

Are the persistent symptoms to proton pump inhibitor therapy due to refractory gastroesophageal reflux disease or to other disorders?

Rimon Sobhi AZZAM

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ABSTRACT – Background – Gastroesophageal reflux disease (GERD) is a clinical condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Transient lower esophageal sphincter relaxation is the main pathophysiological mechanism of GERD. Symptoms and complications can be related to the reflux of gastric contents into the esophagus, oral cavity, larynx and/or the lung. Symptoms and other possible manifestations of GERD are heartburn, regurgitation, dysphagia, non-cardiac chest pain, chronic cough, chronic laryngitis, asthma and dental erosions. The proton pump inhibitor (PPI) is the first-choice drug and the most commonly medication used for the treatment of GERD. The most widespread definition of Refractory GERD is the clinical condition that presents symptoms with partial or absent response to twice-daily PPI therapy. Persistence of symptoms occurs in 25% to 42% of patients who use PPI once-daily and in 10% to 20% who use PPI twice-daily. **Objective** – The objective is to describe a review of the current literature, highlighting the causes, diagnostic aspects and therapeutic approach of the cases with suspected reflux symptoms and unresponsive to PPI. **Conclusion** – Initially, the management of PPI refractoriness consists in correcting low adherence to PPI therapy, adjusting the PPI dosage and emphasizing the recommendations on lifestyle modification change, avoiding food and activities that trigger symptoms. PPI decreases the number of episodes of acid reflux; however, the number of “non-acid” reflux increases and the patient continues to have reflux despite PPI. In this way, it is possible to greatly reduce greatly the occurrence of symptoms, especially those dependent on the acidity of the refluxed material. Response to PPI therapy can be evaluated through clinical, endoscopic, and reflux monitoring parameters. In the persistence of the symptoms and/or complications, other causes of Refractory GERD should be suspected. Then, diagnostic investigation must be initiated, which is supported by clinical parameters and complementary exams such as upper digestive endoscopy, esophageal manometry and ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring). Causes of refractoriness to PPI therapy may be due to the true Refractory GERD, or even to other non-reflux diseases, which can generate symptoms similar to GERD. There are several causes contributing to PPI refractoriness, such as inappropriate use of the drug (lack of patient adherence to PPI therapy, inadequate dosage of PPI), residual acid reflux due to inadequate acid suppression, nocturnal acid escape, “non-acid” reflux, rapid metabolism of PPI, slow gastric emptying, and misdiagnosis of GERD. This is a common cause of failure of the clinical treatment and, in this case, the problem is not the treatment but the diagnosis. Causes of misdiagnosis of GERD are functional heartburn, achalasia, megaesophagus, eosinophilic esophagitis, other types of esophagitis, and other causes. The diagnosis and treatment are specific to each of these causes of refractoriness to clinical therapy with PPI.

HEADINGS – Gastroesophageal reflux. Proton pump inhibitor. Refractory gastroesophageal reflux disease. Refractory symptoms.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications⁽¹⁾. GERD is a common disease attended by the gastroenterologist⁽²⁾. A systematic review found a prevalence of GERD of 10% to 20% in the Western World (Western Europe and North America) with a lower prevalence in Asia^(3,4). However, epidemiologic estimates of the prevalence of GERD are based primarily on symptoms of heartburn and regurgitation. These are the typical symptoms of GERD and the

frequency of heartburn and regurgitation in GERD is 75%-98% and 48%-91%, respectively⁽¹⁾.

Symptoms and complications can be related to the reflux of gastric contents into the esophagus, oral cavity, larynx and/or the lung⁽²⁾. Other possible manifestations of GERD are dysphagia, non-cardiac chest pain, chronic cough, chronic laryngitis, asthma, dental erosions and epigastric pain⁽¹⁾. However, many patients empirically treated empirically with the proton pump inhibitor (PPI) for suspected reflux symptoms do not respond to this medication⁽²⁾. Furthermore, all these symptoms (typical symptoms and other manifestations) can have causes unrelated to reflux⁽¹⁾.

