WEAKLY IN FAVOR; STRONGLY IN FAVOR; WEAKLY AGAINST; STRONGLY AGAINST.

4. **Is a proton pump inhibitor trial recommended to diagnose GERD in patients with chest pain as the dominant symptom?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: A PPI trial is not a reasonable first step in patients with chest pain, as placebo effect may delay a correct diagnosis, and the most favorable response to PPI is seen when GERD is confirmed by pH-metry or EGD.

Chest pain similar to that caused by heart ischemia but with negative cardiac testing is termed NCCP.[42] Since GERD is a frequent cause of NCCP with a prevalence range of 30%–60%,[43] a PPI trial has been recommended as an initial approach.

The quantitative analysis included 11 studies evaluating the PPI test compared to AET to diagnose GERD in patients with NCCP, yielding a sensitivity of 42%–94% and specificity of 25%–89%[41,44-53] (Table S4). The risk of bias was high due to small sample sizes, high heterogeneity, and considerable differences in design, PPI dose and treatment length. Importantly, chest pain improvement was most likely when GERD was objectively confirmed by pH-metry or EGD findings.

In contrast, other studies that did not meet criteria for inclusion in our quantitative analysis have yielded more favorable results.[54-57]

The expert panel was strongly against using the PPI test to diagnose GERD in NCCP patients, as placebo effect could delay a clear diagnosis, and the most favorable response to PPI is seen when GERD is confirmed by pH-metry or EGD. Agreement level: 87%.

5. **Is a proton pump inhibitor trial recommended to diagnose extraesophageal GERD (dysphonia, cough, asthma) in patients with typical GERD symptoms (heartburn, regurgitation)?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: A PPI trial is not a useful first step to diagnose GERD in patients with extraesophageal presentations, even in the presence of typical symptoms. Of course, it may be useful for the concomitant typical symptoms.

Symptoms like chronic cough, globus, dysphonia and throat clearing, may suggest an extraesophageal GERD syndrome (EES).[4,58] However, the correlation between EES and GERD is uncertain and difficult to prove,[59] leading to substantial expenditures with the cost of evaluation and treatment of EES patients being five times that of GERD with typical symptoms.[60]

The quantitative analysis included three studies[61-63] evaluating the resolution of EES after empirical PPI therapy in patients with and without typical reflux symptoms, limiting our ability to directly answer this question. Sensitivity range was 52%–86%, specificity 41%–58% (Tables S5 and S6). There was heterogeneity due to small sample sizes and variable design and methodology.

Of note, the American College of Gastroenterology (ACG) GERD Guidelines suggest empirical PPI therapy for 8–12 weeks prior to diagnostic workup for patients with extraesophageal symptoms who have concomitant typical GERD symptoms.[64]

The expert panel recommended against the PPI test to diagnose GERD in patients with EES and concomitant typical GERD symptoms but recognized that empirical PPI therapy can be considered if ambulatory reflux monitoring is not available. Agreement level: 73%.

6. **Is a proton pump inhibitor trial recommended to diagnose extraesophageal GERD in patients WITHOUT typical GERD symptoms?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: A PPI trial is not a good first step to diagnose GERD in patients with extraesophageal symptoms without concomitant typical symptoms. Testing to establish GERD presence is recommended prior to therapy.

In clinical practice GERD is often blamed for extraesophageal symptoms, in some cases even despite lack of concomitant typical symptoms, no response to PPI, and negative reflux monitoring studies.[65]

The quantitative analysis is the same as for question 5, because the available studies included EES patients with and without typical GERD symptoms[61-63] (Tables S5 and S6).

A qualitative analysis included a randomized, double-blind, placebo-controlled study of 346 patients with persistent pharyngeal symptoms, in whom 16 weeks of lansoprazole BID had no advantage over placebo for improving symptom scores.[65]

Given the difficulties in establishing an association between EES and GERD, and the high cost of evaluation and treatment,[60] the ACG GERD Guidelines and the American Gastroenterological Association (AGA) Clinical Practice Update recommend that in patients with extraesophageal manifestations attributable to GERD but without concomitant typical symptoms, other etiologies should be ruled out, and testing for GERD should be performed prior to treatment with PPIs.[6,64]

The expert panel recommended against a PPI test to diagnose GERD in patients with EES without concomitant typical symptoms. Agreement level: 100%.

7. **Is esophagogram recommended to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: Esophagogram is not recommended to diagnose GERD, although it is useful to assess esophageal anatomy.

Barium esophagram is widely available and useful to assess anatomy and esophageal emptying.[66,67] However, presence of reflux on esophagram correlates poorly with pH monitoring. ACG GERD

guidelines and the Lyon consensus both recommend against esophagram to diagnose GERD.[17,64]

The quantitative analysis included two studies (Table S7),[68,69] yielding a sensitivity of 50% (95% CI 32–68) and specificity of 64% (95% CI 45–80) for esophagram to diagnose GERD.

The expert panel recommended against esophagram to diagnose GERD. Agreement level: 100%.

