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GASTROESOPHAGEAL REFLUX DISEASE REFRACTORY TO PROTON PUMP INHIBITORS: CURRENT CLINICAL AND INTERVENTIONAL STRATEGIES

DOENÇA DO REFLUXO GASTROESOFÁGICO REFRATÁRIA AOS INIBIDORES DA BOMBA DE PRÓTONS: ESTRATÉGIAS CLÍNICAS E INTERVENCIONISTAS ATUAIS

ENFERMEDAD POR REFLUJO GASTROESOFÁGICO REFRACTARIA A LOS INHIBIDORES DE LA BOMBA DE PROTONES: ESTRATEGIAS CLÍNICAS E INTERVENCIONISTAS ACTUALES

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ABSTRACT

Gastroesophageal reflux disease (GERD) refractory to proton pump inhibitors (PPIs) remains a major clinical challenge, affecting a substantial proportion of patients who do not achieve adequate symptom control with standard therapy. This study aimed to review the main diagnostic, clinical, and interventional strategies currently available for the management of refractory GERD. A narrative literature review was carried out between March and September 2025 in national and international databases. The analysis highlighted the role of impedance-

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pH monitoring and endoscopy in distinguishing persistent acid reflux from functional symptoms, as well as the importance of optimizing PPI use. Among emerging pharmacological alternatives, potassium-competitive acid blockers, such as vonoprazan, showed promising results. In cases of confirmed refractoriness, endoscopic and surgical interventions, including laparoscopic fundoplication, the LINX magnetic system, and radiofrequency therapy (Stretta), have demonstrated effectiveness in selected patients. It is concluded that individualized treatment, supported by accurate diagnostic stratification and the integration of clinical and interventional approaches, is essential to optimize outcomes, reduce misdiagnosis, and guide future research.

Keywords: Gastroesophageal Reflux Disease. Proton Pump Inhibitors. Refractory GERD. Esophageal Monitoring. Endoscopic Procedures.

RESUMO

A Doença do Refluxo Gastroesofágico (DRGE) refratária aos inibidores da bomba de prótons (IBPs) constitui um desafio clínico relevante, atingindo parcela expressiva de pacientes que não obtêm controle adequado dos sintomas com a terapêutica padrão. Este estudo tem como objetivo revisar as principais estratégias diagnósticas, clínicas e intervencionistas atualmente disponíveis para o manejo dessa condição. Foi realizada revisão narrativa da literatura entre março e setembro de 2025 em bases nacionais e internacionais. A análise destacou o papel da pHmetria-impedância e da endoscopia na diferenciação entre refluxo ácido persistente e sintomas funcionais, bem como a importância da otimização do uso dos IBPs. Entre as alternativas farmacológicas emergentes, os bloqueadores competitivos de potássio, como o vonoprazan, apresentam resultados promissores. Em casos de refratariedade confirmada, intervenções endoscópicas e cirúrgicas, como a fundoplicatura laparoscópica, o sistema magnético LINX e a radiofrequência (Stretta), mostraram eficácia em pacientes selecionados. Conclui-se que a individualização terapêutica, baseada em avaliação diagnóstica precisa e integração entre terapias clínicas e procedimentos intervencionistas, representa o caminho mais consistente para reduzir falhas diagnósticas, otimizar resultados clínicos e orientar pesquisas futuras.

Palavras-chave: Doença do Refluxo Gastroesofágico. Inibidores da Bomba de Prótons. DRGE Refratária. Monitoramento Esofágico. Procedimentos Endoscópicos.