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Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, Departamento de Gastroenterologia, São Paulo, SP, Brasil.

Corresponding author: Rimon Sobhi Azzam. Orcid: 0000-0002-9156-2185. Email: rimon@usp.br.

The diagnosis of GERD is achieved by using some combination of reported symptoms, responsiveness to antisecretory therapy, and objective testing with endoscopy and ambulatory reflux monitoring (pH monitoring or impedance-pH monitoring)⁽²⁾. GERD can be classified by the endoscopy examination as Nonerosive Reflux Disease (NERD) or Erosive Reflux Disease (ERD) when there is presence of symptoms without erosions on endoscopic examination or with erosions present, respectively⁽²⁾.

The PPI is the first choice drug and the most commonly medication used for the treatment of GERD⁽⁵⁾. Among the available drugs, PPI blocks gastric acid secretion more effectively and presents better rates of symptom relief, healing of esophagitis and prevention of complications^(6,7). Although it does not significantly reduce the number of reflux episodes, it leads to a significant change in their acidity. That is: there is still reflux; however, episodes of reflux become less acidic. In this way, it is possible to reduce greatly the occurrence of symptoms, especially those dependent on the acidity of the refluxed material⁽⁸⁾.

Refractory GERD was defined, by the majority of researchers, as the condition that presents a missing or partial response after four to eight weeks of twice-daily PPI treatment⁽⁹⁻¹¹⁾. However, the concept of Refractory GERD is controversial, since some publications suggest that the absence of a satisfactory symptomatic response to PPI once-daily would be sufficient to consider refractoriness⁽¹²⁾.

Refractory GERD is a frequent cause of medical care in Gastroenterology. Despite the use of PPI, a large group of patients continues with clinical manifestations. It is estimated that 20% to 40% of patients with GERD symptoms do not respond well to PPI treatment^(13,14). Regarding the failure to respond to treatment, total or partial persistence of symptoms occurs in 25% to 42% of patients who use PPIs once-daily and in 10% to 20% of patients who use PPI twice-daily^(11,15).

There are several factors involved in refractoriness. Classically, it is considered that there is influence of the type of GERD. Several publications report greater refractoriness in the NERD compared to ERD. After four weeks of once-daily PPI treatment, symptomatic response failure was 44% in the group of patients with ERD and significantly greater (63%) in the NERD group. However, recent studies, with a better characterization of reflux, indicate similar refractoriness rates, around 20%, in the NERD and in the ERD⁽¹⁶⁾. Among the erosive forms, it is emphasized that the occurrence of refractoriness is directly proportional to the degree of esophagitis. That is, it is greater in the most intense forms⁽⁵⁾. Furthermore, the Refractory GERD produces significant reduction on the quality of life, regarding the physical and mental health⁽¹⁷⁾.

From a practical point of view, it is considered that there is PPI refractoriness when the patient persists with symptoms during the treatment. Nevertheless, response to therapy of Refractory GERD can be evaluated through clinical, endoscopic and ambulatory reflux monitoring parameters. Thus, Refractory GERD can occur in relation to the presence of persistent symptoms (heartburn, regurgitation and/or other manifestations), erosive esophagitis and pathological gastroesophageal reflux (GER). Symptoms can be evaluated for persistence (complete or incomplete), frequency and intensity.

Hereafter, our purpose is to describe a review of the current literature of the causes and treatment of suspected reflux symptoms unresponsive to PPI.

CAUSES AND TREATMENT OF REFRACTORINESS TO PPI

Initially, the management of PPI refractoriness consists in correcting low adherence to PPI therapy, adjusting the PPI dosage and emphasizing the recommendations on lifestyle modification, before indicating diagnostic exams, except in the presence of alarm symptoms. Lifestyle modification consists of dietary and behavioral orientations for GERD, avoiding food and activities that trigger symptoms.

