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REVIEW ARTICLE

Pharmacological treatment of gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) is a common condition affecting a significant portion of the global population. Pharmacological treatment primarily focuses on reducing acid secretion, protecting the esophageal mucosa, and relieving symptoms. This article reviews the main pharmacological groups used in GERD management, including proton pump inhibitors, potassium-competitive acid blockers, H2 receptor antagonists, antacids, alginates, and mucosal protectants. The mechanisms of action, efficacy, adverse effects, and clinical considerations of each therapeutic class are discussed.

Keywords: Treatment. Drugs. Gastroesophageal reflux disease.

Tratamiento farmacológico de la enfermedad por reflujo gastroesofágico

Resumen

La enfermedad por reflujo gastroesofágico (ERGE) es una condición común que afecta a una parte significativa de la población mundial. El tratamiento farmacológico se centra principalmente en reducir la secreción ácida, proteger la mucosa esofágica y aliviar los síntomas. Este artículo revisa los principales grupos farmacológicos utilizados en el manejo de la ERGE, incluyendo los inhibidores de la bomba de protones, los bloqueadores de ácido competitivos de potasio, los antagonistas H2, los antiácidos, los alginatos y los protectores de la mucosa. Se discuten los mecanismos de acción, la eficacia, los efectos adversos y las consideraciones clínicas de cada clase terapéutica.

Palabras clave: Tratamiento. Fármacos. Enfermedad por reflujo gastroesofágico.

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Introduction

Gastroesophageal reflux disease (GERD) is a chronic pathology characterized by the return of gastric contents toward the esophagus, which produces bothersome symptoms such as heartburn and regurgitation, affects quality of life, and may lead to complications[1-3]. Pharmacological treatment is the basis of its management, especially in moderate to severe forms of the disease[3,4].

Therapeutic options

Proton pump inhibitors

Proton pump inhibitors (PPIs) constitute the cornerstone in the pharmacological treatment of GERD. They have proven to be the most effective drugs for gastric acid suppression and for the healing of erosive esophagitis.

Classification

PPIs available clinically are classified as:

– Delayed-release PPIs: they have an enteric coating that dissolves at pH 5.5 in the duodenum. This group includes omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dexrabeprazole, and ilaprazole.
– Dual delayed-release PPIs: they are presented in granules with two enteric coatings; one dissolves at pH 5.5 in the duodenum and the other at pH 6.75 in the terminal ileum. Dexlansoprazole belongs to this group.
– Immediate-release PPIs: combination of 20 mg of omeprazole and 1100 mg of bicarbonate. In this formulation, the PPI does not have an enteric coating, and the bicarbonate buffers the acid, protecting the omeprazole molecule[4-6].

They all have similar mechanisms of action, although they differ slightly in their pharmacokinetics, hepatic metabolism, and relative potency.

Mechanism of action

PPIs act by irreversibly inhibiting the H^+/K^+ ATPase enzyme (proton pump) located in gastric parietal cells, which is responsible for the secretion of hydrochloric acid in the stomach. By covalently binding to this enzyme, PPIs suppress basal and stimulated acid secretion.

PPIs are prodrugs that require two protonations in the acidic environment of the parietal cell to transform into the active drug. They bind only to proton pumps activated by food. Therefore, they should be administered 30 to 60 minutes before breakfast or dinner. Their absorption is rapid, but their plasma half-life is short; in delayed-release PPIs, it is an average of 2 hours. In the case of dexlansoprazole, the dual release allows prolonging the plasma half-life up to 4 hours. Ilaprazole has a half-life of 5 hours.

PPIs are metabolized primarily in the liver by the CYP450 enzyme system, especially CYP2C19 and CYP3A4.

There is significant interindividual variability due to genetic polymorphisms of CYP2C19. In slow metabolizers, they may have higher plasma concentrations and more effect, and in ultrarapid metabolizers, they may have lower efficacy.

Rabeprazole and ilaprazole are the PPIs that have the least metabolism by the 2C19 isoenzyme[6].

The parameter to evaluate the clinical efficacy of an antisecretory agent in GERD is the ability to maintain intragastric pH above 4. Dexlansoprazole and esomeprazole maintain pH above 4 for up to 17 and 15 hours, respectively[7].