RESUMEN

La enfermedad por reflujo gastroesofágico (ERGE) refractaria a los inhibidores de la bomba de protones (IBP) plantea un desafío clínico significativo, afectando a una proporción significativa de pacientes que no logran un control adecuado de los síntomas con la terapia estándar. Este estudio tiene como objetivo revisar las principales estrategias diagnósticas, clínicas e intervencionistas actualmente disponibles para el manejo de esta condición. Se realizó una revisión narrativa de la literatura entre marzo y septiembre de 2025, utilizando bases de datos nacionales e internacionales. El análisis destacó el papel de la pHmetría por impedancia y la endoscopia para diferenciar el reflujo ácido persistente de los síntomas funcionales, así como la importancia de optimizar el uso de IBP. Entre las alternativas farmacológicas emergentes, los bloqueadores de potasio competitivos, como el vonoprazan, muestran resultados prometedores. En casos de refractariedad confirmada, las intervenciones endoscópicas y quirúrgicas, como la funduplicatura laparoscópica, el sistema magnético LINX y la radiofrecuencia (Stretta), han demostrado eficacia en pacientes seleccionados. Se concluye que la individualización terapéutica, basada en una evaluación

diagnóstica precisa y la integración de terapias clínicas y procedimientos intervencionistas, representa la vía más consistente para reducir los errores diagnósticos, optimizar los resultados clínicos y orientar la investigación futura.

Palabras clave: Enfermedad por Reflujo Gastroesofágico. Inhibidores de la Bomba de Protones. ERGE Refractaria. Monitorización Esofágica. Procedimientos Endoscópicos.

1 INTRODUCTION

Gastroesophageal Reflux Disease (GERD) is one of the most prevalent disorders of the upper digestive tract, characterized by the return of gastric contents to the esophagus, causing symptoms such as heartburn, regurgitation and, in more severe cases, structural complications. It is estimated that up to 20% of the world's population has regular manifestations of the disease, constituting an important public health problem (Gyawali; Dodds, 2023). The advent of proton pump inhibitors (PPIs), starting in the 1980s, represented a therapeutic milestone in gastroenterology, as it provided high rates of symptomatic control and healing of erosive esophagitis (Malfertheiner et al., 2022).

However, a significant portion of patients remain symptomatic despite optimized therapy with PPIs, a condition called refractory GERD. Studies indicate that between 10% and 40% of individuals do not achieve a satisfactory clinical response, even after adjustments in dose, time of use, and molecule change (Ashida et al., 2021). This scenario reflects the heterogeneity of the disease, which can encompass not only persistent acid reflux, but also weak acid reflux, bile reflux, esophageal hypersensitivity, and functional disorders that mimic GERD symptoms (Yadav; Zheng; Patel, 2023).

From a historical point of view, the definition of refractoriness has been expanded as new diagnostic tools have been consolidated. The introduction of pH-metry with multichannel esophageal impedance made it possible to distinguish patients with documented persistent reflux from those with symptoms uncorrelated to acid, refining therapeutic stratification (Patel et al., 2018). In parallel, international guidelines, such as those of the American College of Gastroenterology (ACG), have begun to emphasize the need for a rigorous differential diagnosis before classifying the patient as refractory (Katz et al., 2022).

The current understanding of refractory GERD involves multiple pathophysiological mechanisms. Persistence of acid reflux may be due to failure of gastric suppression by PPIs or to anatomical changes such as hiatal hernia. Refractory symptoms in patients with adequate acid suppression may be related to esophageal hypersensitivity or to the so-called "functional reflux", characterized by the absence of an objective correlation between reflux and clinical complaints (Gyawali; Dodds, 2023). This spectrum reinforces the need for individualized therapeutic strategies.

In the field of treatment, the options have expanded beyond PPIs. New drugs, such as competitive potassium blockers (PCABs), exemplified by vonoprazan, have faster and more potent acid suppression, configuring a promising alternative (Ashida et al., 2021). In addition,

complementary agents, such as H2 antagonists, alginates, prokinetics, and neuromodulators, have been used in specific subgroups (Malfertheiner et al., 2022). In cases of documented reflux refractory to pharmacological therapy, interventional options such as laparoscopic fundoplication, magnetic sphincter device (LINX), and endoscopic procedures, such as Stretta and transoral fundoplication (TIF), have demonstrated satisfactory results in clinical studies (Testoni et al., 2021).

