ORIGINAL ARTICLE
CLINICAL GASTROENTEROLOGY

doi.org/10.1590/S0004-2803.24612023-154

Brazilian clinical guideline for the therapeutic management of Gastroesophageal Reflux Disease (Brazilian Federation of Gastroenterology, FBG)

Joaquim Prado P **MORAES-FILHO**[1], Gerson **DOMINGUES**[2*], Decio **CHINZON**[1] and Brazilian GERD Counselors[*]

[1] Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brasil.
[2] Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brasil.

HIGHLIGHTS

- Gastrointestinal specialists rely heavily on guidelines to manage digestive pathologies effectively. The Brazilian clinical guideline for therapeutic management of gastroesophageal reflux disease (GERD) is an invaluable tool for these specialists.
- It critically analyzes practical aspects of therapy through 12 questions covering a wide range of topics, from behavioral measures to surgical and endoscopic indications.
- The recommendations in this guideline are justified using the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation), and experienced experts provide comments and suggestions at the end of each question.

Received: 7 November 2023
Accepted: 29 November 2023

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Artificial intelligence was not used in this manuscript.
Corresponding author: Joaquim Prado de Moraes-Filho.
E-mail: joaquim.prado@usp.br

ABSTRACT – Background – Gastroesophageal Reflux Disease (GERD) is a prevalent condition in Brazil, affecting 12% to 20% of the urban population, with significant implications for patient quality of life and potential for complications. **Objective –** This paper focuses on the recent update of the Brazilian guidelines for GERD, a necessary revision due to advancements in knowledge and practice since the last publication over a decade ago. The update pays particular attention to the role and safety of proton pump inhibitors (PPIs), acknowledging the growing concerns about their long-term use, adverse events, and overprescription. **Methods –** The methodology of the guideline update involved an extensive literature review in multiple languages (English, French, Italian, Spanish, and Portuguese), drawing from major databases such as Medline, Embase, and SciELO-Lilacs. **Results –** This comprehensive approach resulted in a carefully curated selection of studies, systematic reviews, and meta-analyses, specifically focusing on PPIs and other therapeutic strategies for GERD. The updated guidelines are presented in a user-friendly question-and-answer format, adhering to the PICO system (Population, Intervention, Comparison, Outcomes) for clarity and ease of interpretation. The recommendations are supported by robust scientific evidence and expert opinions, enhancing their practical applicability in clinical settings. To ensure the reliability and clarity of the recommendations, the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation) was employed. This system categorizes the strength of recommendations as strong, weak, or conditional and classifies evidence quality as high, moderate, low, or very low. These classifications provide insight into the confidence level of each recommendation and the likelihood of future research impacting these guidelines. **Conclusion –** The primary aim of these updated guidelines is to offer practical, evidence-based advice for the management of GERD in Brazil, ensuring that healthcare professionals are equipped with the latest knowledge and tools to deliver optimal patient care.

Keywords – Reflux disease; consensus; guidelines.

*Conselheiros Brasileiros de DRGE: Abadia G.B. Matoso (Universidade Federal de Uberlândia, MG); Eliza Maria de Brito (Universidade Prof. Edson Antonio Velano, Alfenas, MG); Eponina Maria O. Lemme (Universidade Federal do Rio de Janeiro, RJ); - Ismael Maguilnik (Universidade Federal do Rio Grande do Sul, Porto Alegre, RGS); Joffre Rezende Filho (Universidade Federal de Goiás, Goiânia, GO); Luiz J. Abrahão Jr. (Universidade Federal do Rio de Janeiro, RJ); Miguel Angelo Nobre e Souza (Universidade Federal do Ceará, Fortaleza, CE); Moisés Copelman (Universidade do Estado do Rio de Janeiro, RJ); Nelson Henrique Michelson (Centro de Motilidade Digestiva São Paulo, SP); Ricardo C. Barbuti (Universidade de São Paulo, SP); Ricardo G. Viebig (Instituto Brasileiro de Estudos e Pesquisas de Gastroenterologia, São Paulo, SP) Schlioma Zaterka (Universidade de São Paulo, SP).

Gastroesophageal Reflux Disease (GERD) is a common condition in gastroenterological practice, with a prevalence of 12% to 20% in the urban Brazilian population[1]. It affects the quality of life of patients and can present complications.

GERD has been the subject of numerous studies focused mainly on pathophysiological interpretation, diagnostic advances, and management. However, the last publication of guidelines in Brazil was more than a decade ago, which calls for careful updating[2]. Since then, observations regarding proton pump inhibitors (PPIs) have increased considerably, and although they continue to play an important role in the treatment of GERD, numerous publications have raised concerns about long-term safety, adverse events, and overprescription[3-7]. Therefore, for the thoughtful final placement of this publication regarding the therapeutic approach to GERD patients, different studies, systematic reviews, and meta-analyses on PPIs and other therapeutic approaches were carefully analyzed. Literature research was conducted in English, French, Italian, Spanish, and Portuguese for publications mainly referenced in Medline, Embase, SciELO-Lilacs. The references cited in this publication constitute only a fraction of all the articles reviewed in each area.

To make the current Guidelines easy to read and interpret, they have been structured in a question-and-answer format. The recommendations are based on the studies that led to the final analysis, and comments on the studies that led to the final analysis are also included. Comments on the recommendations are made with suggestions associated with the opinion of experienced experts. The questions were formulated according to the PICO system (population, intervention, comparison, outcomes) with careful literature research[8,9]. This publication, therefore, represents a practical therapeutic update on the management of patients with a confirmed diagnosis of GERD, with strong support from the scientific literature.

As a means of characterizing and justifying the recommendations of the cited evidence, the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation) was used, where the support for the recommendations is classified as strong, weak, or conditional. Strong support is indicated when the benefits of the recommendation clearly outweigh any negative aspects. On the other hand, a conditional recommendation should be considered of lower certainty when most gastroenterologists accept and consider the suggested action valid, but eventually some may not[10].

Regarding the quality of evidence that supports GRADE recommendations, they are classified into the following levels: high, moderate, low, and very low. High-quality evidence implies that future studies are unlikely to change the current statements of high confidence. Moderate-quality evidence is associated with moderate confidence in the careful literature findings on a particular topic. Low-quality evidence indicates that future studies may have a significant impact on outcomes, and the quality estimate may eventually change. Very low-quality evidence indicates little certainty about the estimated effect[11]. As for support for GRADE recommendations, a strong index is indicated when the benefits clearly outweigh any negative aspects. A conditional recommendation should be considered of lower certainty when most authors accept and consider the suggested action valid, but some may not.

The main objective of the Brazilian Guideline for the therapeutic management of GERD is to provide practical approaches and suggestions for conduct, based primarily on the current high-quality scientific and editorial literature available.

QUESTIONS

1. Are there differences in the treatment of erosive and non-erosive forms of gastroesophageal reflux disease (GERD)?

Recommendation

- There are no differences in the treatment of erosive and non-erosive forms of GERD, which is independent of genotype. Proton pump inhibitors (PPIs) and competitive potassium-competitive acid blockers (PCABs) are the drugs of choice in the treatment of acid reflux.
- **Evidence quality:** strong / recommendation strength: strong.

Non-erosive reflux disease (NERD) is characterized as a condition in which reflux symptoms and demonstrated gastroesophageal reflux occur in the absence of mucosal lesions detected by conventional endoscopic examination, in patients without effective acid-suppressive therapy prior. It is important to note that the range and severity of symptoms experienced in NERD are similar to those observed in cases with erosions/erosive esophagitis, and symptoms do not correlate linearly with endoscopic findings[7].

The main therapeutic goal in the case of NERD is a satisfactory response of symptoms to therapy[12], which should be performed with a standard dose of PPI administered once daily for a period of 4 to 8 weeks[13,14]. It should be noted that there are few studies evaluating the efficacy of PCABs in NERD, unlike what is observed in erosive forms, where the administration of PCABs can lead to faster symptomatic improvement and more effective healing and can be administered once daily regardless of mealtime[15].

Patients with NERD who do not respond after 4 weeks of conventional treatment with PPIs may have their dose increased to twice daily, although there is little conclusive evidence that this approach provides additional symptom relief. As a rule, it is recommended to continue PPI treatment once daily for 12 weeks. Non-responsive patients in this case are considered less likely to have a NERD diagnosis, and the use of PPIs should be reconsidered[16].

