



Review Article

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Recent Advances in the Diagnosis and Treatment of Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) is a common, chronic condition that significantly affects patient quality of life and may lead to complications such as erosive esophagitis, Barrett's esophagus, and peptic strictures. In recent years, diagnostic approaches to GERD have evolved, with the updated Lyon Consensus 2.0 and the 2020 Seoul Consensus providing more structured, evidence-based criteria. These include not only conventional endoscopic and pH-monitoring findings but also impedance-based parameters such as the mean nocturnal baseline impedance (MNBI) and the post-reflux swallow-induced peristaltic wave (PSPW) index, which enhance diagnostic accuracy and allow better phenotyping of GERD. In terms of treatment, lifestyle modification remains the cornerstone of GERD management and is essential for reducing long-term dependence on pharmacologic therapy. Proton pump inhibitors (PPIs) are the mainstay of pharmacologic treatment, and their effectiveness can be improved through modified-release or immediate-release buffered formulations. Recently, potassium-competitive acid blockers (P-CABs) such as tegoprazan, fexuprazan, and zastaprazan have emerged as effective alternatives to PPIs, offering advantages such as rapid onset of action, prolonged acid suppression, and more predictable pharmacokinetics, particularly in East Asian populations. However, concerns remain regarding long-term safety, including the risk of hypergastrinemia. This review summarizes recent advances in GERD diagnosis and treatment, highlighting the importance of individualized management strategies that incorporate updated diagnostic criteria and the evolving pharmacologic landscape.

Keywords: Gastroesophageal reflux disease, Seoul Consensus, Lyon Consensus, Proton pump inhibitors, Potassium-competitive acid blockers

Introduction

Gastroesophageal reflux disease (GERD) is a prevalent gastrointestinal disorder defined by the retrograde movement of gastric contents into the esophagus, resulting in bothersome symptoms that can markedly diminish patients' quality of life. As a chronic and often relapsing condition, GERD is associated with complications including esophageal erosions, strictures, and the development of Barrett's esophagus [1]. In recent years, the incidence of GERD has risen sharply in Korea, contributing to its growing relevance in daily clinical practice [2]. The persistent nature of the disease, its tendency to recur, and its potential for long-term complications underscore the importance of timely diagnosis and evidence-based therapeutic strategies [2,3]. This review provides an updated overview of recent advances in diagnostic evaluation and therapeutic approaches to GERD, aiming to support clinical decision-making based on contemporary evidence.

Diagnosis of GERD

GERD Symptom Questionnaires

Standardized symptom-based questionnaires serve as valuable tools to enhance the diagnostic accuracy of GERD and to help determine appropriate candidates for acid-suppressive therapy. Among the most widely validated instruments are the Gastroesophageal Reflux Disease Questionnaire (GerdQ) and the Reflux Disease Questionnaire (RDQ), both of which have been utilized across diverse clinical settings [4,5]. Additional tools, including the GERD Symptom Assessment Scale (GSAS) and the Frequency Scale for the Symptoms of GERD (FSSG), have also shown utility in select patient populations [6-8].

In a validation study of the Korean version of the GerdQ, a cutoff score of ≥ 8 yielded a sensitivity of 64.9% (95% CI, 56.2–73.7%) and a specificity of 71.4% (95% CI, 56.5–86.4%), with an area under the receiver operating characteristic (ROC) curve of 0.741 (standard error 0.042). The positive predictive value was notably high at 88.1% (95% CI, 81.2–95.0%), whereas the negative predictive value was relatively modest at 38.5% (95% CI, 26.2–50.3%) [9].

Proton Pump Inhibitor (PPI) Test

Heartburn and regurgitation, the hallmark symptoms of GERD, have demonstrated moderate diagnostic accuracy, with a reported sensitivity of approximately 62% and specificity of 67% [10]. The proton pump inhibitor (PPI) test, which entails a short course of empiric high-dose PPI therapy followed by an evaluation of symptom response, has been widely adopted as a practical diagnostic tool. A meta-analysis of 17 studies reported a pooled sensitivity of 78% (95% CI, 71–84%) and a specificity of 40% (95% CI, 31–48%) for the PPI test [11]. Importantly, neither dosage (standard vs. high dose) nor treatment duration (< 2 weeks vs. ≥ 2 weeks) significantly influenced diagnostic performance. Although the diagnostic utility of the PPI test may be limited in individuals presenting with atypical or extraesophageal manifestations, it remains a cost-effective and convenient strategy, especially in settings where 24-hour pH-impedance monitoring is inaccessible. Recently, trials evaluating potassium-competitive acid blockers (P-CABs) as an alternative empirical diagnostic approach have been introduced [12], but supporting clinical evidence remains insufficient [13].