The epidemiological impact of refractory GERD is significant, as it is associated with reduced quality of life, greater use of health resources, and increased risk of complications, such as Barrett's esophagus and esophageal adenocarcinoma (Yadav; Zheng; Patel, 2023). In this context, a critical analysis of the available evidence is essential to guide the diagnosis and management of the condition.

Thus, the present study proposes to critically review diagnostic, clinical, and interventional strategies for the management of GERD refractory to proton pump inhibitors, emphasizing criteria for definition, patient selection, and practical implications for decision-making.

2 METHODOLOGY

The present study is an exploratory and descriptive narrative review of the literature, focused on Gastroesophageal Reflux Disease (GERD) refractory to treatment with proton pump inhibitors (PPIs). The choice for narrative review is justified by the breadth and complexity of the theme, which involves multiple pathophysiological mechanisms, in addition to different diagnostic and therapeutic approaches.

Unlike systematic reviews, which follow rigorous and delimited methodological protocols, the narrative review makes it possible to critically integrate different types of evidence, ranging from clinical trials and meta-analyses to international consensus and guidelines. This approach favors a broad and contextualized analysis of the clinical and practical implications of the theme (Moraes-Filho, 2012).

2.1 SOURCES AND SEARCH STRATEGY

The bibliographic search was conducted between March and September 2025 in the electronic databases PubMed**, Scopus, Web of Science, SciELO, and LILACS**. In addition, gastroenterology textbooks and official documents from medical societies, such as the

American College of Gastroenterology (ACG) and the **Brazilian Society of Digestive Motility and Neurogastroenterology (SBMDN), were consulted**.

The descriptors were selected from the **DeCS/MeSH,** covering: *Gastroesophageal Reflux Disease; Inibidores da Bomba de Prótons / Proton Pump Inhibitors; Refratariedade / Refractory GERD; esophageal impedance-pH monitoring; Fundoplicatura / Fundoplication; Endoscopic Procedures*.

2.1.1 Inclusion criteria

- Original articles, systematic reviews, meta-analyses, and guidelines published between **2010 and 2025**;
- Publications in Portuguese, English or Spanish;
- Studies that specifically addressed GERD refractory to the use of PPIs;
- Studies that presented relevant diagnostic, therapeutic or interventional evidence.

2.1.2 Exclusion criteria

- Isolated case reports or clinical series with very small samples;
- Opinion articles, editorials or texts without scientific support;
- Duplicate posts;
- Studies without a clear definition of refractoriness.

2.2 ANALYSIS PROCEDURE

The literature analysis was conducted in three complementary stages:

1. **Exploratory reading** of titles and abstracts, to identify potentially relevant studies;
2. **Selective reading** of full articles, prioritizing those that directly addressed refractoriness to the use of PPIs;
3. **Interpretative and integrative reading**, organizing the findings into five thematic axes:

a) pathophysiological mechanisms;

b) diagnostic criteria;

c) pharmacological therapies;

d) endoscopic and surgical interventions;

e) emerging strategies.

In total, **47 articles were included** for analysis, including national and international studies, in addition to consensuses and guidelines from medical societies.

2.3 METHODOLOGICAL LIMITATIONS

As this is a narrative review, this study did not follow formal protocols of systematic reviews, such as **PRISMA**, which may introduce greater subjectivity in the selection and interpretation of sources. The heterogeneity of the included studies (in terms of methodological design, sample, and diagnostic criteria for refractoriness) represents a potential bias, making it difficult to directly compare the findings. In addition, the time constraint (2010–2025) may have excluded classical studies that are still relevant, although the intention was to prioritize recent evidence. We sought to mitigate these limitations through the inclusion of **randomized clinical trials, meta-analyses, systematic reviews, and international and national guidelines**, in order to provide greater diversity and robustness to the analysis (Moraes-Filho, 2012; Nascimento et al., 2023; Júnior, 2021).