In the persistence of the symptoms, in spite of this described management, other causes of Refractory GERD should be suspected. Then, diagnostic investigation must be initiated, which is supported by complementary exams such as upper digestive endoscopy, esophageal manometry, ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring) and, eventually, scintigraphy for evaluation of gastric emptying.

Causes of refractoriness to PPI therapy may be due to the true Refractory GERD or even other non-reflux diseases, which can generate symptoms similar to GERD.

There are several causes of PPI refractoriness, such as inappropriate use of the drug (lack of patient adherence to PPI therapy, inadequate dosage of PPI), residual acid reflux due to inadequate acid suppression, nocturnal acid escape, "non-acid" reflux, rapid metabolism of PPI, slow gastric emptying and misdiagnosis of GERD. This is a very common cause of clinical treatment failure and the causes are functional heartburn, achalasia, megaesophagus, eosinophilic esophagitis, other types of esophagitis and other causes. The diagnosis and treatment is specific to each of these causes of refractoriness to clinical therapy with PPI.

These etiologies and differential diagnoses of Refractory GERD will be described below, with their respective diagnostic exams and specific treatments.

Inappropriate use of the drug

In cases of refractoriness, the first step is to check whether the patient is using the prescribed PPI correctly. It should be noted that, in some cases, physicians prescribe PPI incorrectly. Lack of patient adherence to PPI therapy and inadequate dose of PPI are inappropriate use of this drug that can cause persistence of symptoms and will be described separately below.

Lack of adherence

Adherence to treatment is the agreement between the patient's behavior and the prescribed medical orientation. It can be classified as non-adherence, low or high adherence. The patient's lack of adherence to PPI therapy is an important cause of pharmacotherapeutic failure of GERD to be considered, and a great challenge for gastroenterologists.

A recent prospective study, evaluating the degree of adherence to PPI treatment in 240 patients with GERD, revealed a high rate of low adherence to omeprazole once-daily or twice-daily: 114 (47.5%) patients had low adherence and 126 (52.5%) high adherence⁽¹⁸⁾. It should be noted that the main causes of low adherence were forgetting to take PPI in 129 (53.8%) patients, change of the ideal time of use in 124 (51.7%), stopping taking PPI after clinical improvement in 72 (30.0%) and interruption of PPI due to side effects occurred in only 7.1% of cases. The risk factors for low adherence were age under 60 years, married civil status and symptomatic patient⁽¹⁸⁾. Other literature studies have shown similar rates of low adherence to PPI. The continuity of daily use of PPI occurs

in 55% of patients after one month of treatment and decreases to only 30% after six months.

In this way, first of all, it is important to check that the patient is effectively using the prescribed PPI in an appropriate manner. Identify the presence and reasons for the lack of adherence to PPI. Emphasize the importance of high adherence, motivating the patient to ingest the PPI regularly and daily. A good doctor-patient relationship is essential. Explain to the patient the chronic characteristic of GERD and the importance of the PPI function.

Inadequate dosage

Adequate dose, time of administration and duration of treatment, as well as PPI quality, are essential for therapeutic success. Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole and pantoprazole magnesium are the PPI options available in Brazil. The standard or full dose of the PPI is once-daily and should be taken in fasting, 30 minutes before breakfast, in order to obtain the maximum power of gastric acid suppression. The double dose is twice-daily and the second dose of the PPI should be taken 30 minutes before dinner.