8. **Are endoscopic findings recommended for GERD diagnosis?**

8a **Are anatomical findings of endoscopy (hiatal hernia and flap valve) recommended to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: Endoscopic anatomical findings, though important for management in some patients, are not recommended to diagnose GERD without other confirmatory evidence.

Esophagogastroduodenoscopy is used to evaluate symptoms suggestive of GERD.[66] Hiatal hernia size correlates with esophagitis severity and AET,[70] but by itself cannot establish a GERD diagnosis.[71] EGD also enables grading of the flap valve through the Hill Classification, which has been found to be associated with erosive esophagitis.[72,73,75,76]

The quantitative analysis for hiatal hernia is based on one study that assessed the relationship between hiatal hernia on EGD pH-metry findings[74] (Table S8). Hiatus hernia had sensitivity of 75% and specificity of 49% for GERD diagnosis.

The expert panel recommended against using hiatal hernia and flap valve alterations in isolation to diagnose GERD. Level of agreement: 87%.

8b **Is the endoscopic finding of severe erosive esophagitis (Los Angeles grade C or D) recommended to diagnose GERD?**

Quality of evidence: VERY LOW ⊕ ◯ ◯ ◯
GRADE Recommendation: STRONGLY IN FAVOR
Clinical relevance: Erosive esophagitis Los Angeles Grade C–D is clearly diagnostic of GERD. Recent studies published after voting for this question, suggest that Grade B esophagitis may also be diagnostic of GERD.

There was no extractable information available for quantitative analysis. According to the Lyon and Porto consensuses, severe esophagitis (LA grades C or D), long-segment Barrett's esophagus (≥3 cm), and peptic stricture are all considered confirmatory evidence of GERD.[17,77-79] However, erosive esophagitis is found in only 30% of untreated patients with heartburn, and in less than 10% of patients receiving PPIs.[80,81] Furthermore, LA grade A esophagitis is nonspecific and found in 5%–8% of asymptomatic controls,[82-84] and mild esophagitis suffers from high interobserver variability. Therefore the Lyon 1.0 and Porto consensuses recommended that when LA grade A or B esophagitis is present, pH-metry is required to confirm GERD.[17,79,85]

Further studies are necessary to clarify whether grade B esophagitis may have a diagnostic performance akin to grades C–D. Of note, recently published ACG guidelines consider grade B esophagitis as objective evidence of GERD.[64]

The expert panel recommended that esophagitis LA C–D is diagnostic of GERD. Level of agreement: 93%. Barrett's esophagus and peptic stenosis were not addressed as they are strongly associated with GERD and endorsed by the Lyon and Porto consensus as diagnostic of GERD.

9. **Is laryngoscopy recommended to diagnose extraesophageal GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: Laryngoscopy is not recommended to diagnose GERD, though it is important to rule out non-GERD pathologies like cancer.

20%–60% of the North American population presents symptoms suggestive of laryngopharyngeal reflux (LPR), but there is no gold standard for its diagnosis.[86-88] A presumptive LPR diagnosis, often made based on symptoms and laryngoscopic findings, has a strong impact on health economics,[60] with a 14-fold increase in PPI prescriptions for this from 1990 to 2001.[89,90]

Given the possibility of non-GERD contributing etiologies, diagnostic evaluation should include history, clinical examination, and laryngoscopy to rule other conditions like cancer or papilloma.[91]

Laryngoscopy signs attributed to LPR are not only multiple and variable, but also nonspecific.[92] The Reflux finding score (RFS) was developed to standardize evaluation assessing the severity of eight laryngoscopic findings.[93,94] However, laryngoscopy and scores like the RFS have low specificity, poor reliability, and high interobserver variability.[92-99] A diagnosis of LPR based solely on laryngoscopy can lead to unnecessary treatment.[100,101]

The quantitative analysis (Table S9) was based on two small studies yielding a sensitivity of 86% (95% CI: 71–85) and a specificity of 9% (95% CI: 3–22) for GERD diagnosis.[102,103]

The expert panel recommended against laryngoscopy to diagnose GERD. Level of agreement: 100%.

10. **Is electronic chromoendoscopy with magnification (for minimal change esophagitis) recommended to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: Electronic chromoendoscopy with magnification is not recommended to diagnose GERD.

Based on EGD findings, patients with GERD can be classified into three groups: non-erosive reflux disease (NERD, i.e., negative endoscopy and abnormal AET), EE, and Barrett's esophagus.[4,104] As NERD accounts for up to 70% of GERD cases, standard EGD has low sensitivity for GERD diagnosis,[84,105] prompting efforts to enhance endoscopic evaluation and detect "minimal change esophagitis" through high-definition white light endoscopy, chromoendoscopy, magnification endoscopy, and electronic chromoendoscopy including narrow band imaging (NBI) or the I-scan system.[105]

The quantitative analysis was based on two studies that evaluated electronic chromoendoscopy (Table S10), yielding a sensitivity 48%–75%, and specificity 83%–100%.[106,107]

The expert panel concluded that although electronic chromoendoscopy and other endoscopic techniques may show some promise for GERD diagnosis, the available evidence is insufficient to consider them clinically useful and recommended against their use for GERD diagnosis. Level of agreement: 80%.