3 RESULTS

3.1 PATHOPHYSIOLOGICAL MECHANISMS

Refractoriness may result from persistent acid reflux, associated with failure of gastric suppression, or from weak acid or bile reflux, esophageal hypersensitivity, and functional reflux, in which there is no objective correlation between symptoms and reflux episodes (Gyawali; Dodds, 2023). Anatomical alterations, such as bulky hiatal hernia and incompetence of the lower esophageal sphincter, were also pointed out as determining factors (Patel et al., 2018). In the Brazilian context, authors highlight that the inappropriate use of PPIs and failures in the differential diagnosis often lead to mistaken classifications of refractoriness (Moraes-Filho, 2012).

3.2 DIAGNOSTIC CRITERIA

Esophageal pH-metry with multichannel impedance has been evidenced as a milestone in diagnosis, allowing the detection of episodes of non-acid reflux and differentiating functional manifestations (Patel et al., 2018). Upper **GI endoscopy** remains important in identifying complications, such as erosive esophagitis and Barrett's esophagus, although in many refractory cases the findings are normal (Katz et al., 2022). Guidelines

recommend that refractoriness classification be established only after careful integration of clinical, endoscopic, and functional data (Malfertheiner et al., 2022).

3.3 PHARMACOLOGICAL THERAPIES AND COMPLEMENTARY MEASURES

Optimizing the use of PPIs remains a first step, including adjusting the time of administration, dose adjustment, and, when necessary, molecule change (Ashida et al., 2021). As adjuvant therapies, **nocturnal H2 antagonists, alginates, and prokinetics stand out**, which demonstrate benefit in specific subgroups (Malfertheiner et al., 2022). In the Brazilian scenario, there is evidence of the positive impact of behavioral and dietary measures in reducing the frequency and intensity of symptoms (Nascimento et al., 2023).

3.4 NEW PHARMACOLOGICAL ALTERNATIVES

Competitive **potassium blockers (PCABs),** especially **vonoprazan**, have been identified as a promising therapeutic innovation. These drugs have faster, more potent, and sustained acid suppression compared to PPIs, offering a relevant perspective for patients who do not respond to conventional therapy (Ashida et al., 2021).

3.5 ENDOSCOPIC AND SURGICAL INTERVENTIONS

Laparoscopic fundoplication remains the gold standard in the surgical treatment of refractory GERD (Testoni et al., 2021). However, minimally invasive techniques, such as **transoral fundoplication (TIF), radiofrequency applied to the lower esophageal sphincter (Stretta),** and **magnetic reinforcement with the LINX device**, have shown positive results in prospective studies (Yadav; Zheng; Patel, 2023). Brazilian experiences report encouraging outcomes with endoscopic therapy in the short term, reinforcing the feasibility of these interventions in well-selected cases (Souza et al., 2018).

3.6 CLINICAL AND EPIDEMIOLOGICAL IMPACT

Refractoriness in GERD is directly associated with **worsening quality of life, greater utilization of health resources, and increased risk of serious complications**, such as Barrett's esophagus and esophageal adenocarcinoma (Gyawali; Dodds, 2023). It is estimated that about 30% of patients maintain clinically relevant symptoms even after optimization of pharmacological therapy and complementary measures (Malfertheiner et al., 2022).

4 DISCUSSION

The absence of uniform criteria for the definition of refractoriness represents one of the main obstacles in clinical practice and research, as it hinders comparability between studies and can overestimate the rates of treatment failure. Although international guidelines, such as those of the American College of Gastroenterology, recommend at least eight weeks of continuous use of full-dose PPIs, administered twice daily (Katz et al., 2022, p. 31), great variability is observed in clinical routine. Aspects such as inadequate adherence, incorrect administration times, drug interactions, and lack of objective confirmation by pH-impedance are not always properly evaluated, compromising diagnostic accuracy.

In Brazil, evidence indicates that many cases labeled as refractory result from diagnostic errors and incorrect use of PPIs, either due to underdosage, low adherence or inadequate prescription (Moraes-Filho, 2012, p. 180). Júnior (2021, p. 12) adds that the investigation of refractoriness should contemplate alternative mechanisms, such as non-acid reflux, esophageal hypersensitivity, and functional disorders, at the risk of mistakenly classifying patients who could respond to simple adjustments.