Upper Endoscopy

The Lyon Consensus 2.0, published in 2023, provides an updated framework for the diagnostic classification of GERD

based on the strength of objective evidence [14]. It categorizes findings into conclusive, borderline, and negative for GERD. Conclusive evidence includes an acid exposure time (AET) greater than 6% on ambulatory pH monitoring and specific endoscopic findings such as erosive esophagitis of Los Angeles (LA) grade B or higher, Barrett's esophagus, and peptic strictures. Conversely, findings such as LA grade A esophagitis, borderline AET (4–6%), and abnormal impedance parameters (e.g., low mean nocturnal baseline impedance or post-reflux swallow-induced peristaltic wave index) are considered suggestive but not definitive. These refined criteria aim to reduce diagnostic ambiguity and guide more evidence-based management strategies [14].

Accordingly, erosive esophagitis classified as LA grades B, C, or D, Barrett's esophagus, and peptic strictures are now recognized as conclusive endoscopic evidence for GERD diagnosis [14]. In contrast, LA grade A esophagitis represents a borderline finding that cannot independently confirm the diagnosis (Fig. 1). Endoscopic evaluation also remains essential to exclude other esophageal disorders such as eosinophilic esophagitis or malignancy [14].

Esophageal Manometry and Its Diagnostic Utility in GERD

Although esophageal manometry does not directly detect reflux episodes, it is an essential diagnostic adjunct in the evaluation of lower esophageal sphincter (LES) function and esophageal body motility, both of which can provide supportive evidence for GERD [15]. According to recommendations from the American Gastroenterological Association, esophageal manometry should not be used as a standalone test for GERD diagnosis. Rather, it serves two primary roles: (1) ensuring accurate localization of the pH probe for 24-hour reflux monitoring and (2) assessing esophageal motility prior to anti-reflux interventions such as fundoplication [16].

Findings such as abnormal esophagogastric junction (EGJ) morphology or weak peristalsis on high-resolution manometry (HRM) may be suggestive of refractory GERD, particularly in patients who do not achieve symptom resolution despite adequate PPI therapy. Furthermore, manometry is invaluable in differentiating other potential diagnoses in patients with PPI-refractory symptoms. Studies have shown that up to 30% of such individuals may ultimately be diagnosed with alternative conditions, including functional heartburn, rumination syndrome, or achalasia [17]. HRM is especially critical for detecting major esophageal motility disorders such as achalasia, distal esophageal spasm, and hypercontractile (jackhammer) esophagus.

