Gastroesophageal reflux disease: a practical approach

Gerson **DOMINGUES**[1] and Joaquim Prado P de **MORAES-FILHO**[2]

ABSTRACT – Gastroesophageal reflux disease (GERD) presents typical manifestations such as heartburn and/or regurgitation as well as atypical manifestations such as throat symptoms, laryngitis, hoarseness, chronic cough, asthma, and sleep alterations. There are two phenotypes of the disease: erosive GERD, when erosions are identified by upper digestive endoscopy, and non-erosive GERD, when the esophageal mucosa presents a normal endoscopic aspect. Relevant clinical findings are usually absent in the physical examination, but it should be highlighted that obesity is an important aggravating factor of reflux. The treatment is established based on clinical findings and, according to the clinical situation, on complementary exams such as upper digestive endoscopy. In dubious cases where a precise diagnosis is required, the indicated test is esophageal pHmetry or impedance-pHmetry. Clinical treatment is divided into behavioral/dietary measures and pharmacological measures. Most patients benefit from clinical treatment, but surgical treatment may be indicated in the presence of a larger hiatal hernia and complications of the disease.

Keywords – Gastroesophageal reflux disease; diagnosis; treatment.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic condition that develops when reflux of the gastric contents causes troublesome symptoms and/or complications[1]. It is one of the most common diagnoses among outpatients of the gastroenterology clinic[1].

A population-based study covering approximately 14,000 people in 22 cities in different regions identified a prevalence of approximately 12% to 20% in the urban Brazilian population[2].

A very important aspect of the disease is the reduction in the quality of life of the affected individuals. For example, the quality of sleep of the affected individuals might be compromised since nocturnal reflux is relatively frequent, causing awakenings, REM sleep interruptions, and the shortening of the individual's sleep time[3]. In addition to health as a whole, the reduction in quality of life has negative consequences on social activities and labor productivity, with a resulting financial impact (absenteeism, cost of medication, medical consultations, loss of working hours, etc).

Traditionally, when GERD is suspected, an acid-suppressive medication is started, particularly proton pump inhibitors (PPIs). However, up to 40% of these patients treated with PPIs may show incomplete or no response to therapy[4-6].

METHODS

In order to achieve a comprehensive narrative review, the relevant literature was assessed in Pubmed, Medline, and other sources using the following search terms: heartburn, pyrosis, gastroesophageal reflux, GERD, refluxate, endoscopy of gastroesophageal reflux disease, esophagitis, and esophageal motility.

1. Etiopathogenesis and pathophysiology

The process by which gastroesophageal reflux causes GERD consists of a sequence of events that involve the esophagogastric junction (EGJ) and esophageal body, as well as mechanisms of visceral sensitivity regulation mediated by the central and peripheral nervous system. The imbalance between protective and aggressive factors is responsible for the development of GERD.

The main protective factors are the lower esophageal sphincter (LES), saliva, peristalsis, and the angle of esophageal passage through the hiatus (angle of Hiss). The aggressive factors are represented by the transient lower esophageal sphincter relaxations, hypotension of the LES, refluxed gastric acid pH, increased distensibility of the LES, prolonged esophageal clearance, reduced gastric emptying speed, and hiatus hernia[7].

Anti-reflux barrier
Esophagogastric junction and angle of Hiss

The EGJ involves the superposition of the lower esophageal sphincter and the diaphragmatic crura (DC) and represents the anti-reflux barrier[7,8], the main defensive factor. The LES maintains a zone of high pressure due to the tone of the intrinsic muscles and the excitatory stimulation of cholinergic neurons[9]. The diaphragmatic crura provides extrinsic compression to the LES, contributing to the resting pressure, with approximately 5 to 10 mmHg[10].

The oblique entry of the esophagus into the stomach creates an acute angle with the great gastric curvature, called Hiss angle, which creates a valve effect that contributes to the competence of the EGJ[8].

2. Mechanisms that favor gastroesophageal reflux

a. Transient lower esophageal sphincter relaxations

The main pathophysiological mechanism of GERD is the transient relaxation of the LES (TLESR)[11,12]. The TLESR is mediated by the vagus nerve and strongly influenced by the proximal gastric distension, food, or gas, which precipitate the activation of mechanoceptors adjacent to the cardia. Patients with GERD do not present a higher number of TLESR episodes than control individuals; however, in patients with GERD, TLESRs are more associated with acid reflux[12].

Acid reflux is much more common than non-acid reflux in the etiopathogenesis of GERD: in less than 10% of the patients, the reflux may be weakly acid or even alkaline[13].