11. **Are esophageal biopsies recommended to diagnose GERD in patients with normal endoscopy?**

Quality of evidence: LOW ⊕⊕◯◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: Findings on esophageal biopsies and histological scores are not recommended to diagnose GERD.

Since ambulatory reflux monitoring can cause discomfort,[108-110] and macroscopic endoscopic evaluation has low sensitivity for GERD diagnosis, assessment of esophageal biopsies for presence of "microscopic esophagitis" (defined by findings like basal cell hyperplasia, papillary elongation, and dilation of intercellular spaces) has been studied as an alternative.[111]

The quantitative analysis was based on five studies that evaluated histological scores (HS) to diagnose GERD, yielding sensitivity of 67%–85%, and specificity of 63%–91% (Table S11, HS).[112-114] Low specificity is problematic, as evidenced by positive HS for GERD in 15%–37% of healthy controls,[112,113] and inability to differentiate NERD from functional heartburn.[115,116]

Despite attempts to standardize histologic evaluation,[117,118] studies differ in chosen parameters, approach to measurements, and biopsy sites.[119,120]

Dilated intercellular space (DIS) is among the most studied histological parameters in GERD. The quantitative analysis for DIS included two studies that yielded a sensitivity of 61%–87%, and specificity of 56%–70% to diagnose GERD. Of note, the ability of DIS to differentiate NERD from functional heartburn is not clear,[33,115,121,122] and it can be caused by lymphocytic esophagitis,[123] eosinophilic esophagitis,[124] esophageal cancer,[125] esophageal candidiasis,[126] obesity,[127] and anxiety.[128] Furthermore, transient DIS has been described minutes after acidification of the esophagus,[129] which could explain why it may be found in 25%–30% healthy controls.[112,114,119]

Based on the available data, and supported in published guidelines, obtaining biopsies to diagnose GERD is not useful, although this is important to rule out eosinophilic esophagitis.[17,66,130]

The expert panel recommended against esophageal biopsies to diagnose GERD. Agreement level: 100%.

12. **Is >48-h wireless pH-metry recommended over 24-h catheter-based pH-metry to diagnose GERD?**

Quality of evidence: LOW ⊕⊕◯◯
GRADE Recommendation: WEAKLY IN FAVOR
Clinical relevance: >48-h wireless pH-metry off PPI is the best method to diagnose GERD. Availability in Latin America is limited.

Ambulatory esophageal pH monitoring by transnasal catheter (C-pH) or wireless capsule (WC-pH), is considered the most useful test for GERD detection, and allows assessment of the symptom-reflux association.[64] C-pH can incorporate one or more pH sensors, but recording is limited to 24 h. WC-pH allows monitoring for up to 96 h.[131]

The tolerance, safety, technical difficulties and diagnostic utility of both tests have been evaluated in a systematic review.[132] The quantitative analysis for safety included 10 studies that compared C-pH to WC-pH[11-20] (Table S12a). Chest pain and foreign body sensation occurred more frequently with WC-pH, while nasal and throat pain, dysphagia, eating difficulties, and interference with daily activities were more frequent with C-pH. Satisfaction with the procedure was higher with WC-pH. In nine studies assessing technical difficulties, problems were three-fold higher with WC-pH mostly premature detachment and intolerance to insertion; catheter-related discomfort with subsequent removal was more common with C-pH.[108,110,133-141]

Diagnostic utility evaluated in eight studies was overall higher for WC-pH (Table S12b).[134,140-146] In the quantitative analysis, based on three studies, sensitivity ranged from 74% to 88% and specificity from 80% to 93%. Earlier studies proposed prolonging WC-pH for up to 96 h, to allow evaluation off and on PPI in a single study, but the practice has been abandoned.[147-150]

In summary, compared to C-pH, WC-pH is better tolerated, addresses the issue of daily variability in pH monitoring, and has greater sensitivity and specificity. Whether WC-pH is better at predicting response to treatment is not known, and the potential to increase false positive results has not been clarified. Importantly, WC-pH is costly, and availability is limited in Latin America c. The expert panel recommended that when available, prolonged WC-pH monitoring is preferable to C-pH. Agreement level: 67%.

13. **Is the use of number of reflux episodes measured by impedance recommended to diagnose GERD?**

Quality of evidence: MODERATE ⊕⊕⊕◯
GRADE Recommendation: WEAKLY IN FAVOR

Clinical relevance: The number of reflux episodes measured by impedance may be a useful complementary parameter in studies off PPI that are inconclusive for GERD. In patients with PPI-refractory typical symptoms, especially regurgitation, it can predict response to treatment.