The response to acid secretion inhibition is more characterized in erosive forms than in non-erosive forms of the disease[14,16-18]. A meta-analysis comparing PPIs vs H2 receptor antagonists (H2RA) and placebo showed that PPI treatment was significantly superior to treatment with H2 receptor antagonists (RR=1.629, 95%CI: 1.422–1.867, *P*=0.000) and placebo (RR=1.903, 95%CI: 1.573–2.302, *P*=0.000) for symptomatic relief of NERD[13,16].

Comments

- Patients with normal acid exposure are not considered to have GERD, with a high likelihood of having functional esophageal manifestations. On the other hand, the confirmed presence of GERD does not exclude the possibility of, in certain cases, simultaneous occurrence of functional esophageal symptoms, which may involve psycho-emotional aspects and corresponding therapeutic approaches[17].
- More severe cases of erosive GERD require more intensive therapeutic approaches, which in some cases are achieved with PCABs[19].

2. Are behavioral measures (lifestyle changes) recommended in the treatment of gerd?

Recommendation

- Behavioral measures (lifestyle changes), with a case-by-case analysis, are recommended in the treatment of GERD.
- Evidence quality: low / recommendation strength: conditional.

Behavioral modifications are recommended as part of GERD treatment, although they can be controversial since other factors may also contribute to the development of the disease. The data supporting these recommendations are limited and variable, substantiated in clinical studies of sometimes unsatisfactory methodology, leading to some difficulty in interpretations. Nevertheless, certain studies and guidelines have effectively suggested benefits in lifestyle modifications, which are eventually corroborated by clinical practice[20].

Recommendations regarding patients' lifestyle indicate changes recommended for each clinical case, such as:

(a) weight loss (in cases of overweight/obesity);
(b) elevating the head of the bed;
(c) smoking cessation;
(d) alcohol cessation;
(e) avoiding food intake before lying down for rest;
(f) avoiding foods that may worsen reflux symptoms;
(g) avoiding right lateral decubitus for rest.

Weight gain has been associated with the occurrence of GERD symptoms, which is consistent with the potential infiltration of fat in the esophagogastric transition, which can compromise the motor action of the lower esophageal sphincter (LES). The benefits of weight loss are supported by strong evidence[21,22].

Elevating the head of the bed has been recommended with the aim of reducing the reflux of acidic content from the esophagus that can occur when patients are in a supine position. Compared to patients who slept with the bed flat, elevating the head of the bed was associated with improved acid clearance, shorter and less frequent reflux episodes. The benefits of elevating the head of the bed are supported by strong evidence[22-25].

Studies using specific questionnaires have reported that smoking is significantly associated with GERD symptoms. Smoking/tobacco can reduce LES pressure and decrease salivary bicarbonate secretion, limiting the physiological neutralizing effect of saliva on refluxed acid to the esophagus, prolonging acid clearance[26]. Extensive cohort study has shown that smoking cessation led to significant improvement in symptoms[27].

Alcohol consumption can reduce LES pressure, increase acid secretion through gastrin stimulation, decrease esophageal motility, and delay gastric emptying, thereby exacerbating GERD symptoms[20]. However, the topic is controversial because while some studies indicate alcohol as an independent risk factor for GERD-related symptoms, others do not corroborate this relationship[28].

Randomized trials have shown that the esophagogastric junction can, depending on the body posture, be exposed to a position that favors the reflux to the esophagus[7]. Keeping a 2–3-hour interval after eating before lying down, as well as avoiding right lateral decubitus, are therefore applicable measures supported by well-conducted studies, as body posture can increase nighttime reflux[29-32].

An association of gastroesophageal reflux with certain foods has been reported (coffee, chocolate, spicy foods, tomatoes, fatty/fried foods). However, objective evidence-based data are limited and variable, often based on smaller and uncontrolled studies, making it difficult to make evidence-based recommendations in this regard[33]. Therefore, it is advisable to exclude food items that patients report, on a case-by-case basis, trigger symptoms[22,34].

Comments

- Lifestyle-related factors such as not lying down immediately after meals, elevating the head of the bed (especially in more severe cases / with nighttime symptoms), not lying on the right side, not smoking, avoiding alcohol consumption, and maintaining physical activity are recommendations that should be personalized for each patient.
- For conclusively effective recommendations regarding dietary habits in GERD treatment, new studies with rigorous Evidence-Based Medicine criteria are needed. Nevertheless, it is advisable for patients to observe and accordingly eliminate foods that may trigger symptoms (examples: fatty foods, fried foods, spicy foods, chocolate, tomatoes).

3. In the treatment of GERD, are there differences in clinical outcomes among different proton pump inhibitors (PPIs) – omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole?

Recommendation

- In the comparison between different groups of PPIs, there are no significant differences in therapeutic effect in the treatment of GERD.
- Evidence quality: moderate / recommendation strength: strong.

Analysis have demonstrated that PPIs are the most prescribed drug class with a consistent therapeutic effect in controlling typical symptoms (heartburn and regurgitation) and healing of esophagitis when compared to placebo. This analysis included 11 controlled randomized studies[35-39] that analyzed 5,396 patients, comparing 2,944 patients on PPI treatment with 2,452 patients on placebo. PPI treatment increased the symptom resolution rate by 22% (95%CI 19–26%) compared to placebo. The magnitude of the response had a slight variation with each PPI: pantoprazole 22%, esomeprazole 23%, omeprazole 17%, and rabeprazole 26%. The percen-

tage of patients with complete symptomatic response was higher in those with erosive GERD (70–80%) when compared to those with non-erosive GERD, probably because the latter phenotype includes patients with functional heartburn and/or esophageal hypersensitivity to reflux with unlikely satisfactory response to PPIs[40]. Although there are variations in the potency of acid suppression among different PPIs[7] with regard to healing of lesions, a meta-analysis that evaluated the efficacy of PPIs involving 15,316 patients with the outcome of healing of erosive esophagitis observed that in the eighth week there was a 5% increase in the relative probability of healing of erosive esophagitis with esomeprazole (RR, 1.05; 95%CI, 1.02–1.08), resulting in an absolute risk reduction of 4% and a number needed to treat of 25, which from a clinical perspective was not significant[40]. It is worth to mention that in this last study, the analysis did not include the use of dexlansoprazole, which is the only PPI with dual release, being first absorbed in the duodenum and subsequently in the ileum. It has been demonstrated that due to this characteristic, dexlansoprazole offers comparable acid control when administered at different times of the day[41,42].

Comments

- The treatment of GERD with PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole) is significantly more effective compared to placebo and the difference in clinical response between PPIs is not significant.

4. In the treatment of GERD, are there differences in clinical outcomes between PPIs and potassium-competitive acid blockers-pcabs (vonoprazan)?

Recommendation

- The use of vonoprazan is a more suitable therapeutic option for the treatment of erosive GERD. There is no difference in the frequency of adverse events between PPIs and vonoprazan.
- **Evidence quality:** moderate / recommendation strength: strongly in favor.

A total of 442 studies were selected. Of these, six controlled randomized studies were included to support the evidence synthesis[43-48]. In patients with GERD, the use of vonoprazan 10 mg or 20 mg for 4 to 8 weeks was non-inferior to PPIs in treating heartburn or the risk of treatment-related adverse events. In a meta-analysis of direct efficacy comparison, vonoprazan showed a relative risk (RR) of 1.06 (95%CI 0.99–1.13) for efficacy and RR of 1.08 (95%CI 0.96–1.22) for adverse events compared to PPIs[49]. In particular for patients with erosive esophagitis the use of vonoprazan increased the percentage of mucosal healing by 8–19.3% (95%CI 4.5–27.6%)[44,45,50]. In patients with more severe esophagitis (Los Angeles grades C and D), a significantly higher percentage (19.6%) of esophagitis healing was found with the use of vonoprazan compared to lansoprazole[50].

Comment

- The results of treating GERD patients with vonoprazan are not inferior to those presented by PPIs. The results with vonoprazan may be superior to PPIs, especially in patients with erosive esophagitis.