However, in part, because they do not receive adequate orientation, the majority (54%) of patients take the PPI incorrectly; of these, 39% take it before bed, and 4% as needed. In the USA, 70% of the general physicians and 20% of the gastroenterologists report in an inappropriate manner the PPI administration⁽¹⁹⁾. A study evaluating the medical prescriptions of the Clinical Hospital of Sao Paulo University has shown that PPI was incorrectly prescribed in 60% of the cases, in relation to dose or time of administration⁽²⁰⁾. In patients with persistent symptoms to once-daily PPI, initial treatment includes emphasizing the correct dosage orientations, respecting the dosage of each PPI, the time of administration and duration of treatment. Verify the quality of the drug used, in relation to the manufacturer and the type, such as compounded or industrialized (generic, similar or reference). Doubling PPI dose or replacing it with another PPI allows for a 25% improvement in the satisfactory response⁽²¹⁾.

Residual acid reflux

Residual acid reflux (RAR) is the remaining acid gastroesophageal reflux (GER) despite the use of PPI, due to inadequate gastric acid suppression. Approximately 10% to 15% of patients refractory to PPI have symptoms due to acid GER that were not adequately blocked by the drug in use. The RAR can be detected through the pH sensor of the esophageal pH monitoring or impedance-pH monitoring, performed on PPI therapy. Most digestive motility laboratories use the same normal values for the pH analysis performed with or without the use of PPI. More rigorous criteria with PPI use is a cut-off level of 1.6% for the percentage of the total reflux time that was proposed by a study evaluating healthy individuals using PPI⁽²²⁾.

RAR is less common in Refractory GERD, since using PPI, the majority of patients with persistent symptoms present normal esophageal pH monitoring. On PPI therapy, acid GER was pathological in only 4% to 16% of patients with Refractory GERD who used twice-daily PPI and in 31% to 36% of patients who used once-daily PPI⁽²³⁻²⁵⁾.

Furthermore, several studies have demonstrated that the characteristics of RAR are similar between responders and non-responders to PPI, raising questions as to the real role of RAR in Refractory GERD, and the need for indication of esophageal

pH monitoring during the use of IBP. The hypothesis is that the persistence of symptoms would be caused by the phenomenon of hypersensitivity of the esophagus, gas presence in reflux, and proximal migration of acid or non-acid reflux.

In such cases, one may increase the dose of PPI in use or change the type of PPI. In practice, the dose is initially increased and the exchange of PPI is reserved for cases that do not respond well to this initial management. Also, follow the orientations of the topics "Lack of adherence" and "Inadequate dosage". If RAR persists, continue investigation of other causes of Refractory GERD.

Nocturnal acid escape

The nocturnal acid escape (NAE) is defined as gastric pH <4, lasting more than 60 minutes at night. NAE is diagnosed by intra-gastric pH monitoring, which uses one sensor in the stomach and another in the distal esophagus. However, NAE investigation has not been performed routinely because of the lack of significant evidence of its correlation with the nocturnal symptoms of GERD, and the failure to respond to PPI.

With regard to treatment, administer nocturnal dose of PPI or histamine H₂-receptor antagonist (H₂-RA). The nocturnal dose of H₂-RA varies according to its type: cimetidine (400 mg), ranitidine (150 mg), famotidine (20 mg), nizatidine (150 mg). H₂-RA can be administered intermittently or on demand, in order to avoid the phenomenon of tachyphylaxis (reduction of the therapeutic effect due to prolonged use).

Non-acid reflux

Symptoms can arise from "non-acid" reflux (NAR). In clinical practice, GER was categorized as acid reflux (AR) when pH <4 and NAR when pH >4. This is the most widely used practical concept. However, it was defined as AR (pH <4), weakly acid reflux (pH >4 and <7) and NAR (pH >7). NAR represents about 10% to 30% of all GER episodes in normal subjects and has higher rates in patients with GERD. About 30% to 40% of Refractory GERD patients have symptoms resulting from NAR.

Transient lower esophageal sphincter relaxation (TLESR) is the main mechanism of AR and NAR. Studies on the pathophysiology of GERD suggest that NAR plays no role in the development of esophageal or extraesophageal lesion, but it is a cause of symptoms, especially in patients with NERD or Refractory GERD.