The so-called "gastric reflux" contains harmful material that is capable of injuring the esophagus and/or generating symptoms. Esophageal exposure to gastric reflux is therefore the primary determinant of disease severity. The greater or lesser intensity of esophagitis is related to the time of acid exposure, pH of the refluxed gastric content, and resistance of the esophageal mucosa[13].

b. Hiatal hernia

Hiatal hernia (HH) is defined by the proximal migration of the LES in relation to the DC, which occurs mainly by the weakening or rupture of the phrenoesophageal ligament and results in a more incompetent anti-reflux barrier[14]. The Brazilian Consensus on GERD based on Evidence quotes HH as a risk factor for the persistence of symptoms to clinical treatment[15]. HH with a size larger than 3 cm or more is related to significantly higher levels of acid exposure in the distal esophagus and erosive esophagitis[14]. Patients with HH have more reflux episodes and higher acid exposure than normal patients[15]. Moreover, the gastric content that is retained in the hernial sac (between the LES and the diaphragmatic crura) refluxes when the LES relaxes during swallowing, characterizing the phenomenon of superimposed reflux[16,17].

c. Acid pocket

After meals, it was observed that the content that refluxes into the esophagus has comparatively more acid than the gastric body and stems from a region near the EGJ where an acid "pouch" is found, resulting from the neoformation of acidic supernatant from the parietal cells in the proximal gastric region[18,19]. The acid pouch volume is larger in patients with GERD than in controls, and larger acid pouches are found in patients with GERD and large HH (>3 cm)[20]. It has been shown that the location of the acid pouch is more important than the volume: supradiaphragmatic pouches result in 74% to 85% of acid reflux during TLESR, while more distal pouches result in 7% to 20% of acid reflux during TLESR[18].

d. Esophageal clearance

After the reflux reaches the esophagus, the main defense against the refluxed acid content is the mechanical esophageal clearance, done by peristalsis and the chemical clearance, promoted by the alkaline pH of saliva[15,21].

e. Slow gastric emptying

The rationale for slow gastric emptying rely on the hypothesis that this phenomenon generates gastric distension, which could trigger TLESR episodes[22].

f. Gastroesophageal valve

Patients with GERD have more obtuse insertion angles than controls, resulting in a higher degree of opening of the EGJ and a higher number of reflux events[15,17].

g. Impairment of reflux clearance

Under normal conditions, the primary peristalsis induced by swallowing brings down the esophageal bicarbonate-rich saliva, promoting chemical clearance and pH normalization. However, it is important to mention that the chemical clearing of reflux is impaired by the reduced amplitude of peristaltic muscle contraction, as observed in patients with erosive esophagitis compared to normal controls[23]. Moreover, volumetric clearing in the distal esophagus is aided by the action of secondary peristalsis, which is a reflex and is mediated by the stimulation of mechanical receptors that respond to distension of the distal esophageal walls caused by reflux[24].

3. Factors that influence symptom perception

There may be a low correlation between the presence of acid reflux and symptoms. This is sometimes observed in patients with more severe GERD symptoms who may have low esophageal acid exposure, while those with mild symptoms often have a high acid exposure in the distal esophagus. This observation suggests that there are other factors besides the acid reflux that influence the perception of symptoms, such as the sensitivity of each individual in the perception of stimuli, which is related to the psycho-emotional aspect. Stress, tension, anxiety, and depression may be factors that influence sensitivity, i.e., the generation of symptoms[18] (visceral hypersensitivity).

a. Characteristics of reflux

With the implementation of impedance-pHmetry, it was possible to characterize the reflux as to its acidity and composition, as well as to identify the level of its rise, allowing the study of the relationship between these variables and GERD symptoms. The reflux may be classified as acid (pH <4) and non-acid, which is subdivided into mildly acid (pH 4–7) and mildly alkaline (pH >7).

Reflux episodes with pH <4 are capable of generating symptoms, but impedance-pHmetry studies suggest that a certain percentage of patients with symptomatic episodes are associated with non-acid reflux[25]. In this context, a recent meta-analysis drew attention to the importance of non-acidic reflux episodes, although in low incidence, as a cause of symptoms, especially in patients who are non-responsive to proton pump inhibitors (PPIs)[25].