Twenty-four-hour MII-pH enables detection of not only acid (with pH <4) but also non-acidic reflux (with pH >4, subcategorized as weakly acidic or weakly alkaline). Manual review of the MII-pH tracings is necessary because the available software can overestimate the number of reflux episodes.[151]

In patients with PPI-refractory symptoms and no objective evidence of GERD on endoscopy, reflux monitoring (C-pH, MII-pH, or WC-pH) off PPI is used to confirm or exclude GERD.[17] In patients with proven GERD and persistent symptoms despite medication, MII-pH on PPI is recommended to ascertain whether the persistent symptoms are related to reflux (acid, non-acid, or both).[16,17,79] The Lyon Consensus proposed that for 24-h MII-pH, >80 reflux episodes is abnormal, <40 is physiological, and 40–80 is inconclusive.[17]

There was no available evidence for an adequate quantitative analysis (Table S13). Based on a single study that compared MII-pH in 213 patients with GERD symptoms (117 with NERD) and 21 healthy controls, sensitivity was estimated as 75% (95% CI 65–82) for the detection of acid reflux, accepting the possibility of imprecision and a high risk of bias.[152]

Earlier studies regarding the usefulness of the number of reflux episodes measured by MII-pH as a predictor of response to treatment showed mixed results.[15,35,153] Subsequently, analysis of data from a randomized controlled clinical trial in regurgitation-predominant GERD patients, revealed that >80 reflux episodes detected by MII-pH on PPI predicted response to laparoscopic magnetic sphincter augmentation.[154] Despite this, the AGA has not endorsed number of reflux episodes to make treatment decisions in refractory GERD patients.[6]

In summary, the number of reflux episodes provides important complementary information when MII-pH off PPI is performed as a first study and is useful in those with PPI-refractory symptoms, especially regurgitation, as this metric may predict response to treatment. The panel recommended the number of reflux episodes measured by impedance to diagnose GERD. Agreement level: 93%.

14a **Is PSPWI measured by impedance recommended as an adjunct parameter to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: PSPWI is not recommended to diagnose GERD.

Esophageal clearance by primary peristalsis after a reflux episode, known as the post-reflux swallow-induced peristaltic wave (PSPW), has been described as a relevant pathophysiological mechanism in GERD.[155,156] Recently, the PSPW index (PSPWI), defined as the percentage of reflux events that are followed by a PSPW, has been proposed as a tool to diagnose GERD.[157,158]

The quantitative analysis was based on three studies yielding a sensitivity of 79%–100%, and specificity of 65%–87% (Table S14a). Two European studies showed adequate diagnostic certainty of PSPWI for GERD diagnosis, especially in terms of sensitivity, based on MII-pH performed both off as well as on PPI.[158,159] However, a recent study from Asia showed lower diagnostic certainty for differentiating GERD from functional heartburn, and the suggested cut-off value was lower than previously described.[160]

In terms of predicting response to medical and surgical treatment, a study showed that PSPWI was useful in patients with intermediate AET (4%–6%).[161] However, a larger multicenter study showed no difference in PSPWI among responders and non-responders to GERD therapy escalation.[162]

Given the absence of a universally established cut-off value, the need for manual calculation (there is no available software for PSPWI), and the suboptimal sensitivity and specificity, PSPWI is not widely used at this time. That said, it could be further explored as an adjunct parameter for GERD diagnosis, in cases of intermediate AET.

The expert panel recommended against the use of PSPWI to diagnose GERD. Agreement level: 100%.

14b **Is mean nocturnal basal impedance recommended as an adjunct parameter to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: WEAKLY IN FAVOR
Clinical relevance: Mean nocturnal baseline impedance measured during 24-h MII-pH may be a useful complementary parameter to aid in GERD diagnosis.

Loss of esophageal mucosal integrity due to GERD can be demonstrated by low baseline impedance, even in the absence of erosive esophagitis.[163,164]

Specialized probes have been developed to be evaluate mucosal impedance during endoscopy.[165-167] However, the most studied and widely available form of mucosal impedance measurement is the mean nocturnal baseline impedance (MNBI) derived from 24-h MII-pH studies, calculated by averaging distal esophageal baseline impedance measured over three 10-min periods during the night, to decrease the likelihood of gas and/or liquid in the esophageal lumen.[168]

In the quantitative analysis based on six studies, MNBI sensitivity ranged from 78% to 94% and specificity from 54% to 90% (Table S14b),[159,160,169,170] with especially good yield when comparing GERD patients to healthy controls.[171]

Of note, up to 30%–40% of symptomatic patients with low MNBI have normal AET, which has brought the specificity of low MNBI into question.[172,173] Furthermore, various cut-off values for MNBI have been proposed based on different studies, ranging from 1100 to 2300 Ohms. The reasons for such disparity are not known, but genetic/ethnic/geographic factors are possible.[171,174]

While MNBI predicts response to medical and surgical treatment in some studies,[157,161,172,173,175] others show lack of predictive ability if logistic regression models include variables such as PSPWI[159] or AET.[162,173]

Mean nocturnal basal impedance measured during MII-pH off PPI seems promising as an adjunct parameter for decision making, especially with indeterminate AET (between 4% and 6%),[17] but available data do not support that MNBI can replace current gold standards for diagnosing GERD.