The suggested hypotheses for triggering the symptoms are esophageal distension due to NAR volume and the hypersensitivity to NAR. The PPI decreases the number of AR episodes, however the number of NAR increases, and therefore the total number of GER episodes (AR and NAR) is similar with or without PPI⁽²⁶⁾. That is, the patient continues to reflux despite the PPI, which may be the cause of the symptoms refractoriness in GERD.

The impedance-pH monitoring allows evaluating the following reflux characteristics: chemical composition (AR, weakly acid or NAR), physical composition (liquid, gaseous or mixed) and reflux migration to the proximal esophagus⁽²⁷⁾. This diagnostic method made it possible to detect, for example, that the proximal extension of AR and NAR is greater in GERD than in healthy individuals; however, the proximal extension of the NAR is significantly smaller than the AR. Impedance-pH monitoring improves the detection and characterization of GER, as it can correlate "non-acid" reflux with the presence of symptoms⁽²⁸⁾. The impedance-pH monitoring has been considered the best diagnostic method for GERD, but it does not measure the reflux volume, it is costly and little available, even at large university centers.

In such cases, it would be useful to have drugs that could effectively reduce the occurrence of reflux and not simply, as PPIs do, reduce their acidity. Baclofen (GABA-B agonist) falls into this category of drugs: modulators of the action of the lower esophageal sphincter (LES). It is known that the transient relaxations of the LES represent the main mechanism favoring reflux. Such drugs have the effect of reducing the occurrence of this type of sphincter relaxation and, consequently, effectively reduce the occurrence of reflux⁽²⁹⁾.

The dose of baclofen described in the literature is 5 to 10 mg three times a day, with a gradual increase up to 20 mg three times a day, but it has important side effects such as somnolence, nausea, vertigo, asthenia and tremors⁽³⁰⁾. Due to the large number of these side effects that usually result, it has very limited clinical use. It is hoped that in the future there may be new drugs with the same action without significant side effects.

Well-selected patients, with symptoms arising from NAR, may be good candidates for surgical treatment of reflux. Thus, in patients with NAR, the proposed therapies, still in the research phase – such as TLESR reducers (agonist of GABA-B receptor), pain modulators and antireflux surgery – should be considered⁽¹⁰⁾.

Rapid metabolism of PPI

Rapid metabolism of PPI may predispose to reflux symptoms due to inadequate acid suppression. PPI is metabolized in the liver by the cytochrome P450 (CYP) enzyme complex, mainly through the CYP2C19 and CYP3A4 isoenzymes. The activity of these enzymes is influenced by endogenous and exogenous factors. The ability to metabolize depends on genotypical differences and type of PPI. The polymorphism of CYP2C19, due to genetic alterations, causes large individual pharmacokinetic variations, producing variability in acid suppression, drug interactions and therapeutic efficacy of PPI^(31,32).

The genotypes of CYP2C19 were classified into three phenotypes: rapid metabolisers (RM), intermediate metabolisers (IM) or slow metabolizers (SM). RM, also called extensive metabolizers, have wild alleles and the SM or poor metabolizers have mutant alleles. RM has a high prevalence: 60% to 70% in Caucasians and 28% to 42% in Asians. In RM, PPI has rapid metabolism and low plasma level, gastric acid suppression is insufficient and symptoms persist, causing Refractory GERD.

Blood genetic testing performs CYP2C19 genotyping. The DNA is extracted from a peripheral blood sample and amplified by conventional polymerase chain reaction (PCR), directed to the specific target alleles. The drug options for the treatment of RM are esomeprazole or rabeprazole⁽¹⁴⁾. Esomeprazole is metabolized more slowly than omeprazole. Rabeprazole is also metabolized non-enzymatically and is less affected by the genetic polymorphism of the CYP2C19⁽³²⁾.

Slow gastric emptying

Slow gastric emptying (SGE) may predispose to reflux of gastric contents. SGE is associated in up to 40% of GERD and in up to 20% of Refractory GERD cases. SGE has non-specific symptoms, such as early satiety, gastric fullness, regurgitation, epigastric pain, nausea and vomiting. Initially, gastric and other gastrointestinal organ damage should be excluded.