5. Are prokinetics (bromopride, domperidone, metoclopramide) recommended for the treatment of GERD?

Recommendation

- Prokinetics are not indicated for the treatment of GERD.
- **Evidence quality:** low / recommendation strength: strong.

Observations regarding the use of prokinetics in GERD treatment are limited. Studies evaluating the therapeutic efficacy of certain prokinetics have reached different conclusions, and often the material selection and methodology were not satisfactory. Metoclopramide has well-characterized motor actions of increasing esophageal peristalsis, gastric emptying, and lower esophageal sphincter pressure. However, the results regarding the therapeutic efficacy of metoclopramide in GERD are scarce, and it has significant central nervous system-related adverse effects. The combination of

pantoprazole with domperidone in patients with refractory GERD was compared to the therapeutic action of the proton pump inhibitor alone, and no statistically significant difference was demonstrated between the two groups[51,52]. The only prokinetic with documented efficacy in the treatment of GERD, cisapride, was withdrawn from the market due to cardiotoxicity[53].

Comments

- The therapeutic use of prokinetics has not shown satisfactory or conclusive results in the treatment of GERD, and therefore, their use is not recommended. It should be noted, however, that prokinetics have proven efficacy in certain cases of gastroparesis that may occur concurrently[54]. Bloating and postprandial discomfort may benefit from prokinetics[55].

6. What are the therapeutic alternatives for the treatment of gerd refractory to PPIs?

Recommendation

- The options for the clinical treatment of refractory GERD patients are: (a) vonoprazan; (b) extending the treatment duration with the standard dose of PPI; (c) increasing the dose of PPI; (d) switching to another PPI from the same therapeutic class; (e) anti-reflux surgery may be an option in selected patients (comparison limited by the small number of patients).
- **Evidence quality:** moderate / recommendation strength: strongly in favor.

A total of 233 studies were selected. Of these, 11 controlled randomized studies were included to support the evidence synthesis[56-61]. Between 19% and 44% of patients with reflux symptoms report a partial response or lack of response to PPI treatment. In these patients, objective improvement was observed when vonoprazan was prescribed, which demonstrated the inhibition of gastric acid secretion within 24 hours and resulted in the healing of erosive esophagitis in 60% of patients with GERD refractory to PPI use[59]. Several mechanisms can explain refractoriness to PPIs, such as: (a) incorrect dose or timing of medication administration; (b) non-acid or bile reflux; (c) mutations in the hepatic enzyme cytochrome P-450; (d) esophageal hypersensitivity to physiological reflux; (e) functional heartburn.

Most cases of GERD refractory to PPIs consist of patients with the non-erosive form of the disease.

The first intervention in patients with refractory GERD is to optimize PPI therapy: improvement of >50% of symptoms was observed in 11–35% of patients when PPI use was optimized[62,63]. It is important to ensure that the patient takes the medication regularly daily, 30–60 minutes before the first meal of the day or before breakfast and dinner, and if the drug is correctly administered 2 times a day[7,60]. Switching from one PPI medication to another of the same class may also be a therapeutic option. Baclofen (a muscle relaxant that stimulates GABA B receptors) reduces the number of postprandial acid and non-acid reflux events but has adverse events and did not show significant benefit in a one-year follow-up study[56]. Its use can be considered for patients with documented symptomatic reflux after optimized PPI therapy[64]. Adherence to a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet did not show any difference in reducing reflux symptoms[57].

In cases where drug treatment does not result in relief, anti-reflux surgery may be necessary. However, it's important to conduct a preoperative evaluation to determine if the patient is a good candidate for surgery. Patients who obtain the best results from surgery are those with typical GERD symptoms who respond to PPIs. It's important to note that symptoms unrelated to reflux are not resolved with surgery[58].

Comments

- The options for patients with GERD refractory to standard PPI treatment are: (a) optimizing PPI treatment (examples: higher doses, twice/day, change of IBP); (b) use of vonoprazan; (c) baclofen in selected cases; (d) careful indication for surgical treatment in patients with proven GERD, especially those with severe esophagitis.

7. What is the pharmacological approach to drug maintenance treatment?

Recommendation

- The maintenance treatment for GERD that has been satisfactorily treated with PPIs (or PCABs) consists of continuous administration (full dose/half dose PPI or PCAB) or on-demand administration of PPIs (or PCABs).
- **Evidence quality:** low / recommendation strength: conditional.

Different studies (randomized trials and meta-analyses) have analyzed the therapeutic possibilities for GERD maintenance treatment on-demand and continuous use. In 15,755 patients observed for 12 to 52 weeks (average: 24 weeks) after satisfactory treatment of erosive esophagitis (mild to severe) and non-erosive esophagitis, maintenance treatment with PPIs (omeprazole, rabeprazole, esomeprazole, pantoprazole and lansoprazole) and in other studies, PCABs (vonoprazan) was prescribed[7,50,65-78]. The results allowed the conclusion that there is no difference in both forms of therapeutic maintenance: continuous treatment or on-demand, depending on the case to be evaluated by the attending physician. The different nature and characteristics of the studies led to variable results, suggesting low or very low evidence quality.

Comments

- Two-thirds of patients with non-erosive GERD may experience symptom recurrence after treatment termination, and nearly all patients with erosive esophagitis grade C and D (Los Angeles classification) will experience a recurrence of the disease within 6 months[79]. These cases require continuous observation and treatment. Pharmacological maintenance therapy for GERD should be individualized in each case, both in the non-erosive and erosive forms (mild, severe with and without complications). Continuous or on-demand maintenance treatment (when the patient reports symptoms again) should, therefore, be related to the characteristics of each case and the therapeutic possibilities evaluated by the attending physician.

8. Are there risks in using proton pump inhibitors (PPIs) for an extended period?

Recommendation

- Definitive conclusions regarding major risks of long-term PPI use have not been established. However, due to the possibility of unforeseen events, special attention should be given to: elderly patients, immunocompromised individuals, as well as those at higher risk of bone, renal, iron, vitamin D, vitamin B12, and magnesium-related diseases.
- **Evidence quality:** very low / recommendation strength: low.

Long-term treatment with PPIs has been associated with observational studies that are susceptible to biases and cannot be considered definitive for determining causality. On the other hand, in a randomized, double-blind, placebo-controlled study that included 17,598 patients, the administration of pantoprazole 40 mg/day for a period of 3 years was associated with a small but significant increase in the incidence of enteric infections, but not of other adverse events[80].

Although further rigorous observations are necessary, calcium absorption can be significantly reduced in the presence of achlorhydria, which theoretically places PPIs in the condition of causative agents for calcium malabsorption and, by extension, a higher risk of fractures[81]. Regarding vitamin B12 malabsorption, studies with patients on long-term PPI use have shown conflicting results, requiring further conclusive studies[81,89]. The same applies to the possibility of hypomagnesemia in these cases[82,89].

Regarding nephropathy, an extensive and careful study analyzing the relationship between higher doses of PPIs demonstrated a significantly positive association, a result also found in a Swedish cohort study[83,84]. The relationship between long-term PPI use and cognitive decline has no conclusive and definitive observations[85]. Therefore in this case further studies (with better adjustments for age, gender, ischemic disease, hypertension, etc.) are needed to obtain conclusive information[86]. It has been

observed that PPI-induced dysbiosis of the intestinal microbiota may increase the risk of intestinal infections such as *Salmonella, Campylobacter,* and *Clostridium difficile*[85,86].

Numerous investigations that evaluated the risk of pneumonia in patients treated with PPIs (based on the hypothesis that micro-aspiration may predispose to respiratory infections) did not reach definitive conclusions, requiring further studies[85,87]. There is no evidence that the use of PPIs increases the risk of gastric cancer, but well-conducted and conclusive studies are needed on this subject[88].

Comments

- Elderly and frail patients undergoing prolonged treatment with PPIs should have their vitamin B12 levels monitored periodically, and serum magnesium levels checked. In patients with kidney disease using PPIs or at risk of nephropathy, it is advisable to periodically monitor renal function. It is important to prevent enteric infections, especially by *Clostridium difficile*, in patients using PPIs, particularly the elderly, immunocompromised, and those hospitalized in urgent care units. In summary, greater attention should be given to elderly patients, those with kidney, bone, and nutritional deficiencies, as well as calcium, vitamin D, and vitamin B12 deficiencies. Observations on cognitive decline are inconclusive, as well as there is no evidence that the use of PPIs increases the risk of gastric cancer.