Reflux may contain other harmful constituents besides gastric hydrochloric acid, such as pepsin, trypsin, or bile acids. Studies have shown that biliary reflux and mixed (acid-biliary) reflux account for only 6–9% and 12% of symptomatic reflux, respectively, in patients not using PPIs[26,27].

b. Contraction of the longitudinal muscle of the esophagus

The presence of acid in the esophagus may also produce symptoms by inducing the spasm of the longitudinal muscles of the esophagus, which is one of the causes of heartburn. This finding suggests that a motor disorder may be the cause of heartburn, associated or not with acid reflux[28].

c. Integrity of the esophageal mucosa

In patients with erosive esophagitis, a clear breakdown of the squamous epithelium barrier is observed, which allows the reflux components to stimulate nociceptors in the lamina propria, causing symptoms. In patients with non-erosive GERD, it has been suggested that a microscopic damage to the mucosa may be a factor associated with the development of symptoms[29]. A microscopic change in the mucosa to be considered is the presence of dilated intercellular spaces (DIS), which increase the esophageal mucosa permeability. It is worth mentioning, however, that the relationship between the presence of these changes and symptom perception has not been proven[30].

d. Hypersensitivity

The perception of symptoms in GERD is related) to the increased sensitivity of the esophagus to several stimuli. This visceral hypersensitivity could be a consequence of the positive regulation of peripheral afferent nerve receptors by the acid-induced inflammation[31].

In addition to peripheral sensitization, sensitization of a central nature plays an essential role in esophageal hypersensitivity. The hypothesis is that acid stimulation in the esophagus promotes sensitization of the cingulate and insular cortex, which are part of the limbic system and process and modulate the sensory signals of the gastrointestinal tract. Consequently, there is a reduction in the pain threshold, which starts to occur with non-painful stimuli[32,33].

DIAGNOSIS

1. Clinical presentation

The typical symptoms of GERD are heartburn and regurgitation. atypical manifestations of the disease, which may not be accompanied by any of the typical symptoms, include: chest pain and otorhinolaryngological and pulmonary manifestations such as cough, laryngitis, asthma, hoarseness, hawking, and globus sensation[34]. Chronic cough, chronic laryngitis, and asthma are multifactorial processes that may have reflux as a potential aggravating factor and, therefore, GERD may not be the only cause of these manifestations[35].

Studies have shown that GERD may interfere in the quality of sleep, and heartburn may occur during the sleep period in 25% of the cases[36]. Therefore it is important to note that nighttime heartburn and complaints related to sleep quality are more frequent in patients with GERD and that the treatment of these patients with PPIs may improve sleep quality[37].

The diagnosis based only on the anamnesis and physical examination for patients aged less than 45 years, with typical GERD symptoms, without warning signs (anemia, digestive hemorrhage, weight loss, dysphagia, and odynophagia), and without further investigation, is a conduct recommended by many authors, including the Latin American GERD Consensus[38]. The III Brazilian Consensus on GERD, however, recommended that every patient with suspected or diagnosed GERD should undergo an upper digestive endoscopy (UDE) before the beginning of treatment[9]. This guideline is based on the fact that the UDE is a safe and an easily performed procedure, widely available, and of low cost in our environment, besides excluding eventual diseases that may occur with non-characteristic symptoms.

2. Non-erosive reflux disease (NERD)

It is the most frequent form of the disease, defined by the presence of classic or atypical GERD symptoms associated with reflux and the absence of lesions in the endoscopic examination[1]. The patients diagnosed with GERD constitute a heterogeneous group, since a portion of these patients present symptoms related to the esophageal exposure to abnormal acid, while others are symptomatic, presenting symptoms associated with reflux, but with a normal total time of acid exposure, which is called esophageal reflux hypersensitivity[39]. On the other hand, some patients with reflux symptoms neither present evidence of the presence of abnormal acid reflux nor of the association with reflux. It has been suggested as a differential diagnosis that the latter present symptoms as a consequence of inflammation, gastrointestinal motility abnormalities, or visceral hypersensitivity (functional pyrosis)[39,40].

The diagnosis of laryngo-pharyngeal reflux (LFR) is more difficult than in typical GERD because of the lack of definitive diagnostic methodology, since most diagnostic tests for LFR, such as laryngoscopy, UDE, and esophageal pHmetry, have shown low sensitivity in detecting that reflux may be the cause of laryngeal symptoms. Therefore, there is no diagnostic test that unequivocally characterizes any extra-esophageal symptom to GERD[41].