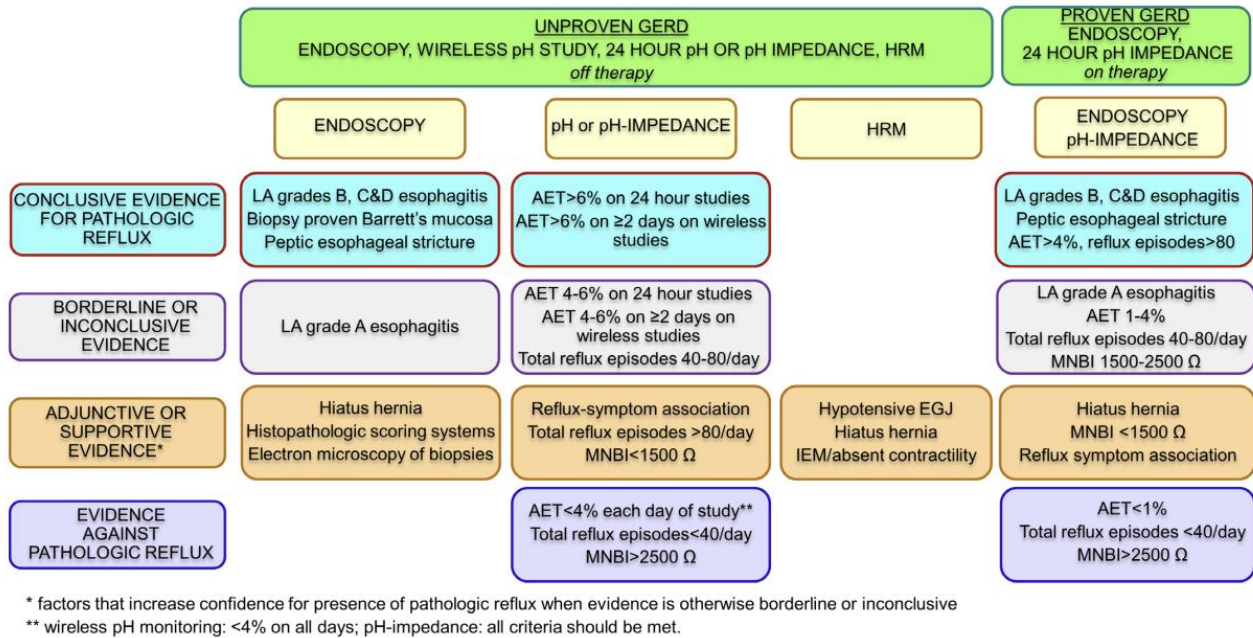


Fig. 1. Contemporary Diagnostic Criteria for GERD Based on the Lyon Consensus 2.0.

The Lyon Consensus 2.0 categorizes objective findings into conclusive, borderline, and negative evidence for GERD. Conclusive evidence includes acid exposure time (AET) > 6%, Los Angeles grade B–D esophagitis, Barrett's esophagus, and peptic strictures. Borderline findings include AET 4–6%, LA grade A, low mean nocturnal baseline impedance (MNBI), or abnormal post-reflux swallow-induced peristaltic wave (PSPW) index. Normal AET (<4%) with normal MNBI and PSPW suggests absence of GERD. Reproduced with permission from [14].

24-hour Ambulatory pH-Impedance Monitoring

1) Acid Exposure Time and Its Diagnostic Significance

AET defined as the percentage of the total monitoring period during which the intra-esophageal pH is below 4, is considered the most reliable and reproducible metric for quantifying pathologic acid reflux [15]. An AET value of less than 4% is indicative of physiological acid exposure, while a value greater than 6% confirms pathologic reflux. Values falling between 4% and 6% are interpreted as indeterminate and require correlation with adjunctive objective parameters, such as the number of reflux episodes and mean nocturnal baseline impedance (MNBI). Interestingly, the 2020 Seoul Consensus recommends a slightly lower diagnostic threshold for Asian populations, suggesting that AET values exceeding 4% may already reflect abnormal acid exposure in this demographic [2].

2) Emerging Impedance-based Metrics

The 2020 Seoul Consensus has highlighted the value of newly established impedance-based parameters, particularly baseline impedance (MNBI) and the post-reflux swallow-induced peristaltic wave (PSPW) index, in enhancing the diagnostic accuracy of GERD [2].

Baseline impedance serves as an indirect marker of esopha-

geal mucosal integrity by reflecting the permeability of the epithelial barrier. Reduced baseline impedance is associated with dilation of intercellular spaces and disruption of epithelial tight junctions. Values below 500 ohms may indicate mucosal inflammation or structural changes such as fibrosis, often seen in conditions including Barrett's esophagus, eosinophilic esophagitis, and esophageal motility disorders [18]. Because impedance values can fluctuate throughout the day due to swallowing and food intake, MNBI is considered more reliable. MNBI is typically decreased in patients with erosive reflux disease (ERD) and non-erosive reflux disease (NERD), whereas it remains relatively preserved in individuals with functional heartburn, suggesting intact mucosal integrity [19].

The PSPW represents a secondary esophageal clearance response to reflux, occurring as a peristaltic wave initiated by a swallow within approximately 30 seconds following a reflux episode (Fig. 2) [20]. It is identified by a forward drop in impedance across multiple channels. The PSPW index, calculated by dividing the number of PSPW events by the total number of reflux episodes [21], is consistently lower in patients with erosive esophagitis and hypersensitive esophagus, while patients with functional heartburn tend to retain a higher PSPW index, indicating more effective reflux clearance (Fig. 3) [22].