The expert panel recommended the use of MNBI as a parameter that could be useful for GERD diagnosis. Agreement level: 73%.

15. **Are symptom association tools (symptom index and symptom association probability) recommended to diagnose GERD?**

No studies were found with extractable information, so a quantitative analysis was not performed.

15a **Are symptom association tools (symptom index and symptom association probability) recommended to diagnose GERD in patients with esophageal symptoms?**

Quality of evidence: VERY LOW ⊕ ◯ ◯ ◯
GRADE Recommendation: WEAKLY IN FAVOR
Clinical relevance: Symptom association tools should not be used in isolation (without other objective documentation of GERD). Although evidence supporting symptom association tools as predictors of treatment response is variable and controversial, they allow categorization of patients into different phenotypes with clinical relevance (GERD, hypersensitive esophagus, functional heartburn).

The symptom index (SI) and symptom association probability (SAP), initially developed to assess association between typical symptoms (heartburn) and reflux measured by pH-metry, have now been extrapolated to include atypical symptoms and reflux measured by MII-pH, in an effort to distinguish GERD from hypersensitivity and functional heartburn, often in the context of PPI-refractory symptoms.[176-180]

Using a 2-min association time window, the SI is the percentage of symptoms preceded by a reflux episode, considered positive if >50%.[181-184] The SAP and Ghillebert's probabilistic estimation (GPE) use more complex statistical calculations to assess the probability of true association between symptoms and reflux episodes, considered positive if the probability of chance association is <5%.[185,186] The SI reflects the effect size, while SAP documents the probability of true association, and they are considered complementary and useful to differentiate reflux hypersensitivity from functional heartburn in patients with normal AET.[178,187,188] The updated 2016 Proto Consensus stated that abnormal AET along with positive SAP and SI represented the strongest evidence of GERD.[79] Moreover, the indices allow sub classification of symptomatic patients into clinically useful phenotypes (GERD, reflux hypersensitivity, and functional heartburn), with treatment implications.

In several studies both SI and SAP predicted response to medical and surgical treatment independent of AET, but sample sizes were small and there was high risk of bias.[15,189-192] In contrast, a recent retrospective analysis of SAP data in 48-h WC-pH off PPI for evaluation of refractory symptoms, found that SAP was not useful to distinguish functional heartburn from reflux hypersensitivity or predict response to fundoplication, and 18% of patients had discordant SAP values between days 1 and 2 of pH-metry; furthermore, SAP did not predict fundoplication outcome.[193] This raised questions about the value of symptom indices for GERD diagnosis.[176,194] Although the evidence is contradictory regarding the usefulness of symptom indices as predictors of response to treatment in patients with typical GERD, they may be useful in selected patients.

The expert panel recommended that SI and SAP may be used as a complementary parameter for GERD diagnosis, but treatment decisions should not be based solely these indices. Agreement level: 73%.

15b **Are symptom association tools (symptom index and symptom association probability) recommended to diagnose GERD in patients with extraesophageal symptoms?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: Symptom association tools have no diagnostic utility in patients with extraesophageal symptoms.

Determining the association between extraesophageal symptoms and GERD is challenging, because these symptoms may have multiple etiologies.

There was no information available in the literature search to perform quantitative analysis for this PICO question.

In a retrospective study of 53 patients with chronic cough, SAP was found to be a predictor of response to treatment in the multivariate analysis.[195] However, the inability of patients to accurately report cough events was demonstrated in a study that used an acoustic monitoring system to detect cough during reflux monitoring.[196] This led the Porto and Lyon Consensuses to recommend addition of a cough detector to identify cough events with precision when evaluation cough-reflux association.[17,79,197,198] Many other extraesophageal symptoms such as hoarseness, are not episodic and thus not suitable for symptom association analysis.

The expert panel recommended that symptom indices are not adequate for the evaluation of extraesophageal symptoms thought to be GERD-related. Agreement level: 80%.

16. **Is salivary pepsin recommended to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: Salivary pepsin is not useful to diagnose GERD.

Laryngopharyngeal reflux (LPR) refers to symptoms (dysphonia, globus, etc.) and morphological changes in the larynx due to direct or indirect damage caused by reflux of gastroduodenal contents such as acid and pepsin.[88,199,200] The true prevalence of LPR is unclear but estimated at 10%–30% in the Western population, accounting for 10% of otolaryngology consultations.[201] The lack of tools to accurately diagnose LPR, and the possible multifactorial etiologies for its symptoms pose a challenge in clinical practice.

Pepsin, which can potentially harm tissue, has been detected in the middle ear, tears and in saliva, providing evidence of reflux of gastric contents into supraesophageal structures.[202-211] Numerous studies have reported the diagnostic utility of pepsin in LPR.[212-215] A recent meta-analysis including 11 studies found the sensitivity and specificity of pepsin for the diagnosis of LPR to be 64% and 68%, but there was remarkable heterogeneity in exclusion criteria and pepsin detection methodology.[214] In practice, the applicability of salivary pepsin is limited by the absence of gold standards for preferred assay, number of samples needed, and normal values.