Table 1 lists the main pharmacokinetic differences and standard doses of PPIs.

Indications and doses in GERD[2-5]

– Erosive GERD: in grades A and B, a standard PPI dose is used for 8 weeks. In grades C and D, a double PPI dose is used for 8 weeks. Maintenance treatment can be with the "on-demand" regimen in mild varieties of esophagitis and with continuous treatment with standard dose in severe varieties.
– Non-erosive reflux disease: a standard PPI dose is recommended for 4 weeks and maintenance treatment with on-demand dosing.
– Barrett's esophagus: continuous PPI dose sufficient to keep the patient symptom-free is recommended.
– Extraesophageal manifestations of GERD: double PPI dose is recommended for 3 months and continuous maintenance therapy with standard dose.
– GERD in pregnancy: PPIs can be used in pregnancy. They have a classification B according to the Food and Drug Administration, except for omeprazole, which belongs to group C[3].

Adverse effects

PPIs are generally well tolerated, but their prolonged use has been associated with some adverse effects (Fig. 1), such as:

Table 1. Differences between proton pump inhibitors[6]

Drug	Plasma half-life (h)	Duration pH > 4 (h/day)	Usual dose (mg/day)
Omeprazole	0.5-1	10	20
Esomeprazole	1-1.5	13	20-40
Pantoprazole	1	10	40
Lansoprazole	1-1.5	12	30
Rabeprazole	1-1.5	12	20
Dexrabeprazole	1-2	13	10-20
Ilaprazole	5	17	10-20
Dexlansoprazole	1-2	17	30-60

– Enteric infections.
– Increased risk of community-acquired pneumonia.
– Malabsorption of vitamin B_{12}, magnesium, and calcium.
– Possible increased risk of bone fractures.
– Hypergastrinemia with prolonged use.
– Acute interstitial nephritis (rare, but serious).

Among these adverse effects, enteric infections are the only ones that have a clinically significant odds ratio (> 3)[8].

Criteria for deprescribing PPIs

Although they are effective, many patients continue using PPIs unnecessarily. It is recommended to periodically evaluate the need to continue treatment. Some criteria for deprescribing are:
– Sustained remission of symptoms (> 6 months).
– Absence of esophagitis upon discontinuation of treatment.
– Use in unconfirmed GERD that has responded to lifestyle changes.
– Patients who use them only as "gastric protection," without concomitant use of nonsteroidal anti-inflammatory drugs.

Withdrawal should be done gradually in patients with prolonged use to avoid a rebound effect of acid hypersecretion. In some cases, switching to an on-demand regimen or using H2 antagonists as bridge therapy may be possible[9].

Potassium-competitive acid blockers

Potassium-competitive acid blockers (P-CABs) are a new class of antisecretory drugs used in the treatment of GERD. Their mechanism of action consists of reversibly and competitively inhibiting H^+/K^+ ATPase in gastric parietal cells, the same therapeutic target as PPIs, but through a different mechanism[10-13].

Unlike PPIs, which need to be activated in an acidic environment, they are not prodrugs and exert their effect rapidly and sustainably, with greater consistency in gastric acid suppression[10-14].

Mechanism of action

P-CABs produce competitive inhibition of potassium at the proton pump H^+/K^+ ATPase. This prevents the exchange of potassium for hydrogen, which impedes the binding of hydrogen ions with chloride, preventing the formation of hydrochloric acid in the parietal cell[10-14].

The irreversible binding of P-CABs with H^+/K^+ ATPase makes it possible for these drugs to inhibit both active and inactive proton pumps in the resting phase of the parietal cell, which allows sustained acid inhibition from the first dose. Additionally, P-CABs are resistant to gastric acid, so they do not have an enteric coating and do not require administration with food[10-14].

Pharmacokinetic differences with PPIs

Table 2 presents the main differences between PPIs and P-CABs. Notably, P-CABs superconcentrate more than 100,000 times in the acidic space of the parietal cell, reversibly inhibit the proton pump, have a longer plasma half-life (up to 9 hours), and completely inhibit acid secretion from the first dose.

Additionally, P-CABs are metabolized by isoenzymes different from CYP2C19, thereby avoiding the polymorphisms of rapid or slow metabolizers, and have fewer drug interactions[10-14].