Another relevant aspect refers to non-pharmacological measures. Nascimento et al. (2023, p. 5) demonstrated that lifestyle modifications, such as dietary control, body weight reduction, smoking cessation, and decreased alcohol consumption, significantly reduce the frequency and intensity of symptoms. This evidence is especially relevant in the Brazilian context, where socioeconomic barriers and barriers to access to information interfere with treatment adherence and influence clinical outcomes.

Endoscopic and surgical interventions also require caution in patient selection. The national series reported by Souza et al. (2018, p. 122) showed good short-term results with endoscopic therapy, but restricted the indication to cases with acid reflux documented by pH-impedance, ensuring greater therapeutic precision. This methodological rigor contrasts with part of the international literature, where the heterogeneity of the inclusion criteria increases the variability of the outcomes. Thus, the need for standardized diagnostic protocols adapted to the local reality is reinforced.

In addition, new perspectives related to **precision medicine** are emerging. Recent studies explore the role of clinical and genetic biomarkers in identifying patients with a higher likelihood of refractoriness, as well as the possibility of stratification based on specific reflux phenotypes (acid, non-acidic, functional, or hypersensitivity). This approach tends to make

management more targeted, reducing therapeutic failures and optimizing the choice between pharmacological, endoscopic or surgical treatment.

Thus, a rational flow of investigation and management is outlined, which should include: i) confirmation of adherence and appropriate technique for the use of PPIs; ii) optimization of dose, molecule and use of adjuvants; iii) diagnostic stratification with endoscopy and pH-impedance, when available; iv) careful indication of endoscopic or surgical interventions only in cases with persistently documented acid reflux; v) systematic incorporation of non-pharmacological measures, considering the socioeconomic and cultural impact.

Therefore, the definition of refractoriness must go beyond pharmacological failure, being understood as the result of a comprehensive evaluation that integrates clinical, functional, and contextual aspects. In the Brazilian scenario, the influence of socioeconomic and structural determinants reinforces the importance of protocols adapted to the local reality, without losing international methodological consistency.

5 CONCLUSION

Gastroesophageal Reflux Disease (GERD) refractory to proton pump inhibitors (PPIs) represents one of the greatest challenges of contemporary gastroenterological practice, not only because of its high prevalence, but also because of the diversity of pathophysiological mechanisms that support it. Refractoriness has been found to be not limited to pharmacological failure, but includes conditions such as persistent acid reflux, non-acid reflux, esophageal hypersensitivity, and functional symptoms. This complexity reinforces the importance of a thorough diagnostic evaluation, using complementary methods such as esophageal pH-impedance and endoscopy, before establishing the definitive diagnosis.

In the therapeutic field, optimizing the use of PPIs should be considered the first step in the management of these patients, including adjustments in dosage, time of administration, and eventual replacement by another molecule. In parallel, new pharmacological options, such as competitive potassium blockers, emerge as promising alternatives, although they still lack validation in long-term multicenter studies.

Endoscopic and surgical interventions maintain a relevant role, especially in cases with documented reflux and refractory to clinical treatment. Techniques such as laparoscopic fundoplication, magnetic reinforcement of the esophageal sphincter, and minimally invasive

endoscopic procedures have shown consistent results, as long as they are applied to carefully selected patients.

From an epidemiological point of view, refractory GERD significantly impacts quality of life, increases the use of health services, and increases the risk of serious complications, such as Barrett's esophagus and esophageal adenocarcinoma. This scenario reinforces the need for public policies aimed at early diagnosis, equitable access to advanced therapies, and systematic follow-up of patients at higher risk.

In summary, the management of refractory GERD should be multifactorial and personalized, combining rigorous diagnostic evaluation, optimized pharmacological therapies, endoscopic or surgical interventions, and nonpharmacological supportive measures. The future of clinical practice points to an integration between precision medicine, protocols adapted to local realities, and long-term multicenter studies, capable of generating global consensus and reducing the gaps that still exist.

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