The quantitative analysis included 10 studies with generally low quality of evidence (Table S15), and high risk of bias (investigators were not blinded to the outcome of the test being compared), yielding sensitivity of 37%–77% and specificity of 43%–89%.

The expert panel recommended against the use of salivary pepsin to diagnose GERD. Agreement level: 73%. Future larger studies could change this recommendation.

17. **Is RESTECH recommended to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: RESTECH is not recommended to diagnose GERD.

Dual-sensor monitoring (esophageal and pharyngeal) and MII-pH are considered by some experts as the gold standard for LPR detection. However, currently published studies report discordant and unreliable results for these techniques.[199-201,216,217] The pharyngeal pH measurement system (RESTECH) was developed as a less invasive and more tolerable test to detect acid in liquid or aerosol form in the hypopharynx during 24 h.[88] However, a study that evaluated 24-h RESTECH monitoring in 10 patients with total gastrectomy and no reflux symptoms, found that the test revealed pathologic reflux in 60% of the subjects,[218] casting doubt on the usefulness of this test in LPR.

The quantitative analysis was based on two studies, yielding a sensitivity of 61%–68% and specificity of 71%–100% (Table S16).

The expert panel recommended against the use of RESTECH to diagnose GERD. Agreement level: 87%.

18. **Is mucosal impedance recommended for GERD diagnosis?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: WEAKLY AGAINST
Clinical relevance: Mucosal impedance measurement is a promising tool, but it cannot be recommended for clinical use at the present time. Future larger studies could change this recommendation.

As explained in PICO question 14b, baseline impedance measurement derived from MII-pH studies appears promising as an adjunct parameter to diagnose GERD, but the timing and duration of baseline impedance assessment are critical to obtain a reliable measurement.[219] Therefore, probes to enable direct measurement of mucosal impedance (MI) during endoscopy have been developed.

The quantitative analysis included one study which compared MI in patients with GERD diagnosed by EE and control patients without GERD.[165] MI had sensitivity of 89% (95% CI 67–99) and specificity of 67% (95% CI 46–83) (Table S17). While these data show promise for MI in GERD diagnosis, sample size was small, investigators were not blinded to GERD diagnosis, and the results have not been replicated elsewhere. Furthermore, given the single short measurement of MI, whether a different result may be obtained in other circumstances (for instance at night or in upright position) is not known.[165] Therefore, additional and larger studies are needed to validate this tool which cannot be recommended for clinical use at the present time.

The expert panel recommended against MI to diagnose GERD, but this may change with additional studies. Agreement level: 87%.

19. **Are high resolution esophageal manometry (HRM) findings recommended to diagnose GERD?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY AGAINST
Clinical relevance: HRM findings are not useful to diagnose GERD. However, HRM can provide information regarding disease mechanisms, and help rule out esophageal motor disorders that may present with GERD-like symptoms.

Some data based on Conventional manometry suggest that a dysfunctional antireflux barrier due to LES hypotension or hiatal hernia, and impaired esophageal clearance due to ineffective esophageal motility (IEM) may help diagnose GERD, but different studies have conflicting results.[220-226]

It has been suggested that HRM findings may better differentiate GERD patients from controls.[224] Based on a single study with low quality of evidence, IEM identified by HRM as a means to diagnose GERD had sensitivity of 27% and specificity of 77% (Table S18a). Findings of small studies (<50 subjects) comparing reflux burden among patients with IEM versus normal motility, range from no association to positive association between IEM and AET.[226-229]

The EGJ contractile integral, a novel HRM metric to assess EGJ basal pressure, had sensitivity of 58% and specificity of 65% (Table S18b) to distinguish GERD from functional heartburn in a retrospective unblinded study with low quality evidence and high risk

of bias.[230] Other studies have shown that HRM abnormalities had low predictive value and insufficient accuracy for GERD diagnosis compared to controls and functional heartburn[231-233] (Table S18c).

The expert panel recommended that HRM is not an adequate method to make a diagnosis of GERD, though it can provide information regarding possible mechanisms of disease, and it helps rule out esophageal motor disorders in the workup of GERD. Agreement level: 100%.

20. **In patients with confirmed GERD who are refractory to PPIs, is pH-impedance recommended over conventional pH-metry to inform treatment changes?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY IN FAVOR
Clinical relevance: pH-impedance on PPI is the diagnostic method of choice to evaluate patients with confirmed GERD and PPI-refractory symptoms.