Table 3 presents the pharmacokinetic characteristics of different P-CABs[14]. In Mexico, tegoprazan and fexuprazan are available.

Clinical efficacy

Clinical trials have demonstrated that P-CABs are as effective as PPIs in the healing of erosive esophagitis and are more effective in cases of severe esophagitis. This superiority has also been observed in maintenance therapy in severe esophagitis. It has also been observed that they achieve a higher percentage of symptom-free patients in the first weeks of treatment. In erosive GERD, a standard P-CAB dose is used for

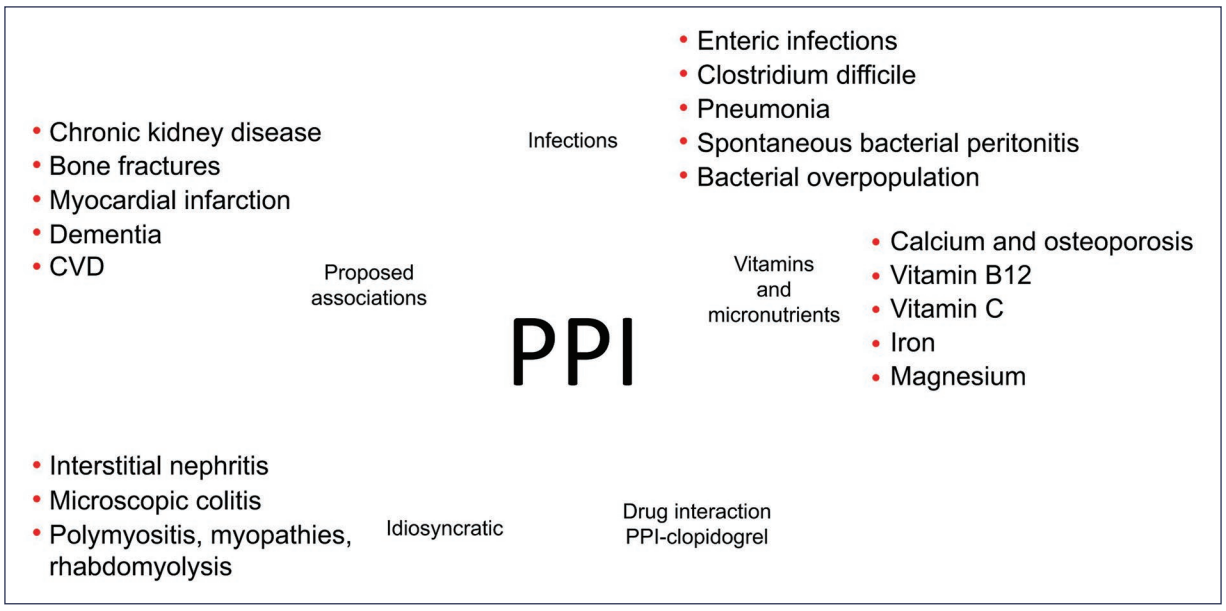

Figure 1. Adverse effects of proton pump inhibitors[8].

Table 2. Pharmacokinetic differences between P-CABs and PPIs[11]

P-CAB	PPI
Act directly (after their protonation) on the H^+/K^+-ATPase pump	Require transformation to the active form, sulfenamide
Superconcentrate in the acidic space of the parietal cell (100,000 times more than in plasma)	Concentrate in the acidic space of the parietal cell (1000 times more than in plasma)
Competitively bind to the K^+binding site of the H^+/K^+-ATPase pump	Covalent binding of sulfenamide with H^+/K^+-ATPase
Reversible binding with the proton pump Half-life 9.06 h	Irreversible binding with the proton pump Half-life 0.5-2.1 h
Duration of effect related to the drug's plasma half-life	Duration of effect related to the half-life of the sulfenamide-proton pump complex
Complete effect from the first dose	Complete effect after repeated doses

PPI: proton pump inhibitors; P-CAB: potassium-competitive acid blockers.

8 weeks. For maintenance treatment, standard doses or half the dose are used continuously[3-14].

P-CABs are superior to placebo in relieving symptoms in non-erosive reflux disease. They are used at a standard dose for 4 weeks. In maintenance treatment, the on-demand regimen can be used[3-14].