3. Erosive reflux disease

It consists of the classic presentation of the disease with the occurrence of suggestive symptoms and the presence of erosions in the UDE, although the exam does not have a high specificity[42]. The most frequently used classification nowadays is the Los Angeles classification[43] (FIGURE 1).
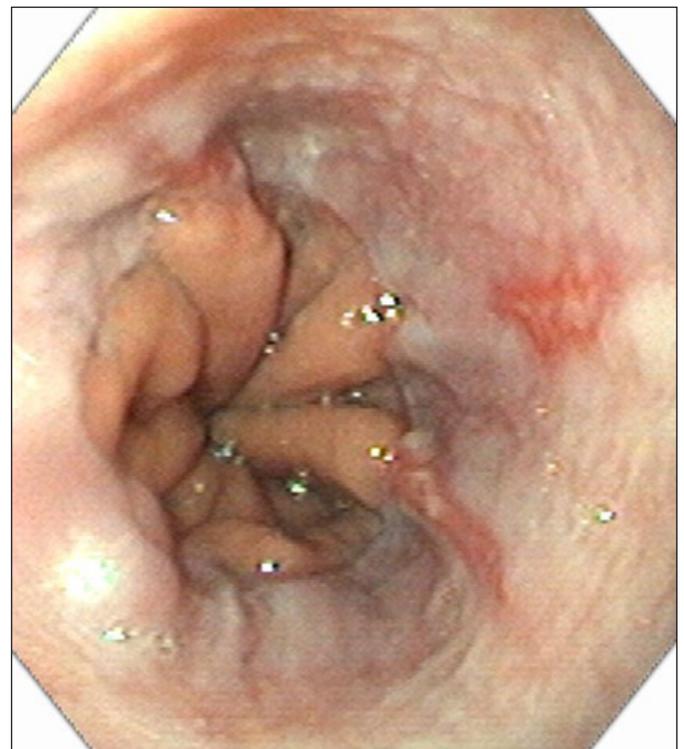

FIGURE 1. Erosive GERD. Presence of mucosal erosions. Esophagitis grade A according to the Los Angeles classification[44].

4. PPI testing

As above mentioned, the empirical therapeutic test with standard-dose PPIs is satisfactory in some cases, allowing the inference of the GERD diagnosis[45]. The test has, however, limitations due to its low specificity and because there is no standardization regarding the drug to be used, the dose, or the observation time. Due to these considerations, the Brazilian GERD Consensus does not recommend the use of the therapeutic test[9].

5. Endoscopic examination and esophageal biopsy

The endoscopic examination is indicated for cases in which it might contribute to the diagnosis of lesions caused by the reflux, such as in the characterization of erosions and enabling the performance of biopsies, which are indispensable for the diagnosis of complications such as Barrett's esophagus, esophageal ulcers, stenosis, and esophageal adenocarcinoma[46,47].

6. 24-hour pHmetry or prolonged ambulatory pHmetry

The test evaluates the acidic pH inside the esophagus. It is particularly indicated for patients with the non-erosive form of the disease, for the evaluation of patients refractory to PPIs, and in situations in which the diagnosis of GERD is questionable. It must be remembered that the 24-hour pH measurement is the only test that allows us to verify the association between reflux and the presence of symptoms[46].

Very satisfactory results in the determination of esophageal acid pH have been described with the use of Bravo® capsule (Medtronics Inc., USA), which is an improvement of extended pHmetry. The capsule allows the period of assessment of intra-esophageal pH to be extended from 24 to 48 hours and up to 96 hours, which may represent an increase of approximately 25% in the diagnostic capacity. Extending the monitoring time may be especially useful for patients with infrequent symptoms and to optimize the reflux-symptom association[48,49].

7. pH-impedance

It is currently considered the gold standard test for the diagnosis of GERD[50,51]. It allows the identification of the food bolus direction, in anterograde (deglutition) or retrograde (reflux), differentiating between the physical (liquid, gaseous or mixed) and chemical properties of the food bolus, characterizing the reflux episodes in acid and non-acid. The 24-hour monitoring by the impedance-pHmetry system has greater sensitivity than pHmetry alone in the detection of gastroesophageal reflux[40] (FIGURE 2). The indications are the same as those of 24-hour pHmetry.

pH-impedance can be performed with or without PPI therapy. Basically, when the diagnosis of GERD has not yet been established, the study should be better performed without the use of PPIs. On the other hand, the study with the use of PPIs is reserved for patients whose GERD diagnosis has already been established, but there is the persistence of symptoms, or in the evaluation of the treatment in patients with Barrett's esophagus[48].

Recently, it has been sugggested a role to non-acid (or weakly acidic) reflux in the genesis of otorhinolaryngological symptoms, especially cough, hoarseness and globus, in patients being treated with PPIs[25]. In these patients with LFR, especially those in whom there was no response to the test with PPIs or the response was partial, pH-impedance may reveal the association of symptoms with acid and non-acid reflux[48]. New parameters in esophageal pH-impedance analysis were recently introduced: the post-reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal basal impedance (MNBI)[52,53]. With the use of these new parameters, it was possible to increase the spectrum of GERD diagnosis in patients whose association between reflux and symptoms was not evident during the test[52,53].