9. How to treat non-acid reflux?

Recommendation

- Different therapeutic modalities have been proposed for the treatment of non-acid reflux, but studies have not provided definitive conclusions. Therefore, therapeutic management is trial-based and should be considered on a case-by-case basis. It may include: behavioral modifications, increased acid suppression, alginate, baclofen, buspirone, prokinetics, and anti-reflux surgery in carefully selected patients[90].
- **Recommendation strength:** conditional / evidence grade: weak.

Non-acid reflux is divided into two categories: alkaline reflux when pH >7 and weakly acidic reflux when pH is between 4 and 7. The frequency of these occurrences is not well determined due to the relative scarcity of data evaluating this condition compared to acid reflux[90,91]. Classifying gastroesophageal reflux as acid or non-acid nature is not accurate because, in most cases, both conditions are present to some degree[92,93]. On the other hand, non-acid reflux is a phenomenon that can be considered normal to some extent. In healthy control patients, 33% to 38% of reflux events are non-acidic, and in patients with GERD, 50% of reflux events are non-acidic. The use of PPIs is the most common cause of non-acid reflux. A multicenter study in patients considered refractory to treatment with PPIs twice a day, found that 82.7% of reflux events were non-acidic, with only 17.3% being acidic. Among the non-acidic events, 89.9% were weakly acidic, and 10.2% were alkaline[94].

It should be considered that classic symptoms of reflux, including heartburn and regurgitation, can be caused by both acid and non-acid reflux, with regurgitation often being referred to as a classic symptom of non-acid reflux. Clinical manifestations can be caused by esophageal hypersensitivity or direct mucosal damage and inflammation[95]. In the treatment of non-acid reflux, it should be considered that additional acid-suppressive therapy may eventually be beneficial by further raising the pH of the refluxate and reducing the likelihood of acid reflux. In a limited study involving 12 patients with esophageal symptoms of non-acid reflux, 50% of cases experienced symptom improvement simply by doubling the dose of PPIs[96].

Alginate is an alternative that acts as a barrier to both acid and non-acid reflux. An uncontrolled study evaluated 25 patients with esophageal symptoms of non-acid reflux refractory to PPIs and treated them with alginate four times a day. The treated patients experienced an average improvement of 75% in overall symptoms, with an overall treatment effectiveness of 92%[96].

Visceral hypersensitivity can exacerbate symptoms. Therefore, the use of neuromodulators can help reduce sensitivity to non-acid reflux due to changes in esophageal mucosal permeability[97]. Baclofen (a GABA receptor stimulator) may decrease transient

lower esophageal sphincter relaxation. It has been studied in cases of non-acid reflux, as shown in a recent meta-analysis of 9 randomized controlled clinical trials. The group that used baclofen reduced acid exposure time, the incidence of GERD, and the number of transient lower esophageal sphincter relaxations. Another study demonstrated that baclofen reduced both acid and non-acid reflux in patients with GERD and healthy controls, as well as improving symptoms in GERD patients[97,98]. However, the use of baclofen is rather limited by the occurrence of side effects such as drowsiness, dizziness, and fatigue.

Prokinetics may have modest benefits in carefully selected patients with GERD refractory to PPIs[12]. On the other hand, side effects limit long-term use.

Comment

- The treatment of non-acid GERD is trial-based and should be considered on a case-by-case basis. In addition to careful adherence to behavioral measures, patients may benefit from the judicious use of pharmacological interventions.

10. When is surgical / endoscopic treatment of GERD indicated?

Surgical Treatment

Recommendation

- Surgical treatment may be indicated in the following cases:

(a) Severe reflux esophagitis (C / D - Los Angeles classification).
(b) Symptomatic hiatal hernias larger than 5 cm;
(c) Adverse events or refractoriness to PPIs.
(d) Proven weakly acidic reflux in selected cases with clear symptomatic association.

- Evidence quality: moderate / recommendation strength: strong.

Identifying patients with true refractory GERD is extremely important because surgery (or endoscopic treatment) may be the therapeutic choice in this group. It is worth noting, however, that high-quality studies are still needed to better define this therapy. A recent systematic review and meta-analysis, although subject to biases, concluded that patients who underwent surgical treatment had better short-term quality of life, but there was no improvement in short or long-term symptomatic control compared to patients treated with medication. On the other hand, a randomized study including patients with GERD and refractory heartburn demonstrated that the percentage of patients who showed satisfactory results in quality of life was significantly higher in the anti-reflux surgery group (67%) compared to those treated with medication (28%)[58].

A well-conducted current review analyzed the results of anti-reflux surgery versus clinical treatment in adults and children, including laparoscopic versus robotic fundoplication, partial versus total fundoplication, and minimal versus maximal dissection in pediatric patients. The authors concluded that the currently available evidence has a high risk of bias and is therefore not entirely conclusive[99].

Surgical treatment is not well established in patients with extraesophageal symptoms and is not recommended in these cases[58,100]. Numerous studies have examined therapeutic options when clinical versus surgical treatment is in question[99-104] having observed that the frequency of endoscopic fundoplication has decreased in recent years[105].

The elevation of lower esophageal sphincter pressure through a magnetic system (LINX) has been described as a satisfactory alternative to laparoscopic fundoplication and superior to the use of PPIs. The device is installed laparoscopically and consists of a flexible titanium ring with a magnetic core that surrounds the terminal portion of the esophagus to elevate the anti-reflux barrier. Global experience is still limited, and long-term observations of device use are quite restricted[106].

Comment

- GERD that has been properly confirmed by evidence and does not respond satisfactorily to clinical treatment may be an indication for anti-reflux procedures after rigorous preoperative evaluation. However, the lack of response to PPIs may serve as a warning sign regarding the cause of symptoms, as patients who have better responses to surgical treatment are those with

typical symptoms who respond well to clinical treatment with PPIs. On the other hand, surgical treatment is not well established in patients with extraesophageal symptoms, and it is not recommended in these cases.

Endoscopic treatment

Recommendation

- The role of endoscopic procedures in the treatment of GERD is still controversial. They may be indicated in particular and well studied cases.
- Evidence quality: low / recommendation strength: conditional.

Transoral fundoplication is an endoscopic anti-reflux procedure conducted in carefully selected GERD patients in the absence of a hiatal hernia[107,108]. The aim is to restore the valvular mechanisms in the distal esophagus in order to restore lower esophageal sphincter function[109]. The results are still not fully defined, especially long-term observations indicating a loss of efficacy over time[110,111].

Minimally invasive endoscopic methods have been developed to improve the anti-reflux barrier, such as the STRETTA procedure, which is a high-frequency energy delivery system that thickens the muscle of the esophagogastric region, making it more efficient[112]. However, the procedure is challenging to evaluate, in part because the anti-reflux function is not entirely clear. One study showed that 6 months after treatment, symptoms and quality of life had improved substantially, but esophageal acid exposure had not been reduced[113].

Comments

- The role of endoscopic procedures is still controversial due to the short duration of observations and comparative data. There is no consensus on indications and outcomes, and more studies are needed in this regard.

11. Is there a therapeutic indication for the use of alginate in the treatment of GERD?

Recommendation

- Alginate is beneficial in symptom control (heartburn and regurgitation). When alginate is compared to placebo, there are no differences in the proportion of adverse events.
- **Quality of evidence:** very low / strength of recommendation: conditional in favor.

Acid reflux usually occurs in the postprandial period, despite the gastric pH rising with ingested food. The phenomenon of postprandial reflux is due to the formation of a gastric acid pocket, a true layer of gastric juice that sits above the ingested food bolus and below the esophagogastric junction. Studies have shown that alginate is capable of neutralizing or relocating the acid contained in this pocket, thus preventing postprandial reflux[62].