Adverse effects

Although generally well tolerated, P-CABs can cause some side effects, such as abdominal pain, diarrhea or constipation, nausea, headache, elevation of liver enzymes, and hypergastrinemia. So far, frequent serious adverse effects have not been reported, but their long-term use is still under evaluation in long-term follow-up studies[14].

H2 receptor antagonists

H2 receptor antagonists were for many years the main pharmacological treatment for GERD, before the development of PPIs. Although they have been largely displaced by the latter, they still have a place in the management of certain patients with gastroesophageal reflux[15].

The most common drugs in this class are ranitidine (withdrawn in many countries due to possibly carcinogenic impurities), famotidine (available in Mexico), nizatidine, and cimetidine.

Mechanism of action

They act by reversibly blocking histamine H2 receptors located in gastric parietal cells. This reduces gastric acid production, especially basal secretion (not related to food intake). They inhibit the action of histamine on acid secretion, mainly decrease nocturnal acid

Table 3. Pharmacology of P-CABs and PPIs

Pharmacokinetics and pharmacodynamics of different P-CABs						
Drug (Maximum dose)	**Revaprazan (200 mg daily)**	**Vonoprazan (40 mg daily)**	**Tegoprazan (200 mg daily)**	**Fexuprazan (160 mg daily)**	**Keverprazan (40 mg daily)**	**Zastaprazan (20 mg daily)**
Structure	Pyrimidine	Sulfonyl pyrrole	Benzimidazole	Pyrrole	Sulfonyl pyrrole	Imidazopyridine
pKa	6.68	9.06	5.2	8.40	9.12	6.02
T_{Max}, h	2.1 ± 1.3	1.5 (0.75-3.0)	1.8 (1.0-4.0)	2.75 (1.5-5.0)	1.40 (1.0-3.0)	1.2 (0.75-2.0)
Half-life, h	2.4 ± 0.2	6.1 ± 1.1	7.1 ± 2.2	7.5 ± 0.8	6.5 ± 1.1	10.28 ± 3.87
24-h pH, U - Day 1	2.2	NA	5.8 ± 0.4	5.8 ± 0.3	NA	4.95 ± 0.49
24-h pH, U - Day 7	2.5	NA	6.4 ± 0.3	6.5 ± 0.3	NA	5.47 ± 0.45
24-h pH > 4 Holding Time, % - Day 1	28.1	85.3 ± 8.3	76.8 ± 10.4	91.3 ± 4.1	85.8 ± 16.9	69.8 ± 15.9
24-h pH > 4 Duration % - Day 7	34.2	100.0 ± 0.0	94.6 ± 3.5	99.2 ± 1.9	100.0 ± 0.0	85.2 ± 11.4
Nocturnal acid breakthrough	Yes	No	No	No	No	No

PPI: proton pump inhibitors; P-CAB: potassium-competitive acid blockers.
Modified from Scarpignato and Hunt[11].

secretion, and their effect is faster than that of PPIs, but less potent and of shorter duration[3].

Indications in GERD

– Patients who do not tolerate PPIs.
– Combination therapy with PPIs for control of nocturnal symptoms.
– Alternative in deprescription or on-demand management regimens.

They are used for short periods of time (2 to 3 weeks) due to the phenomenon of tachyphylaxis.

Adverse effects

They are generally well tolerated, but some adverse effects may occur, more frequently with cimetidine, such as headache, dizziness or fatigue, diarrhea or constipation, mental confusion (in elderly patients or with renal insufficiency), gynecomastia and sexual dysfunction (especially with cimetidine), and drug interactions (cimetidine inhibits several hepatic enzymes)[2,3].

Antacids

They act by neutralizing already secreted gastric acid. They offer rapid symptomatic relief, but of short duration. They contain compounds such as magnesium hydroxide, aluminum, and calcium carbonate (Table 4).

Their use in GERD is restricted to the relief of occasional symptoms. They should not be used as long-term treatment due to their poor efficacy. Prolonged use may cause adverse events such as diarrhea, constipation, and hypomagnesemia.

Table 4 details the main antacids and their adverse effects[2,3].