PSPW evaluates the effectiveness of esophageal chemical clearance, referring to a swallow that occurs within 30 seconds of a reflux event. The PSPW index is defined as the number of events followed by a PSPW divided by the total number of reflux events, being very useful in the distinction between GERD and functional heartburn. This parameter is an independent predictor of refractoriness to IBP[54]. The percentage value of PSPW is lower in patients with abnormal acid exposure compared to healthy volunteers and patients with functional heartburn[52].

The nocturnal basal impedance of the esophageal mucosa MNBI is a measure of permeability and, therefore, translates the integrity of the esophageal mucosa in the distal esophagus. This parameter is measured during sleep, where we observe a lower number of swallows that can impact the result of the evaluation. MNBI increases the diagnostic range of pHmetry because, like PSPW, it helps in the differential diagnosis between NERD and functional heartburn[54]. A prospective study showed that MNBI has a predictive value for symptomatic response to anti-reflux therapies[55]. Patients with abnormal acid exposure time have lower baseline impedance values in the distal esophagus compared to healthy controls and patients with functional heartburn[45].

8. Lyon Consensus

According to the Lyon Consensus[50], the main modifications proposed for the diagnosis of GERD are as follows:

In the endoscopic examination, confirmatory evidence for GERD must be considered: esophagitis grades C and D (Los Angeles classification) and peptic stenosis. Esophagitis grades A and B may be nonspecific, provided that they may occasionally be present in normals. Barrett's epithelium must be confirmed by biopsy.

On pH-impedance, esophageal acid exposure time <4% is normal (physiologic) and >6% abnormal. Intermediate values: inconclusive.

Reflux monitoring (pHmetry/impedance-pHmetry) should be performed without the use of PPIs.
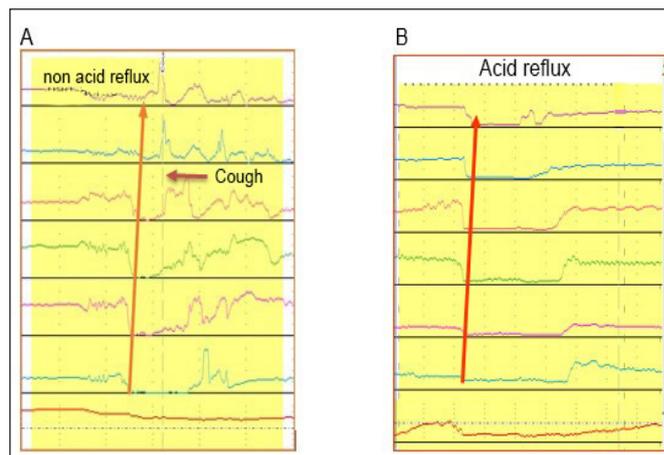

FIGURE 2. pH-impedance tracing demonstrating the presence of: A. An episode of non-acid reflux (slightly acidic) associated with a cough episode. B. An episode of acid reflux.

TREATMENT

The clinical therapy aims to minimize the harmful effects to the esophagus of the refluent material (reflux), whose pH in the absolute majority of times is acidic. It aims, therefore, to relieve symptoms, heal lesions when present, avoid recurrences, and prevent complications. Behavioral, pharmacological, endoscopic, and surgical therapeutic modalities are available for the treatment of GERD. The endoscopic treatment, although quite promising, is still not consensually indicated and therefore, it must not be recommended as an alternative[56].

The ideal therapy should aim at correcting the motor defects of the disease, particularly the TLESR. With this objective, products such as Baclofen, a type B agonist of the gamma-aminobutyric acid (GABA) receptor, showed some satisfactory therapeutic results; however, it presents side effects that limit its use[57].

1. Clinical treatment

The great majority of patients benefit from clinical treatment that should encompass behavioral and pharmacological measures.

Apparently, patients with erosive GERD may respond better to treatment than those with the non-erosive form[58]. However, it is worth highlighting that a well conducted meta-analysis showed that, when the diagnosis is accurately established with the inclusion of functional tests, patients with the non-erosive form respond in a similar manner as those with the erosive form[59].

a. Behavioral measures

Change in lifestyle is part of the GERD treatment, comprising the so-called behavioral measures, which aim to avoid situations that promote or facilitate gastroesophageal reflux (FIGURE 3).