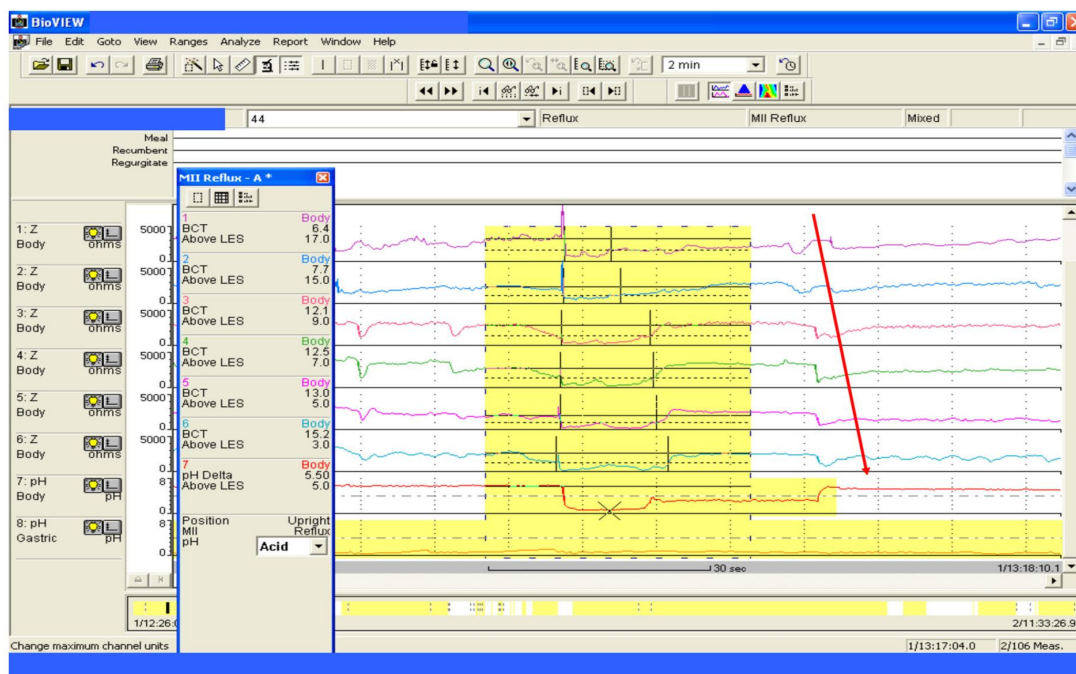


Fig. 2. Post-reflux swallow peristaltic wave

An acid reflux episode is characterized by a forward (antegrade) movement of a bolus from the distal to the proximal esophagus, typically occurring within 30 seconds (indicated by the red arrow). Reproduced with permission from [20].

Treatment of GERD

Lifestyle Modifications

Lifestyle modification remains the foundational and most essential approach in the management of GERD [23,24]. From a pathophysiological standpoint, it is critical to avoid behaviors that either elevate intra-abdominal pressure or trigger transient LES relaxation. Risk factors that increase abdominal pressure include poor mastication, rapid or excessive food intake, recumbency immediately after meals, and central obesity related to visceral fat accumulation. In contrast, substances such as alcohol, tobacco, and caffeine are known to promote transient LES relaxation [25].

It is crucial that clinicians assess patients' lifestyle habits and counsel them on the potential long-term consequences of untreated behavioral risk factors. Failure to implement lifestyle changes often leads to prolonged dependence on acid-suppressive pharmacotherapy. Practical recommendations include remaining upright for at least one hour postprandially, consuming smaller and slower meals, and limiting or eliminating alcohol, caffeine, and smoking. Additionally, patients are encouraged to elevate the head of the bed and adopt a left lateral decubitus position while sleeping, which facilitates gastric emptying and reduces the likelihood of reflux episodes [26].