Alginates

Alginates are compounds derived from brown algae (such as *Laminaria*) that are frequently used in the symptomatic treatment of GERD, especially in mild forms or as a complement to other therapies[2,3].

Mechanism of action

Unlike drugs that act by reducing gastric acid production, alginates form a physical barrier that prevents the reflux of gastric contents toward the esophagus. Upon contact with gastric acid, alginates react, forming a thick, viscous, low-density gel. This gel floats on the gastric contents like a raft, acting as a mechanical barrier that prevents acid ascent toward the esophagus.

When reflux occurs, what reaches the esophagus is this gel, not the acidic content, reducing esophageal injury. Some formulations combine alginates with antacids (for example, sodium bicarbonate and calcium

Table 4. Main non-absorbable antacids

Magnesium hydroxide Mg salts are osmotically active: diarrhea; 15-20% renal excretion
Aluminum hydroxide Al reacts with intestinal mucosa proteins: constipation Impairs phosphate absorption: hypomagnesemia; 17-30% renal excretion
Aluminum and magnesium salts Magaldrate (Mg and Al hydroxysulfate) Almagate (hydrated Al and Mg hydroxycarbonate) Melox®: Al and Mg hydroxide
Calcium carbonate $CaCO_3$ Constipation
Combinations Melox® night: calcium carbonate/magnesium alginate/magnesium carbonate/aluminum hydroxide

carbonate), which improves both mechanical protection and acid neutralization.

Efficacy

They are especially useful in patients with postprandial symptoms or acid regurgitation. They can be used as on-demand treatment or as an adjuvant together with PPIs in patients with persistent symptoms. They do not heal erosive esophagitis, but significantly improve symptomatic control[16].

Adverse effects

Alginates are well tolerated. Their adverse effects, infrequent and mild, include abdominal distension, occasional nausea, constipation, or diarrhea. Due to their safety profile, they can be used in pregnant women and pediatric patients under medical supervision[16].

Bioadhesive barriers

Esoxx One is a medical device containing hyaluronic acid, chondroitin sulfate, and bioadhesive polymers (poloxamers), which is used in the adjuvant treatment of GERD.

Mechanism of action

In vitro studies have shown that hyaluronic acid repairs and regenerates the mucosa, and chondroitin sulfate protects against acid-pepsin-bile damage. Both compounds, combined with poloxamer, form a mucoadhesive barrier that coats the esophagus with a protective film over the esophageal mucosa[17].

Indications in GERD

In controlled clinical trials, Esoxx One in adjuvant therapy with PPIs has been shown to be superior to PPIs alone for symptom control in non-erosive reflux disease. It is also used in combination with PPIs to accelerate the healing of erosive esophagitis. It can be used in pregnancy and lactation[17].

Adverse effects

In general, Esoxx One is well tolerated. Mild nausea or hypersensitivity to any of the components has been occasionally described[17].

Treatment of refractory GERD

It is important to know how to differentiate patients who have persistent GERD symptoms from those who have refractory GERD. The former are patients who have already been studied with endoscopy or esophageal pH monitoring, have objective evidence of GERD, and after treatment with double-dose PPIs for 8 weeks, continue with symptoms. Patients with refractory GERD are those who have demonstrated evidence of GERD and have not responded to treatment with double-dose PPIs for 8 weeks, and who, in a new diagnostic evaluation under PPI treatment, persist with esophagitis, with abnormal acid exposure, or with nocturnal baseline impedance < 1500 ohms or the number of reflux episodes > 80 in 24 hours[18].

Treatment of persistent GERD symptoms includes the following options:

– Insist on lifestyle modifications (weight loss, head-of-bed elevation, early dinner, etc.) and adequate PPI dosing, 30 to 60 minutes before breakfast and dinner.
– Optimization of PPI treatment, which consists of using a different drug from the one initially used, preferably one that is not metabolized by CYP2C19, such as rabeprazole or ilaprazole, to circumvent the possibility of accelerated PPI metabolism.
– Use of adjuvant treatments, such as antacids, alginates, mucosal protectants, or a nocturnal dose of famotidine for short periods of 2 to 3 weeks.

– Change PPI treatment to a P-CAB. There is evidence that P-CABs can be effective in cases of PPI-refractory GERD symptoms.