The reduction in body weight is important. There is evidence of a significant association between symptomatology improvement and body mass index (BMI) reduction in obese patients who have lost at least 2 kg/m^2 in BMI[60]. So, the reduction in body weight is important.

Behavioral measure	Note
Elevation of the head of the bed (15 cm). Preference for right lateral decubitus.	Indicated in more severe cases, especially when there is nocturnal reflux.
Avoid lying down after meals: wait for 2–3 hours.	Important measure particularly in nocturnal reflux.
Body weight reduction in obese people and overweight patients.	Elevated intragastric pressure and fatty infiltration of the esophagogastric junction in these cases are factors that favor gastroesophageal reflux.
Avoid: fatty foods, alcohol, chocolate, tomatoes, coffee, tea, carbonated drinks.	Selective elimination, particularly when there is a food/symptom correlation.

FIGURE 3. Behavioral measures in the treatment of GERD[17,69].

No consistent associations in the relationship between GERD and certain diets have been demonstrated, with varying levels of evidence and degrees of recommendation. However, from a practical point of view, instructions regarding the diet such as eating slowly, avoiding liquids at meals, and avoiding foods that notoriously trigger symptoms (such as fatty foods, chocolate, tomatoes, etc.) may be recommended according to the clinical conditions and the patient's acceptance, with satisfactory results.

b. Pharmacological treatment

Pharmacologic options are: I) proton pump inhibitors, II) antacids, III) histamine H2 receptor blockers, IV) alginate.

I. Proton pump inhibitors (PPIs)

In clinical practice, the treatment of choice are the PPIs, which have high healing rates and are safe and effective drugs. PPIs inhibit acid secretion by inactivating the hydrogen-ATPase molecules (proton pump) of parietal cells (TABLE 1).

TABLE 1. Proton pump inhibitors. Daily doses.

Proton pump inhibitor	Daily standard dose/mg
Omeprazole	40
Lansoprazole	30
Pantoprazole/pantoprazole	40
Rabeprazole	20
Esomeprazole	40
Dexlansoprazole	30–60

PPIs have been widely used for decades, but the number of recent publications questioning their safety has increased dramatically, causing considerable patient anxiety. Evidence has shown that they are risk-free drugs with relatively rare adverse effects and very low mortality[61,62]. There are certainly cases where there is a risk of vascular complications, regardless of the use of PPIs, such as in elderly patients with diabetes, hypertension, and history of strokes, who often require aspirin for prophylaxis of cardio-cerebrovascular events[63].

International guidelines have indicated that young patients with typical symptoms should first undergo a therapeutic trial with PPIs[64]. The test consists of administering a full dose of PPI for 4 to 8 weeks and observing whether the clinical outcome is satisfactory. However, some restrictions should be remembered because there is no standardization regarding which PPI to use, the dose, and effective observation time, in addition to limitations regarding the diagnostic establishment for this type of conduct: 78% sensitivity and 54% specificity[65]. On the other hand, in young patients with typical complaints and without other comorbidities, the therapeutic test may be the initial option.

PPIs should be prescribed for eight-week treatment periods (although healing can often occur in four weeks) for symptomatic relief and healing of the erosive form of the disease. In general, there are no major differences between the various PPIs, but in certain cases, they may determine different clinical responses. Hence the recommendation that: if the response with one PPI is unsatisfactory, it should be replaced by another[12].

Pharmacological treatment with PPIs should be started with the standard dose once a day, approximately 30–40 minutes before breakfast, except for dexlansoprazole, which can be taken regardless of food and has a longer plasma concentration time[66,67].

There are no major differences between the use of one daily morning dose or two half-doses (morning and before dinner) and, therefore, when there is a predominance of nocturnal symptoms, the PPI (half dose) can be prescribed twice a day[9]. In cases in which there is a partial response to treatment, the double dose of the product should be considered, and eventually the change to another PPI[68].

In patients under treatment with PPIs, the recovery of nocturnal gastric acid secretion characterizes nocturnal acid escape, which leads to the occurrence of symptoms during the night. Acid leak is frequently observed with the most currently used PPIs, whose pharmacokinetic characteristic involve the release of the drug at a single time point when used in a single daily dose in the morning. Although increasing the PPI dose to two daily doses is a common medical procedure, patients may eventually continue to experience symptoms related to nocturnal acid leak[69].

It is important to mention that in up to 40% of patients, the result might not be totally satisfactory due to the perpetuation of symptoms or only partial resolution of symptoms[5]. In these cases, it is relevant to carefully observe patient compliance with the medical prescription, since the level of patient adherence to treatment may be low, impairing the therapeutic outcome[70,71].