A total of 117 articles were selected. Out of these, 27 were included, and seven were specific in comparing alginate to PPIs or a placebo[114-120]. The studied patients were either refractory to conventional treatment, usually with PPIs, or not, and the analyzed outcomes consisted of symptom resolution or improvement (heartburn and/or regurgitation) and the occurrence of adverse events. In this analysis, 897 patients with non-erosive GERD were treated with PPIs combined with alginate or with alginate alone and were compared with 929 patients on maintenance treatment with PPIs or placebo. An increase of 14% (95%CI 2–25%) in symptom control (heartburn and regurgitation) was observed compared to the aggregate result of using PPIs alone and placebo[115-121]. There was no difference in the frequency of adverse events in the comparison between alginate and PPIs. Any potential low-quality evidence is due to the relatively limited number of patients studied.

Comments

- In GERD patients, alginate provides benefits as a rescue medication for symptom control and can be used alone or in combination with an acid suppressor.

12. Therapeutic trial with PPI. When to prescribe?

Recommendation

- The empirical use of PPIs for 8 weeks is a controversial diagnostic and therapeutic approach that should not be routinely used but only in selected cases.
- **Quality of evidence:** moderate / strength of recommendation: weak.

The indication for the empirical use of PPIs with the purpose of indirectly indicating the presence of GERD is a controversial subject, as recommendations from different highly representative gastroenterology groups and societies are not the same. The American Gastroenterological Association (AGA), for example, formally recommends its use[7]. The Lyon Consensus, on the other hand, states that although pragmatic, the response to PPI therapy does not necessarily equate to a diagnosis of GERD, with the major limitation being the strong variation/modulation of symptoms by esophageal hypersensitivity[122].

It should be considered that symptom relief with PPIs is described by 68% of patients with reflux esophagitis, 49% of patients with GERD with normal endoscopy, and 35% of patients with normal endoscopy and pH monitoring[123].

In patients reporting heartburn, the PPI trial has a sensitivity of 71–78% and specificity of 44–54% when compared to the combination of endoscopy and pH monitoring in the diagnosis of GERD[122,124].

There is a clinical situation where the extra-esophageal manifestations can be atributed to GERD, such as: cough, clearing of throat, hoarseness, dysphonia and globus. In these cases, empirical therapeutic testing with PPI should not be performed and the diagnostic tests for GERD should be conducted without medication use[109].

Limitations of the therapeutic PPI trial, in addition to relatively low specificity, do not include the significant role of visceral hypersensitivity in symptom modulation, and the different concentrations of different PPIs[125].

Comments

- It should be noted that studies that have shown a satisfactory level of evidence with the diagnostic PPI trial are heterogeneous in terms of the PPI used, doses, and evaluation of therapeutic response. On the other hand, certain GERD patients may not show a satisfactory therapeutic response to the trial because they may eventually require higher doses of PPIs or because visceral hypersensitivity has led to an accentuation of clinical manifestations. Therefore, the therapeutic trial is not recommended as routine. However, in certain cases, such as young patients with typical symptoms and a strong diagnostic suspicion of GERD, the diagnostic/therapeutic contribution of the PPI trial may be satisfactory.

ACKNOWLEDGEMENTS

Prof Wanderley Bernardo - University of Sao Paulo Medical School, for the literature survey and statistical research of bibliographical references.

Tiago Alves Barreto - Federação Brasileira de Gastroenterologia, for final alignment of bibliographic references.

Authors' contribution

Moraes-Filho JPP, Domingues G and Chinzon D did the literature search - in addition to that carried out by Wanderley Bernardo, and wrote the text. Moraes-Filho JPP revised the final version of the manuscript.

Orcid

Joaquim P P de Moraes-Filho: 0000-0003-1280-6047.
Gerson Domingues: 0000-0003-0431-451X.
Decio Chinzon: 0000-0003-3030-6687.

Moraes-Filho JPP, Domingues G, Chinzon D, Brazilian GERD Counselors. Diretriz brasileira de conduta terapêutica na doença do refluxo gastroesofágico (Federação Brasileira de Gastroenterologia, FBG). Arq gastroenterol. 2024;61:e23154.

RESUMO – Contexto – A doença do refluxo gastroesofágico (DRGE) é uma condição prevalente no Brasil, afetando 12% a 20% da população urbana, com implicações significativas na qualidade de vida dos pacientes e potencial para complicações. **Objetivo** – Este artigo foca na recente atualização das diretrizes brasileiras para a DRGE, uma revisão necessária devido aos avanços no conhecimento e na prática desde a última publicação há mais de uma década. A atualização presta atenção especial ao papel e à segurança dos inibidores da bomba de prótons (IBPs), reconhecendo as crescentes preocupações sobre seu uso a longo prazo, eventos adversos e prescrição excessiva. **Métodos** – A metodologia da atualização das diretrizes envolveu uma extensa revisão da literatura em múltiplos idiomas (inglês, francês, italiano, espanhol e português), com dados de importantes bases de dados como Medline, Embase e SciELO-Lilacs. **Resultados** – Esta abordagem abrangente resultou em uma seleção cuidadosamente curada de estudos, revisões sistemáticas e meta-análises, focando especificamente em IBPs e outras estratégias terapêuticas para a DRGE. As diretrizes atualizadas são apresentadas em um formato de perguntas e respostas de fácil utilização, aderindo ao sistema PICO (População, Intervenção, Comparação, Resultados) para clareza e facilidade de interpretação. As recomendações são apoiadas por evidências científicas robustas e opiniões de especialistas, aumentando sua aplicabilidade prática em ambientes clínicos. Para garantir a confiabilidade e clareza das recomendações, foi empregado o sistema *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE). Este sistema categoriza a força das recomendações como forte, fraca ou condicional e classifica a qualidade da evidência como alta, moderada, baixa ou muito baixa. Essas classificações fornecem insights sobre o nível de confiança de cada recomendação e a probabilidade de pesquisas futuras impactarem nessas diretrizes. **Conclusão** – O objetivo principal destas diretrizes atualizadas é oferecer conselhos práticos e baseados em evidências para o manejo da DRGE no Brasil, garantindo que os profissionais de saúde estejam equipados com os conhecimentos e ferramentas mais recentes para proporcionar um cuidado ótimo ao paciente.

Palavras-chave – Doença do refluxo; consenso; diretrizes.

REFERENCES

1. Moraes-Filho JPP, Chinzon D, Eisig J, Hashimoto C, Zaterka S. Prevalence of heartburn and gastroesophageal reflux disease in the urban Brazilian population. Arq Gastroenterol. 2005;42:122-7.
2. Moraes-Filho JPP, Navarro-Rodriguez T, Barbuti R, Eisig J, Chinzon D, Bernardo W, et al. Guidelines for the diagnosis and management of gastroesophageal reflux disease: an evidence-based consensus. Arq Gastroenterol. 2010;47:99-115.
3. Qader MA, Phillips CO, Phillips AR, Steward DL, Noordzj JP, WO JM, et al. Proton pump inhibitory therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controled trials. Am J Gastroenterol. 2006;101:2646-54.
4. El-Serag H, Becher A, Jones R. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. Alim Pharmacol ther. 2010;32:720-37.
5. Zhang H, Yang Z, Ni Z, Shi H. A meta-analysis and systematic review of efficacy of twice daily PPIs versus once daily for treatment of gastroesophageal reflux disease. Gastroenterol Res Pract. 2017;9865963.
6. Yadlapati R, Vaezi MF, Vela MF, Spechler SJ, Shaheen NJ, Richter J, et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: Recommendations from an expert panel. Am J Gastroenterol. 2018;113:780-6.
7. Katz PO, Dunbar KB, Schnoll-Sussman F, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2022;117:27-56.
8. Santos CMC, Pimenta CAM, Nobre MRC. A estratégia PICO para construção da pergunta de pesquisa e busca de evidências. Rev Lat Am Enferm. 2007:15;3.
9. Stone PW. Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res. 2002;15:197-18.
10. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Norris S, et al. GRADE guidelines:1. Introduction-Grade evidence profiles and summary of finding tables. J Clin Epidemiol. 2011;64:383-94.
11. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, et al. GRADE-guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401-6.
12. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scand J Gastroenterol. 2005;40:275–85.
13. Sigterman KE, Van Pinxteren B, Numans ME, Bonis PA, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastroesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2006;3 CD002095.
14. Modlin IM, Hunt RH, Malfertheiner P, Moayyedi P, Quigley EM, Tytgat J, et al. Diagnosis and Management of Non-Erosive Reflux Disease – The Vevey NERD Consensus Group. Digestion. 2009;80:74-88.
15. Oshima T, Arai E, Taki M, Takashi K, Tomita T, Fukui H, et al. Randomised clinical trial: vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive oesophagitis. Aliment Pharmacol Ther. 2019;49:140-6.
16. Zhang JX, Ji MY, Song J, Hong-Bo L, Qiu S, Wang J, Ming-Hua A, et al. Proton pump inhibitor for non-erosive reflux disease: A meta-analysis. World J Gastroenterol. 2013;19:8408-19.
17. Ashida K, Sakurai Y, Nishimura A, Kudou K, Hiramatsu N, Umegaki E, et al. Randomised clinical trial: a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the treatment of erosive oesophagitis. Aliment Pharmacol Ther. 2015;42:685-95.
18. DeVault KR. Review article: the role of acid suppression in patients with non-erosive reflux disease or functional heartburn. Aliment Pharmacol Ther. 2006;23(Suppl 1):33-9.
19. Shinozaki S, Osawa H, Hayashi H, Sakamoto H, Kobayashi Y, Lefor AK, et al. Vonoprazan 10 mg daily is effective for the treatment of patients with proton pump inhibitor-resistant gastroesophageal reflux disease. Biomed Rep. 2017;793:231-5.
20. Kaltenbach T, Croclett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease ? An evidence-based approach. Arch Intern Med. 2006;166:965-71.