30%–40% of patients with GERD symptoms do not fully respond to PPI therapy.[234] Unlike conventional pH monitoring, MII-pH detects both acid and non-acid reflux episodes, and the latter can explain persistent symptoms in up to one third of refractory patients.[235,236] A recent consensus from the European and North American Neurogastroenterology Associations (ESNM/ANMNS) distinguishes between refractory symptoms (may or may not be GERD-related), refractory GERD symptoms (persistent symptoms in patients with proven GERD, regardless of the relationship to ongoing reflux) and refractory GERD (objective evidence of GERD despite standard-dose for 8 weeks).[5] Objective GERD evidence includes EE, pathologic AET, and/or a high number of reflux episodes by MII-pH on PPI. When evaluating PPI-refractory symptoms in patients with previously confirmed GERD, testing should be performed while on PPI to elucidate mechanisms underlying the ongoing symptoms (acid, weakly acid, or non-acid reflux, or a lack of reflux altogether), with treatment recommendations based on the findings.

In a study that compared MII-pH to pH alone in PPI-refractory patients, MII-pH was abnormal in 36%, pH-metry was abnormal in 28%. The calculated sensitivity and specificity was 93% and 40%, respectively (Table S19a), supporting that in patients with refractory GERD, MII-pH represents a better strategy for the evaluation of PPI-refractory symptoms.[237] Additional evidence examining possible diagnostic gains for MII-pH compared to pH-metry (both performed while on PPI) is shown in (Table S19b).

The expert panel recommended that in patients with confirmed GERD and PPI-refractory symptoms, MII-pH is the best method to guide further therapy as it helps to delineate treatment failure mechanisms. Agreement level: 100%.

21. **In patients with unconfirmed GERD and heartburn refractory to PPI, is pH-impedance off PPI recommended over conventional pH-metry to inform treatment changes?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: WEAKLY IN FAVOR
Clinical relevance: pH-impedance off PPI is recommended to confirm GERD in patients with heartburn as it provides additional GERD parameters and can guide management. 96-h wireless pH is also valuable in this context, but this is not widely available in Latin America.

When evaluating patients with symptoms attributed to reflux but refractory to PPI, it is essential to have an objective marker that allows establishing the presence of GERD and the relationship between symptoms and reflux.[5] In this context, erosive esophagitis (Los Angeles grades C–D) on EGD clearly confirms GERD. If endoscopy is negative, abnormal AET confirms GERD, and symptom association analysis helps determine whether GERD explains those symptoms. These patients should undergo reflux monitoring by pH-metry or MII-pH while off PPI, to confirm GERD, or establish a diagnosis of esophageal hypersensitivity or functional heartburn.[5,6,64]

The quantitative analysis was based on a single study (Table S20) which showed that MII-pH off PPI had greater diagnostic yield and led to treatment changes more frequently than conventional pH-metry (RR of 1.31, 95% CI 1.02–1.70).[238] However, the study did not assess treatment outcomes based on reflux monitoring, so whether the results truly guide a change in therapy is not clear. Importantly, MII-pH also enables measurement of additional parameters that may be helpful when there is diagnostic uncertainty, such as PSPWI and MNBI.

The expert panel recommended MII-pH off PPI over conventional pH-metry to study patients with unconfirmed GERD and PPI-refractory heartburn, as the results could increase the likelihood of change in therapeutic behavior. Agreement level: 93%. However, 96-h wireless pH monitoring (described in question 12) is also valuable as this may increase diagnostic yield through a longer monitoring window. That said, wireless pH is less available and more costly in Latin America.

22. **In patients with PPI-refractory symptoms in whom rumination is suspected as a confounder, is pH-impedance recommended (vs. not doing it and vs. HRM with impedance)?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: WEAKLY AGAINST
Clinical relevance: In patients with suspected rumination, while pH-impedance may suggest rumination, it does not provide conclusive evidence. Impedance-manometry with postprandial monitoring remains the gold standard to confirm rumination.

Persistent postprandial regurgitation despite PPI may be due to ongoing GERD but can also be caused by rumination, a functional gastrointestinal disorder characterized by regurgitation of recently ingested food into the mouth, often repetitive, in the absence of structural abnormalities. Objective testing can help distinguish GERD from rumination; that said, the two may overlap in some patients.[239,240] HRM combined with impedance (HRM-IMP) with postprandial testing is currently one of the most widely used methods to assess rumination.[241]

In patients with suspected GERD symptoms refractory to PPI, MII-pH is often used to confirm or exclude GERD, and it may also help identify rumination.

The quantitative analysis for this question included only one small study (Table S21). A rumination pattern and corresponding score (0–2 points) was identified in MII-pH studies of patients who had rumination confirmed by HRM-IMP with postprandial protocol. The MII-pH rumination score was then applied to patients with PPI-refractory GERD symptoms to diagnose rumination. Sensitivity and specificity of MII-pH for rumination were 92% and 79% for a score of 1, 93% and 58% for a score of 2.[239]

Multichannel intraluminal impedance with pH-metry is not the method of choice for rumination, but it could help identify this condition in patients with high clinical of this disorder. However, the expert panel recommended that HRM-IMP with postprandial protocol is the gold standard for the diagnosis of rumination, and there is insufficient evidence to confidently use the score derived from the MII-pH to diagnose this condition. Agreement level: 80%.