Treatment of refractory GERD involves optimization of antisecretory agents, as noted, and the use of advanced treatments such as fundoplication in cases of large hiatal hernias, gastrojejunal bypass in patients with GERD and morbid obesity, and in selected patients endoscopic treatments, such as gastroplication, performed by endoscopists trained in these procedures[18].

Conclusions

The treatment of GERD has evolved with the development of faster, more effective drugs with greater antisecretory potency. The appropriate use of P-CABs and PPIs represents the cornerstone in the medical treatment of this condition.

Knowledge of the pharmacology, pharmacodynamics, therapeutic efficacy, and safety of P-CABs and PPIs is indispensable for their correct prescription. Phenotyping of the patient with GERD through available diagnostic tests allows precision medicine and guarantees greater therapeutic success.

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Conflicts of interest

The author declares having been a speaker for Carnot, Chinoin, and M8.

Ethical considerations

Protection of people and animals. The author declares that no experiments were performed on humans or animals for this research.

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

Declaration on the use of artificial intelligence. The author declares that no type of generative artificial intelligence was used for the writing of this manuscript.

References

1. Vakil N, Van Zanten SV, Kahrilas P. The Montreal definition and classification of gastroesophageal refluxdisease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900-20.
2. Katz PO, Dunbar KB, Schnoll-Sussman FH. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2022;117:27-56.
3. Valdovinos Díaz MA, Amieva-Balmori M, Carmona-Sánchez R. Good clinical practice recommendations for the diagnosis and treatment of gastroesophageal reflux disease. An expert review from the Asociación Mexicana de Gastroenterología. Rev Gastroenterol Mex. 2024;89:121-43.
4. Yadlapati R, Gyawali CP, Pandolfino JE. AGA clinical practice update on the personalized approach to the evaluation and management of GERD: expert review. Clin Gastroenterol Hepatol. 2022;20:984-94.
5. Huerta-Iga F, Bielsa-Fernández MV, Remes-Troche JM. Diagnóstico y tratamiento de la enfermedad por reflujo gastroesofágico: recomendaciones de la Asociación Mexicana de Gastroenterología. Rev Gastroenterol Mex. 2016;81:208-22.
6. Rouby NE, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol. 2018;14:447-60.
7. Katz PO. Review article: intragastric and oesophageal pH monitoring in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2006;23(Suppl 1):3-11.
8. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology. 2017;153:35-48.
9. Valdovinos-García LR, Villar-Chávez AS, Huerta-Iga FM. Good clinical practice recommendations for proton pump inhibitor prescription and deprescription. A review by experts from the AMG. Rev Gastroenterol Mex. (Engl Ed). 2025;90:111-30.
10. Hunt RH, Scarpignato C. Potassium-competitive acid blockers (P-CABs): are they finally ready for prime time in acid-related disease? Clin Transl Gastroenterol. 2015;6:e119.
11. Scarpignato C, Hunt RH. Towards extended acid suppression – the search continues. Aliment Pharmacol Ther. 2015;42:1027-9.
12. Scarpignato C, Hunt RH. Potassium-competitive acid blockers for acid-related diseases-tegoprazan, a new kid on the block. Aliment Pharmacol Ther. 2019; 50:960-2.
13. Leowattana W, Leowattana T. Potassium-competitive acid blockers and gastroesophageal reflux disease. World J Gastroenterol. 2022;28: 3608-19.
14. Scarpignato C, Hunt RH. Potassium-competitive acid blockers: current clinical use and future developments. Curr Gastroenterol Rep. 2024; 26:273-93.
15. Wang WH, Huang JQ, Zheng GF. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. World J Gastroenterol. 2005;11:4067-77.
16. Leiman DA, Riff BP, Morgan S. Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis. Dis Esophagus. 2017;30:1-9.
17. Savarino V, Visaggi P, Marabotto E. Topical protection of esophageal mucosa as a new treatment of GERD. J Clin Gastroenterol. 2025; 59:197-205.
18. Zerbib F, Bredenoord AJ, Fass R. ESNM/ANMS consensus paper: diagnosis and management of refractory gastro-esophageal reflux disease. Neurogastroenterol Motil. 2021;33:e14075.