21. Jacobson BC, Somers SC, Fuch CS, Kelly CP, Camargo-Jr CA. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med. 2006;354:2340-8.
22. Fass R. Gastroesophageal Reflux Disease. N Engl J Med. 2022;387:1207-16.
23. Chen JW, Vela M, Peterson KA, Carlson DA. AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal Gastroesophageal Reflux Disease. Expert Review. Clin Gastroenterol Hepatol. 2023;21:1414-21.e3.
24. Allampati S, Lopez R, Thota PN, Ray M, Birgisson S, Gabbard SL. Use a positional therapy device significantly improves nocturnal gastroesophageal symptoms. Dis Esophagus. 2017;30:1-7.
25. Khan BA, Sodhi JS, Zargar SA, Javid G, Yattoo GN, Shah A, et al. Effect of bed head elevation during sleep in symptomatic patients of nocturnal gastroesophageal reflux. J Gastroenterol Hepatol. 2012;27:1078-82.
26. Watanabe Y, Fujiwara, Shiba M, Watanabe K, Tominaga K, Oshitani N et al. Cigarette smoking and alcohol comsumption associated with gastro-esophageal reflux disease in Japanese men. Scand J Gastroenterol. 2003;38:807-11.
27. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Tobacco smoking cessation and improved gastroesophageal reflux: a prospective population based cohort study. The HUNT study. Am J Gastroenterol. 2014; 109:171-7.
28. Price SF, Smithson KW, Castell DO. Food sensitivity in reflux esophagitis. Gastroenterology. 1978;75:240-3.
29. Person E, Rife C, Freeman J, Asron C, Gastell DO. A novel sleep positioning devices reduces gastroesophageal reflux: a randomized controlled trial. J Clin Gastroenterol. 2015;49:655-9.
30. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal reflux disease. A review. JAMA. 2020;324:2536-47.
31. Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, et al. American Gastroenterological Association medical position statement on the management of gastroesophageal reflux disease. Gastroenterology. 2008;135:1383-91.e5.
32. Ness-Jensen E, Hveem K, El-Serag H, Lagergren J. Life style intervention in gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2016;14:175-182.e1-e3.
33. El-Serag HB, Satia JA, Rabeneck L. Dietary intake and the risk if gastro-esophageal reflux disease. A cross sectional study in volunteers. Gut. 2005;54:11-17.
34. Mehta RS, Nguyen LH, Ma W, Staller K, Song M, Chan AT. Association of diet and lifestyle with the risk of gastroesophageal reflux disease symptoms in US women. JAMA Intern Med. 2021;181:552-4.
35. Cho YK, Choi MG, Park H, Kim JW, Lee DH, KO KH, et al. Efficacy of S-pantoprazole 10 mg in the Symptom Control of Non-erosive Reflux Disease: A Phase III Placebo-controlled Trial. J Neurogastroenterol Motil. 2021;27:223-30.
36. Peura DA, Le Moigne A, Wassel H, Pollack C. Sustained efficacy following resolution of frequent heartburn with an over-the-counter regimen of esomeprazole 20 mg or placebo for 14 days: two randomized trials. BMC Gastroenterol. 2018;22;18:69.
37. Katz PO, Le Moigne A, Pollack C. Analysis of 2-Week Data from Two Randomized, Controlled Trials Conducted in Subjects with Frequent Heartburn Treated with Esomeprazole 20 mg. Clin Ther. 2017;39:960-70.
38. Tan VP, Wong WM, Cheung TK, Lai KC, Hung IFN, Chan P. Treatment of non-erosive reflux disease with a proton pump inhibitor in Chinese patients: a randomized controlled trial. J Gastroenterol. 2011;46:906-12.
39. Zheng RN. Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis. World J Gastroenterol. 2009;15:990-5.
40. Gralnek IM, Dulai GS, Fernnety MB, Spiegel BMR. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol. 2006;4:1452-8.
41. Graham DY and Tansel A. Interchangeable Use of Proton Pump Inhibitors Based on Relative Potency. Clin Gastroenterol Hepatol. 2018;16:800-8.e7.
42. Lee RD, Mulford D, Wu J, Atkinson SN. The effect of time-of-day dosing on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR: evidence for dosing flexibility with a Dual Delayed Release proton pump inhibitor. Aliment Pharmacol Ther. 2010;31:1001.
43. Kinoshita Y, Sakurai Y, Takabayashi N, Kudou K, Araki T, Miyagi T, et al. Efficacy and Safety of Vonoprazan in Patients With Nonerosive Gastroesophageal Reflux Disease: A Randomized, Placebo-Controlled, Phase 3 Study. Clin Transl Gastroenterol. 2019;10:e 00101.
44. Xiao Y, Zhang S, Dai N, Fei G, Goh KG, Chun HJ, et al. Phase III, randomized, double-blind, multicentre study to evaluate the efficacy and safety of vonoprazan compared with lansoprazole in Asian patients with erosive oesophagitis. Gut. 2020;69:224-30.
45. Sakurai K, Suda H, Fujie S, Takeichi T, Okuda A, Murao T, et al. Short-Term Symptomatic Relief in Gastroesophageal Reflux Disease: A Comparative Study of Esomeprazole and Vonoprazan. Dig Dis Sci. 2019;64:815-22. doi:10.1007/s10620-018-5365-0.
46. Kinoshita Y, Sakurai Y, Shiino M, Kudou K, Nishimura A, Miyagi T, et al. Evaluation of the Efficacy and Safety of Vonoprazan in Patients with Nonerosive Gastroesophageal Reflux Disease: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. Curr Ther Res Clin Exp. 2016;81-82:1-7.
47. Ashida K, Sakurai Y, Hori T, Kudou K, Nishimura A, Hiramatsu N, et al. Randomized clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. Aliment Pharmacol Ther. 2016;43:240-51.
48. Dent J, Kahrilas PJ, Hatlebakk J, Vakil N, Denison H, Franzén S, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. Am J Gastroenterol. 2008;103:20-6.
49. Cheng Y, Liu J, Tan X, Dai Y, Xie C, Li X, et al. Vonoprazan versus proton-pump inhibitors for gastroesophageal reflux disease: a systematic review and meta-analysis. Dig Dis Sci. 2021;66:19-28.
50. Laine L, DeVault K, Katz P, Mitev S, Lowe J, Hunt B, et al. Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial. Gastroenterology. 2023;164:61-71.
51. Ren LH, Chen WX, Qian LJ, Li S, Gu M, Shi R, et al. Addition of prokinetics to PPI therapy in gastroesophageal reflux disease: a meta-analysis. World J Gastroenterol. 2014;20:2412-9.
52. Tghvaei T, Kazemi A, Hosseini V, Hamidian M, Fakheri H, Hashemi S, et al. Evaluation of the additive effect of domperidone on patients with refractory gastroesophageal reflux disease; a randomized double blind clinical trial. Middle East J Dig Dis. 2019;11:24-31.
53. Scarpignato C, Sloan JA, Wang DH, Hunt R. Gastrointestinal pharmacology: practical tips for the esophagologist. Ann N Y Acad Sci. 2020:1-18.
54. Zerbib F, Bredenoord AJ, Fass R, KahrilaS PJ, Roman S, Savarino E, et al. ESNM/ANMS consensus paper: diagnosis and management of refractory gastroesophageal reflux disease. Neurogastroenterol Motil. 2021;33:e14075.
55. Lacy BE, Cangemi D, Vasquez-Roque M. Management of chronic abdominal distension and bloating. Clin Gastroenterol Hepatol. 2021;19:219-31.
56. Pauwels A, Raymenants K, Geeraerts A, Boecxtaens V, Masuy I, Broers C, et al. Clinical trial: a controlled trial of baclofen add-on therapy in PPI refractory gastro-oesophageal reflux symptoms. Aliment Pharmacol Ther. 2022;56:231-9.
57. Rivière P, Vauquelin B, Rolland E, Melchior C, Roman S, Varannes SB, et al. Low FODMAPs diet or usual dietary advice for the treatment of refractory gastroesophageal reflux disease: An open-labeled randomized trial. Neurogastroenterol Motil. 2021;33:e14181.
58. Spechler SJ, Hunter JG, Jones KM, Lee R, Smith BR, Mashimo H, et al. Randomized Trial of Medical versus Surgical Treatment for Refractory Heartburn. N Engl J Med. 2019;381:1513-23.
59. Iwakiri K, Sakurai Y, Shiino M, Okamoto H, Kudou K, Nishimura A, et al. A randomized, double-blind study to evaluate the acid-inhibitory effect of vonoprazan (20 mg and 40 mg) in patients with proton-pump inhibitor-resistant erosive esophagitis. Therap Adv Gastroenterol. 2017;10:439-51.
60. Mizuki A, Tatemichi M, Sakakibara T, Miura Y, Zeki S, Ohata M, et al. A Multicenter, Randomized, Open-Label Trial: Efficacy of Once-Daily Versus Twice-Daily Double-Dose Rabeprazole on Refractory Gastroesophageal Reflux Disease-Related Symptoms and Quality of Life. Curr Ther Res Clin Exp. 2016;79:1-7.
61. Fass R, Murthy U, Hayden CW, Malagon B, Pulliam G, Wendel C, et al. Omeprazole 40 mg once a day is equally effective as lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease (GERD) who are resistant to conventional-dose lansoprazole therapy-a prospective, randomized, multi-centre study. Aliment Pharmacol Ther. 2000;14:1595-1603.
62. Savarino V, Marabotto E, Zentilin P, Demarzo MG, Bortoli N, Savarino E. Pharmacological management of gastro-esophageal reflux disease: an update of the state-of-the-art. Drug Des Devel Ther. 2021;15:1609-21.