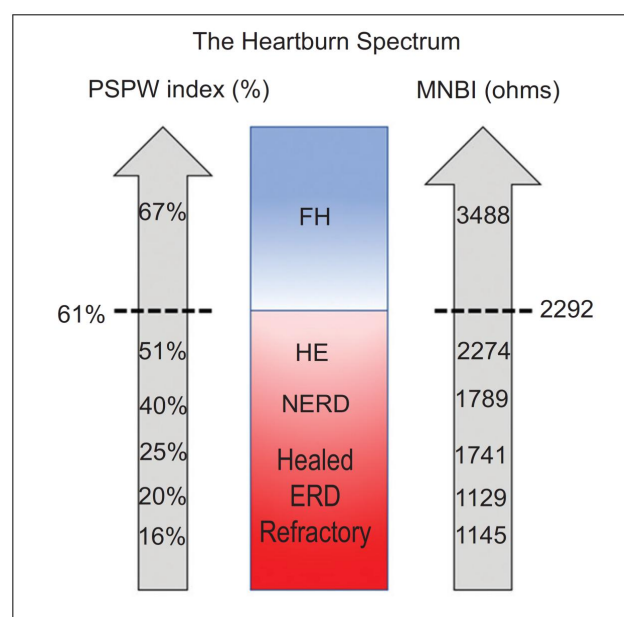


Fig. 3. Median values and cutoff thresholds of PSPW index and MNBI across different diagnostic categories within the heartburn spectrum. Dashed lines indicate the cutoff values. ERD, erosive reflux disease; FH, functional heartburn; HE, hypersensitive esophagus; MNBI, mean nocturnal baseline impedance; NERD, non-erosive reflux disease; PSPW, post-reflux swallow induced peristaltic wave. Reproduced from [22] under CC BY-NC 4.0.

A summary of key lifestyle recommendations is presented in [Table 1](#), which highlights the target mechanisms, common risk behaviors, and specific patient education points aimed at reducing acid exposure and enhancing esophageal protection. Furthermore, chronic suppression of gastric acid may impair its physiological antimicrobial function, potentially increasing the risk of gastrointestinal infections and aspiration pneumonia. For this reason, efforts to minimize the long-term use of PPIs or P-CABs through effective lifestyle modification are not merely advisable, but essential to sustainable GERD care [27].

Strategies to Enhance the Effectiveness of Proton Pump Inhibitors (PPIs)

Given the chronic and recurrent nature of GERD, many patients require not only initial treatment but also long-term maintenance therapy. As such, strategies to optimize the therapeutic efficacy of PPIs are of clinical importance [27]. Two key approaches have been developed to enhance acid suppression and improve patient adherence.

The first involves modified-release PPI formulations, such as dexlansoprazole, the R-enantiomer of lansoprazole. This agent employs dual delayed-release technology, resulting in a sustained drug release profile that allows for once-daily dosing regardless of meal timing [28]. This pharmacokinetic advantage may be particularly beneficial for patients who struggle with the pre-meal timing required by conventional PPIs or who take multiple medications postprandially. However, the extended-release profile of dexlansoprazole is associated with a slower onset of action compared to immediate-release PPI formulations.

A second strategy focuses on immediate-release PPIs co-formulated with buffering agents, such as sodium bicarbonate, to accelerate drug absorption. These formulations neutralize intragastric acid rapidly, thereby protecting the PPI from acid degradation and promoting quicker uptake in the proximal duodenum. For example, the esomeprazole/sodium bicarbon-

ate combination (40/800 mg or 20/800 mg) achieves a peak plasma concentration within 30 minutes, compared to 1.5 hours for standard esomeprazole, and thus may offer faster symptom relief [29]. Importantly, this formulation has demonstrated a safety profile comparable to that of conventional PPIs. One limitation of such combinations is the increased tablet size due to the buffering component. To mitigate this, newer formulations containing reduced sodium bicarbonate content have been developed. These versions are approximately 38% smaller in size while maintaining bioequivalence to the original high-dose combinations, which may enhance patient adherence [30].

Role of Potassium-Competitive Acid Blockers (P-CABs)

P-CABs are no longer viewed as novel agents in the management of GERD; rather, they have become established therapeutic options with unique pharmacologic properties that distinguish them from conventional PPIs [13]. Unlike most PPIs, which require acid activation and pre-prandial dosing to irreversibly inhibit active proton pumps, P-CABs exert their effect independently of gastric acidity. They bind reversibly to the H^+/K^+ -ATPase, offering both rapid onset and sustained acid suppression by inhibiting not only active but also newly synthesized proton pumps [31]. Another notable distinction lies in their metabolism. While PPIs are primarily metabolized via the CYP2C19 pathway, rendering their efficacy vulnerable to genetic polymorphisms, P-CABs are metabolized predominantly through CYP3A4, resulting in more predictable pharmacokinetics. This difference is particularly significant in East Asian populations, where the prevalence of CYP2C19 loss-of-function alleles is relatively high. In such cases, P-CABs may provide more consistent therapeutic responses and are especially advantageous in patients who are also receiving antiplatelet therapy [32]. The pharmacologic differences between PPIs and P-CABs are summarized in [Table 2](#). Despite these advantages, concerns have emerged regarding hypergastrinemia associated with the