Other less potent agents can be used in cases where symptoms are mild or intermittent or as supplemental therapy to PPIs[9]. These are:

II. Alkalines (or antacids)

Alkalines (or antacids) are used to neutralize gastric acid secretion, but they have a low neutralization capacity and short duration, which leads to low compliance by patients, serving for immediate relief of symptoms.

III. H$_2$ histamine receptor blockers

H$_2$ histamine receptor blockers (cimetidine, nizatidine, ranitidine, and famotidine). They were very important as the first inhibitors of acid secretion since the launch of cimetidine in the late 1970 s. Currently, they correspond to the second line of PPIs. They can eventually be used in the control of nocturnal acid secretion, although the tachyphylaxis that they present after a few days of use is a restrictive factor that must be considered[72].

IV. Alginate

Extracted from seaweed, it forms a real barrier on the esophageal mucosa and is associated with sodium bicarbonate and calcium carbonate[73]. The formulation containing alginate, sodium bicarbonate and calcium carbonate relief of symptoms irrespective of the nature of the stimulus (acid, pepsin, bile). They can be administered in association with PPIs, achieving satisfactory therapeutic results[73,74].

c. Maintenance treatment

GERD is a chronic condition, and the improvement of symptoms observed with the acid suppression, promoted by the full (or possibly doubled) dose of PPIs, may be followed by the return of symptoms when treatment is discontinued, since the pathophysiological defect persists. The return of clinical manifestations may occur particularly in cases of more intense reflux, and in this sense, up to 80% of patients with erosive esophagitis, within 12 months of treatment discontinuation, and after the satisfactory response of the first phase of treatment, have a major or minor relapse of symptoms[15,75].

Thus, at the end of the acute phase of treatment, certain patients require maintenance care: PPIs can be prescribed in half-daily doses or on-demand (administration when the patient presents symptoms)[76]. Interestingly, approximately 20% of patients remain asymptomatic with the use of antacids, or alginate and behavioral measures after standard IBP treatment[17].

The risk of adverse events from long-term PPI use is relatively modest[77], although publications (some of which have been criticized for inadequacies) have reported that these can occur with prolonged PPI use. A well-conducted randomized controlled trial showed no association between adverse events and the use of PPIs administered for three years, with the possible exception of an increased risk of enteric infections[78]. In summary, frail elderly patients on chemotherapy should be more carefully monitored, particularly regarding the dosages of calcium, vitamin B12, and magnesium as well as enteric infections.

2. Surgical treatment

Surgical treatment (fundoplication) is indicated in the presence of complications such as stenosis, ulcerations, and hiatal hernias larger than 3 cm, being an option for long-term therapy, or for cases where symptoms are refractory to clinical treatment. In general, however, surgical intervention is not recommended for patients who do not respond satisfactorily to clinical treatment[79].

There is an equivalence between clinical treatment with IBP (93%) and surgical Nissen fundoplication treatment (90%) among patients who have been in remission for three years[79]. Long-term surgical follow-up studies are not yet available, in which case patients should be informed that over time, reintroduction of clinical treatment or reoperation is often necessary[79].

3. New therapies

Despite the therapeutic success of PPIs in the pharmacological treatment of GERD, there are still areas with unmet needs such as: severe erosive esophagitis (grades C and D), with possible therapeutic failure in 20–40%, and non-erosive reflux disease, which may have up to 40% of unsatisfactory therapeutic response. In this context, new options of clinical, endoscopic, and surgical therapeutic modalities have been developed, some still in the research area[5].

a. Pharmacological treatment
I. PCABs (potassium competitive acid blockers)

An innovative approach was the development of PCABs, which are reversible proton pump blockers (H+/K+-ATPase) that block the K+ exchange channel, resulting in rapid, competitive, and reversible inhibition of gastric acid secretion. Among the PCABs in clinical use in Brazil, Japan and South Korea, Vonoprazan stands out with important clinical data available[80]. Considering the limitations of the currently available anti-secretory compounds, particularly PPIs, this new class of drugs achieves faster, more potent, and prolonged acid suppression, with the possibility of solving many of the clinical needs not achieved by PPIs[81].

II. Mucous membrane protector

Rebamipide is an amino derivative of quinolinone that serves as a mucosal protector by increasing the production of prostaglandin EP4 and epidermal growth factor, with antioxidant properties. It is marketed in south-east Asian countries and is indicated for the treatment of acid-related diseases of the oesophagus, including after endoscopic submucosal resection procedures[82].