63. Ribolsi M, Cicala M, Zentilin P, Neri M, Mauro A, Efthimakis K, et al. Prevalence and clinical characteristics of refractoriness to optimal proton pump inhibitor therapy in non-erosive reflux disease. Aliment Pharmacol Ther. 2018;48:1074-81.
64. Vela MF, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. Aliment Pharmacol Ther. 2003;17:243-51.
65. Cho JH, Koo JY, Kim KO, Lee SH, Jang BI, Kim TN, et al. On-demand versus half-dose continuos therapy with esomeprazole for maintenance treatment of gastroesophageal reflux disease. A randomized comparative study. Medicine (Baltimore). 2018;43:e12732.
66. Ashida K, Iwakiri K, Hiramatsu N, Sakurai Y, Hori T, Kudou K, et al. Maintenance for healed erosive esophagitis: phase III comparison of vonoprazan with lansoprazole. World J Gastroenterol. 2018;24:150-1.
67. Bayerdörffer E, Bigard MA, Weiss W, Mearin F, Rodrigo L, Muñoz JED. Randomized multicenter study: on-demand versus continuous maintenance treatment with esomeprazole in patients with non-erosive gastroesophageal reflux disease. BMC Gastroenterol. 2016;16:48.
68. Nagahara A, Hojo M, Asaoka D, Sasaki H, Watababe S. A randomized prospective study comparing the efficacy of on-demand therapy versus continuous therapy for 6 months for long term maintenance with omeprazole 20mg in patients with gastroesophageal reflux disease in Japan. Scand J Gastroenterol. 2014;49;409-17.
69. Fass R, Delemos B, Nazareno L, Kao R, Xiang J, Lu Y. Clinical trial: maintenance intermitent therapy with rabeprazole 20mg in patients with symptomatic gastroesophageal reflux disease : a double-blind, placebo-controlled, randomized study. Aliment Pharmacol Ther. 2010;31: 950-60.
70. Tepes B, Stabuc C, Kocijancic B, Ivanusa M. Maintenance therapy of gastroesophageal reflux disease patients with omeprazole. Hepatogastroenterology. 2009;56:67-74.
71. Morgan DG, O'Mahony MF, O'Mahony WF, Roy J, Camacho F, Dinniwell J, et al. Maintenance treatment of gastroesophageal reflux disease: an evaluation of continuous and on-demand therapy with rabeprazole 20 mg. Can J Gastroenterol. 2007;21:820-6.
72. Gohl KL, Benamouzig R, Schwan T. Efficacy of pantoprazole 20 mg daily compared with esomeprazole 20 mg daily in the maintenance oh healed gastroesophageal reflux disease: a randomized double-blind comparative trial - the EMANCIPATE study. Eur J Gastroenterol Hepatol. 2007;19:205-11.
73. Sjöstedt S, Befrits R, Sylvan A, Harthon C, Jörgensen J, Carling L, et al. Daily treatment with esomeprazole is superior to that taken on-demand for maintenance of healed erosive esophagitis. Aliment Pharmacol Ther. 2005;22:183-91.
74. Bour B, Staub JL, Chousterman M, Labayle D, Nalet B, Nouel O, et al. Long term treatment of gastroesophageal reflux disease patients with frequent symptomatic relapsesusing rabeprazole on-demand treatment compared with continuous treatment. Aliment Pharmacol Ther. 2005:21:805-12.
75. Scholten T, Dekkers CP, Schültze K, Körner T, Bohuschke M, Gatz G. On demand therapy with pantoprazole 20 mg as effective long term management of reflux diseases in patinets with mild GERD: the ORION trial. Digestion. 2005;72:76-85.
76. Tsai HH, Chapmen R, Shepherd A, McKeith D, Anderson M, Vearer D, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lanzoprazole 15 mg in the long-term maintenance of endoscopy-negative gastroesophageal reflux patients: the COMMAND study. Aliment Pharmacol Ther. 2004;20:657-65.
77. Talley NJ, Venables TL, Green JRB, Armstrong D, O'Kane KPJ, Giaffer M, et al. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-oesophageal reflux disease: a placebo-controlled trial of on-demand therapy for 6 months. Eur J Gastroenterol. 2002;14:857-63.
78. Talley NJ, Lauritsen K, Tunturi-Hihnala H, Lind T, Moum B, Bang C, et al. Esomeprazole 20 mg maintain symptoms in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of "on-demand" therapy for 6 months. Aliment Pharmacol Ther. 2001;15:347-54.
79. Schindlbeck NE, Klauser AG, Berghammer G, Londong W, Müller-Lissner SA. Three year follow-up of patients with gastroesophageal reflux disease. Gut. 1992;33:1016-9.
80. Moyayyedi P, Eikelboom JW, Bosch J, Connoly S, Dyal L, Shestakovska O, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxabanor aspirin. Gastroenterology. 2019;1579:682-91.e2.
81. Freedberg DE, Lawrence S K, Yu-Xiao Y. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterology Association. Gastroenterology. 2017;152:706-15.
82. Srinutta T, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, et al. Proton pump inhibitors and hypomagnesemia: a meta-analysis of observational studies. Medicine. 2019;98:e17788.
83. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang A, Coresh J, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176:238-46.
84. Klatte DCF, Gasparini A, Xu H, Deco P, Trevisan M, Johansson ALV, Wettermark B, et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. Gastroenterology. 2017;153:702-10.
85. Jaynes M, Kumar AB. The risks of long term use of proton pump inhibitors: a critical review. Ther Adv Drug Saf. 2019;10: 2042098618809927.
86. Clooney AG, Berstein CW, Leslie WD, Vagianos K, Sargent M, Laserna-Mendieta EJ, et al. A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. Aliment Pharmacol Ther. 2016;43:974-84.
87. Sarkar M, Hennessy S, Yang Y-X. Proton pump inhibitor use and the risk for community adquired pneumonia. Ann Intern Med. 2008;149:391-8.
88. Schneider JL, Kolitsopoulos F, Corley DA. Risk of gastric cancer, gastrointestinal cancers and other cancers: a comparison of treatment with pantoprazole and other proton pump inhibitors. Aliment Pharmacol Ther. 2016;43:73-82.
89. Castellana C, Pecere S, Furnari M, Telese A, Matteo MV, Haidry R, et al. Side effects of long-term use of proton pump inhibitors: practical considerations. Pol Arch Intern Med. 2021;131:541-9.
90. Zicos TA, Clarke JO. Non-acid Reflux: When It Matters and Approach to Management. Curr Gastroenterol Rep. 2020;22:43-53.
91. Zerbib F, des Varannes SB, Roman S, Ponderoux P, Artigue F, Chaput U, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. Aliment Pharmacol Ther. 2005;22:1011-21.
92. Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol. 2004;99:1037-43.
93. Zerbib F, Smout AJ. Review article: the measurement of non-acid gastroesophageal reflux. Aliment Pharmacol ther. 2007;26(Suppl 2):7-12.
94. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut. 2004;53:1024-2031.
95. Frazzoni M, de Bortoli N, Frazzoni L, Tolone S, Savarino V, Savarino E. Impedance-pH monitoring for diagnosis of disease:new perspectives. Dig Dis Sci. 2017;62:1881-9.
96. Xiao Y, Liang M, Peng S, Zhang N, Chen M. Tailored therapy for the refractory GERD patients by combined multichannel intraluminal impedance-pH monitoring. J Gastroenterol Hepatol. 2016;31:350-4.
97. Farré R, Fornari F, Blondeau K, Vieth M, Vos RD, Bisschops R, et al. Acid and weakly acidic solutions impair mucosal integrity of distal exposed and proximal non-exposed human oesophagus. Gut. 2010;59:164-9.
98. Li S, Shi S, Chen F, Lin J. The effects of baclofen for the treatment of gastroesophageal reflux disease: a meta-analysis of randomized controlled trials. Gastroenterol Res Pract. 2014;2014:307.
99. McKinley SK, Dirks KC, Walsh D, Hollands C, Arthur LE, Rodriguez N, et el. Surgical treatment of GERD: systematic review and meta-analysis. Surg Endosc. 2021;35:4095-4123.
100. Kahrilas PJ, Altman KW, Chang AB, Field SK, Harding SM, Lane AP, et al. Chronic cough due to gastroesophageal reflux in adults: CHEST guideline and expert panel report. Chest. 2016;150:1341-60.
101. Anvari M, Allen C, Marshall J, Armstrong D, Goere R, Ungar W, et al. Randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-years outcomes. Surg Endosc. 2011;25:2547-54.