23. **In patients with PPI-refractory symptoms in whom supragastric belching is suspected as a confounder, is pH-impedance recommended?**

Quality of evidence: LOW ⊕ ⊕ ◯ ◯
GRADE Recommendation: STRONGLY IN FAVOR
Clinical relevance: In patients with suspected supragastric belching (SGB), pH-impedance is the diagnostic method of choice to confirm SGB.

Belching, the audible escape of air from the esophagus or stomach into the pharynx, occurs in all healthy subjects, but is considered bothersome when it becomes excessive and/or triggers reflux symptoms.[242,243] In gastric belching (GB), a physiological phenomenon to vent gastric gas, air moves from stomach to esophagus to pharynx to be expelled.[244] Supragastric belching (SGB) is a behavioral disorder whereby the patient quickly sucks air into the esophagus through abrupt voluntary diaphragmatic contraction, followed by rapid air expulsion.[245]

A careful clinical history can often help distinguish SGB from GB, but MII-pH monitoring is the diagnostic modality of choice to evaluate belching, since it provides objective evidence of the direction of gas movement in the esophagus, as well as its potential relationship with reflux and the patient's symptoms. SGB has been postulated as an important factor in PPI-refractoriness in some patients with GERD, through its ability to trigger reflux episodes and also by causing esophageal distension.[241,243,245,246]

In patients with confirmed GERD and PPI-refractory symptoms, SGB prevalence may be up to 42%,[247] with variability according to reflux phenotype: 38% in NERD, 40% in hypersensitive esophagus, 22% in functional heartburn.[248]

The quantitative analysis (Table S22) included one small study with low quality of evidence that did not deal with PPI-refractory GERD symptoms, but evaluated the ability of MII-pH to discriminate SGB perceived as bothersome by the patient in the context of GERD symptoms, yielding a sensitivity of 60% and a specificity of 64%.[244]

In conclusion, in patients with GERD symptoms refractory to PPI, MII-pH enables objective confirmation or exclusion of SGB.

The expert panel recommended that MII-pH is useful in patients with frequent belching and GERD symptoms refractory to PPIs. Agreement level: 93%. This method would be cost-effective in this population, and it can lead to a change in treatment strategy.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: JAO, JEP, MMP, MG, AH, HPL, JMRT, MAVD, LRVG, EV, LFPO, DC, GD, MMR, MFV, NZ. Drafting the work or revising it critically for important intellectual content: JAO, JEP, MMP, MG, AH, HPL, JMRT, MAVD, LRVG, EV, LFPO, DC, GD, MMR, MFV, NZ. Final approval of the version to be published: JAO, JEP, MMP, MG, AH, HPL, JMRT, MAVD, LRVG, EV, LFPO, DC, GD, MMR, MFV, NZ. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: JAO, JEP, MMP, MFV.

AFFILIATIONS

[1]Neurogastroenterology Sector, Hospital de Clinicas Jose de San Martin, Universidad de Buenos Aires, Buenos Aires, Argentina
[2]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
[3]Hospital San José de Pergamino, Buenos Aires, Argentina
[4]UNAM, Ciudad de Mexico, Mexico
[5]Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[6]Institute of Medical Biological Research, Universidad Veracruzana, Veracruz, Mexico
[7]Neurogastroenterology Unit, Gastroenterology Service, Hospital San Martín de La Plata, Buenos Aires, Argentina
[8]Hospital San Ignacio-Pontificia Universidad Javeriana, Bogotá, Colombia
[9]Gastrointestinal Motility Laboratory, Fundación Clínica Médica Sur, Mexico City, Mexico
[10]Digestive Motility Service, Instituto Ecuatoriano de Enfermedades Digestivas–IECED, Guayaquil, Ecuador
[11]State University of Rio de Janeiro, Rio de Janeiro, Brazil
[12]Neuromotility Unit, Clínica Angloamericana, Lima, Peru
[13]Universidad Nacional Mayor de San Marcos, Lima, Peru
[14]Internal Medicine, Gastroenterology and Digestive Endoscopy Service, Hospital Vivian Pellas, Managua, Nicaragua
[15]Neurogastroenterology and Motility Service Motility Instituto Gut Médica, Bogotá, Colombia
[16]Clínica Alemana de Santiago, School of Medicine, Universidad del Desarrollo, Clínica Alemana, Vitacura, Chile
[17]Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA

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CONFLICT OF INTEREST STATEMENT

This consensus has been conducted with complete independence and free of bias. Individual conflicts of interest for the expert panel are listed at the end of the document. JAO: Medtronic: consultant, speaker, and grant support. JEP: Medtronic: speaker, consultant, grant support, intellectual property, and commercial interests. MMP: Medtronic: grant support. MG: Medtronic: consultant, speaker. MAVD, JMRT, AH, LRVG, HPL, GD, EV, MMR, LFPO, DC: no conflicts of interest. MV: Diversatek: non-monetary support in equipment for research; Medtronic; consultant.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

José M. Remes Troche https://orcid.org/0000-0001-8478-9659
Marcelo F. Vela https://orcid.org/0000-0002-5350-4654

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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