III. Prokinetics

As mentioned above, there is no indication for the use of pro-kinetics in the treatment of GERD. Recently, however, preliminary studies have shown that acotiamide and prucalopride[83,84] may play a role in the clinical treatment of GERD. Acotiamide[83,84] is indicated for the treatment of functional dyspepsia and prucalopride in the treatment of chronic constipation, and both drugs have shown beneficial effects on esophageal function such as an increase in the EGJ pressure and in the distal esophageal contraction, with an improvement in primary peristalsis, reduction in the number of reflux episodes, decrease in the acid exposure time, and acceleration of gastric emptying[83,85].

b. Endoscopic therapy

Minimally invasive endoscopic or endoluminal procedures for GERD treatment have been proposed as alternative therapeutic strategies to medical or surgical treatment. Cases with indication for endoscopic procedures include patients with typical GERD symptoms, presence of erosive esophagitis grades A and B (Los Angeles), normal endoscopic examination and abnormal acid exposure, and HH of dimensions <3 cm with partial response to IBP treatment[86].

Of the various endoscopic techniques proposed for the treatment of GERD, we highlight:

(I) Stretta® procedure with radiofrequency. The system applies radiofrequency energy to the LES and cardia. The motor response responsible for the effect depends on the increased thickness of the EGJ consequent to the modulation of local muscles and the decrease in the frequency of transient relaxations of the LES. Meta-analysis involving 28 studies and 2,468 patients indicated that the Stretta procedure significantly improved GERD-related symptoms and decreased the percentage of patients using PPIs[86]. Future long-term follow-up studies are needed.

(II) TIF procedure (transoral incisionless fundoplication). It is an endoscopic technique performed with EsophyX® to create an anterior fundoplication. The procedure is performed under general anesthesia and a 3 to 5 cm long valve with a circumference of 200 to 300 degrees is constructed to prevent gastroesophageal reflux. Studies have characterized the efficacy and safety of the procedure, showing improvement of symptoms, quality of life, and reduction of acid exposure time and the use of PPIs[87]. The durability of the effectiveness of the procedure is a point to be better defined[88]: follow-up studies are needed.

c. Surgical therapy

Laparoscopic fundoplication is the traditional recommendation for patients who do not wish to use PPIs chronically and eventually do not respond to the doubled dose of daily PPIs. It has an initial success rate of over 90% in centers with good esophageal surgical training[89]. It is worth mentioning, however, that fundoplication is technically difficult to perform and is associated with some adverse effects during the post-procedure, such as the patient's inability to eructate or vomit, and distension sensation present in up to 25% of patients (gas bloat syndrome)[89]. Recurrence is also relatively high with a 10-year average of 10–15%[90].

Recently, LINX® (magnetic sphincter augmentation) was introduced as a surgical alternative for GERD treatment aiming at reducing adverse events observed in the traditional laparoscopic fundoplication[91]. The device consists of interconnected magnets wrapped in a titanium cover forming a ring like a bracelet, positioned circumferentially around the esophagus near the JEG[92]. The procedure is safe and minimally invasive with good results in many centers, with contraindication for patients with allergy to titanium and nickel[93]. Future studies should determine the long-term efficacy.

Authors' contribution

Domingues G and Moraes-Fiho JPP collected and analyzed data, drafted, critically revised de manuscript and approved the final manuscript draft.

Orcid

Gerson Domingues: 0000-0003-0431-451X.
Joaquim Prado P de Moraes-Filho: 0000-0003-1280-6047.

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RESUMO – A doença do refluxo gastroesofágico (DRGE) apresenta manifestações típicas, pirose e/ou regurgitação, assim como, manifestações atípicas, pigarro, laringite, rouquidão, tosse crônica, asma, alterações do sono. Existem dois fenótipos da doença: a DRGE erosiva, quando são identificadas erosões pela endoscopia digestiva alta (EDA) e a DRGE não-erosiva, com mucosa esofágica de aspecto endoscópico normal. Ao exame físico não costumam ser encontrados achados relevantes, mas a obesidade deve ser destacada como importante fator agravante do refluxo. O tratamento é estabelecido com base nos achados clínicos e, conforme a situação clínica, em exames complementares como a EDA. Nos casos duvidosos onde o diagnóstico preciso se impõe, o exame indicado é a pHmetria esofágica ou a impedância-pHmetria. O tratamento clínico é dividido em medidas comportamentais/dietéticas e medidas farmacológicas. A maioria dos pacientes se beneficia com o tratamento clínico, mas o tratamento cirúrgico pode estar indicado como na presença de hérnia hiatal de maior dimensão e nas complicações da doença.

Palavras-chave – Doença do refluxo gastroesofágico; diagnóstico; tratamento.

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