102. Galmiche JP, Hatlebakk J, Atwood S, Ell C, Fiocca R, Eklund S, et al. Laparoscopic antireflux surgery versus esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA. 2011;305: 1969-77.
103. Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Thor K, Lamm M, et al. Long term management of gastro-oesophageal reflux disease with omeprazole or open antireflux surgery: results of a prospective, randomized clinical trial. Eur J Gastroenterol Hepatol. 2000;12:879-87.
104. Lundell L, Miettinen P, Myrvold HE, Hatlebakk JG, Wallin L, Malm A, et al. Seven-year follow-up of a randomized clinical trial comparing proton pump inhibition with surgical therapy for reflux oesophagitis. Surg. 2007;94:198-203.
105. Swidnicka-Siergiejko AK, Marek T, Wasko-Czopnik D, Gasiorowska A, Skrzdlo-Radomanska B, Janiak M, et al. Diagnostic and therapeutic management in gastroesophageal reflux disease: consensus of the Polish Society of Gastroenterology. Polskie Archiwum Medycyny Wewnetrznej. 2022;132:1-77.
106. Bell R, Lipham J, Louie BE, Williams V, Luketich J, Hill M, et al. Magnetic sphincter augmentation superior to proton pump inhibitors for regurgitation in a 1-year randomized trial. Clin Gastroenterol Hepatol. 2020;135:1392-1413.e5.
107. Hunter JG, Kahrilas PJ, Bell RC, Wilson EB, Trad KS, Dolan JP, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. Gastroenterology. 2015;148:324-333.e5.
108. Yadlapati R, Gyawali P, 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.e1.
109. Chang KJ, Bell R. Transoral Incisionless Fundoplication. Gastrointest Endosc Clin N Am. 2020;30:267-89.
110. Huang X, Chen S, Zhao H, Zeng X, Lian J, Tseng Y, et al. Efficacy of transoral incionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis. Surg Endosc. 2017;31:1032-104.
111. Santiago ER, Albeniz A, Estremera-Arevalo F, Sanchez-Vegazo CT, Lorenzo-Zúñica V. Endoscopic anti-reflux therapy for gastroesophageal reflux disease. World Gastroenterol. 2021;27:6601-6.
112. Fass R, Cahn F, Scotti DJ. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. Surg Endosc. 2017;31:4865-82.
113. Corley DA, Katz P, Wo JM, Stefan A, Patti M, Rothstein, et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham- controlled trial. Gastroenterology. 2003;125: 668-76.
114. Fletcher J, Wirz A, Young J, Vallance R, McColl KEL. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. Gastroenterology. 2001;121:775-83.
115. Kim JH, Lee YC, Kim EH, Park JC, Shin SK, Lee SK, et al. The Clinical Efficacy of a Pure Alginate Formulation (Lamina G) for Controlling Symptoms in Individuals with Reflux Symptoms: A Randomized Clinical Study. Gut Liver. 2019;13:642-8.
116. Reimer C, Lødrup AB, Smith G, Wilkinson J, Bytzer P. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. Aliment Pharmacol Ther. 2016;43:899-909.
117. Sun J, Yang C, Zhao H, Zheng P, Wilkinson J, Ng B, et al. Randomised clinical trial: the clinical efficacy and safety of an alginate-antacid (Gaviscon Double Action) versus placebo, for decreasing upper gastrointestinal symptoms in symptomatic gastroesophageal reflux disease (GERD) in China. Aliment Pharmacol Ther. 2015;42:845-54.
118. Thomas E, Wade A, Crawford G, Jenner B, Levinson N, Wilkinson J, et al. Randomised clinical trial: relief of upper gastrointestinal symptoms by an acid pocket-targeting alginate-antacid (Gaviscon Double Action) - a double-blind, placebo-controlled, pilot study in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2014;39:595-602.
119. Chiu CT, Hsu CM, Wang CC, Chang J-J, Sung CM, Lin CJ, et al. Randomised clinical trial: sodium alginate oral suspension is non-inferior to omeprazole in the treatment of patients with non-erosive gastroesophageal disease. Aliment Pharmacol Ther. 2013;38:1054-64.
120. Pouchain D, Bigard MA, Liard F, Childs M, Decaudin A, McVey D. Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. A direct comparative randomised trial. BMC Gastroenterol. 2012;23;12-18.
121. Chatfield S. A comparison of the efficacy of the alginate preparation, Gaviscon Advance, with placebo in the treatment of gastro-oesophageal reflux disease. Curr Med Res Opin. 1999;15:152-9.
122. Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM. et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018;67: 1351-62.
123. Bytzer P, Jones R, Vakil N, Junghard O, Tind T, Werbersson B, et al. Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease.Clin Gastroenterol Hepatol. 2012;10:1360-6.
124. Gyawali CP, Fass R. Management of Gastroesophageal Reflux Disease. Gastroenterology. 2018;154:302-18.
125. Roman S, Keefer L, Imam H, Korrapati P, Mogni B, Eident K, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. Neurogastroenterol Motil. 2015;27:1667-74.