Table 1. Summary of Lifestyle Modification in GERD Management

Category	Details
Pathophysiological Targets	Avoid increased intra-abdominal pressure and transient LES relaxation
Risk Behaviors (Increased Pressure)	Poor chewing, rapid eating, overeating, lying down post-meal, abdominal obesity
Risk Factors (LES Relaxation)	Alcohol, tobacco, caffeine
Assessment	Clinicians should identify modifiable behaviors
Patient Education	Avoid lying down within 1 hour after meals, reduce portion size, eat slowly, avoid alcohol/tobacco/caffeine
Positioning Advice	Elevate upper body, sleep on the left side
Rationale	Lifestyle modification reduces long-term need for medication and lowers infection risk from acid suppression

Table 2. Pharmacologic Differences Between P-CABs and PPIs

Characteristic	P-CAB	PPI
Mechanism of action	Acts directly without need for acid activation	Requires activation in acidic environment (prodrug form)
Binding to proton pump	Reversible	Irreversible
Target of inhibition	Both active and inactive proton pumps	Only active proton pumps
Stability in acid	Stable in gastric acid	Unstable in acidic environment
Half-life	Relatively long	Short
Meal dependency	Can be taken regardless of meals	Typically requires administration before meals
Metabolism pathway	Mainly via CYP3A4	Mainly via CYP2C19
Genetic variability	Minimal influence of genotype	High variability, especially in East Asians
Dosing convenience	Flexible timing improves compliance	Strict timing before meals is needed

strong and prolonged acid suppression characteristic of P-CABs. As such, further long-term safety data is needed to determine whether these agents carry distinct risks compared to PPIs.

In Korea, three P-CABs are currently available for clinical use: tegoprazan, fexuprazan, and the more recently introduced zastaprazan. Pharmacokinetic studies indicate that tegoprazan achieves peak plasma concentrations within 0.5–1 hour, fexuprazan within 1.75–3.5 hours, and zastaprazan also appears to be rapidly absorbed, although robust real-world data remain limited. Thus, tegoprazan may offer a relatively faster onset of action, although immediate-release PPI formulations such as esomeprazole/sodium bicarbonate also reach peak levels within 0.5 hours and may provide comparable or even faster symptom relief in acute settings [29,33,34]. P-CABs are additionally characterized by longer half-lives, contributing to their effectiveness in controlling nocturnal acid breakthrough. For instance, tegoprazan exhibits a half-life of approximately 4.1 hours, whereas fexuprazan extends to nearly 9.7 hours. Although pharmacodynamic data on zastaprazan remain preliminary, early studies suggest that its duration of action is comparable [35].

Conclusion

GERD is a chronic and multifactorial disorder that requires a comprehensive diagnostic and therapeutic approach. Recent advancements, including updated diagnostic frameworks such as the Lyon Consensus 2.0 and the Seoul Consensus, have emphasized the importance of integrating pH-impedance metrics, esophageal mucosal integrity markers, and symptom association parameters to improve diagnostic precision.

In terms of treatment, lifestyle modification remains the cornerstone of GERD management and should be actively addressed to minimize unnecessary long-term pharmacologic therapy. Among pharmacologic options, PPIs continue to be

first-line agents, and their efficacy can be further enhanced through modified-release or immediate-release buffered formulations. The emergence of P-CABs, including tegoprazan, fexuprazan, and zastaprazan, has provided clinicians with alternative options offering rapid onset, prolonged duration, and more consistent acid suppression, especially in populations with genetic variations in drug metabolism.

Ultimately, individualized treatment strategies—grounded in symptom patterns, diagnostic findings, pharmacologic profiles, and patient preference—are essential for optimizing clinical outcomes. By understanding and applying the evolving concepts in GERD diagnosis and therapy, clinicians can offer more precise, effective, and patient-centered care.

In this context, it is also important to consider the diagnostic environment and the accessibility of available tools. In primary care settings, where advanced diagnostic tools may not be readily available, symptom-based questionnaires and empiric PPI trials remain pragmatic initial approaches. In contrast, pH-impedance monitoring, mucosal impedance, and manometry are more feasible in tertiary care centers. Moreover, emerging diagnostic techniques such as endoscopic mucosal impedance and novel pharmacologic agents like P-CABs show great promise for patients who are unresponsive to conventional treatments. Ongoing research will clarify their role in advancing the personalized management of GERD.

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Conflict of interest

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