SGE is evaluated by direct, non-invasive methods (contrasted radiological exam, ultrasound or scintigraphy) or indirect (absorption of paracetamol or respiratory tests with carbon-13 or

carbon-14). Ultrasonography is non-invasive and can evaluate the sectional area or the volume of the gastric antrum, after time intervals of the ingestion of liquid or semi-liquid meal, determining the time of the gastric emptying. Gastric scintigraphy is considered the gold standard method for evaluation of the gastric emptying. It uses a low dose of radiation and quantifies gastric emptying of liquid, pasty or solid diets. It allows to evaluate velocity of the gastric emptying [slow, fast or mixed (fast initial phase and slow late phase)]; intragastric distribution of the bolus; and antral contractility pattern⁽³³⁾. However, the method has low availability, high cost and impossibility of use in children and pregnant women.

Dietary orientation aimed at improving SGE and treatment using prokinetics drugs can improve the symptoms of GERD. An experimental alternative, botulinum toxin was applied in a few cases, resulting in a short period (five months) of symptomatic improvement of GERD.

Misdiagnosis of GERD

Although not presented at the beginning of this text, the wrong diagnosis of GERD represents a very common cause of failure of the clinical treatment. One of the initial steps in refractoriness analysis is to assess whether there is actually proven GERD. Patients with other conditions such as functional heartburn, eosinophilic esophagitis, esophagitis of other causes, and even achalasia or megaesophagus can be mistakenly characterized as having GERD. In these cases, the problem is not the treatment but the diagnosis. Some causes of misdiagnosis of GERD will be described below.

Functional heartburn

In clinical practice, patients who present heartburn with normal esophagus at the digestive endoscopy, physiological reflux and normal symptom index at the reflux monitoring test (pH monitoring or impedance-pH monitoring), are supposedly characterized as having Functional Heartburn (FH) and need specific approach⁽⁵⁾.

FH was defined in the Rome IV Consensus as burning retrosternal discomfort or pain, without relief despite optimal antisecretory therapy, in the absence of GERD, eosinophilic esophagitis or esophageal motor disorders. All these diagnostic criteria must be present in the last three months, with symptom onset at least six months before diagnosis, with a frequency of at least twice a week^(34,35). Structural, histopathological and metabolic changes should be excluded prior to the diagnosis of FH. The absence of GERD should be suggested through normal exams (upper gastrointestinal endoscopy without esophageal lesions and esophageal pH monitoring demonstrating physiological reflux unrelated to symptoms) and absence of symptomatic improvement with the PPI therapeutic test.

FH is the most common cause of Refractory DRGE and corresponds to up to 58% of patients refractory to twice-daily PPI. Of patients with heartburn and without esophagitis, 20% to 60% belong to the FH group and 40% to 80% to the NERD group.

FH predominates in women, and the presence of other functional gastrointestinal disorders is frequent, such as functional dyspepsia and irritable bowel syndrome. The pathophysiological mechanism of FH is not yet established, however, the main factor suggested is the phenomenon of visceral hypersensitivity. Studies have shown increased sensitivity of the esophagus to mechanical and electrical stimuli.

The treatment consists of behavioral and pharmacological therapy. Tricyclic antidepressants (amitriptyline, clomipramine,

nortriptyline), trazodone and selective serotonin reuptake inhibitors (fluoxetine, paroxetine) can be used in smaller doses and act as modulators of visceral sensitivity. Histamine H₂-receptor antagonist (H₂-RA), commonly used as antisecretor drugs, may play some role in the treatment of FH because of its likely modulation effect on visceral sensitivity. GABA-B receptor agonists (baclofen and lesogaberan), which decrease the transient relaxation of the lower esophageal sphincter, are being investigated. Psychotherapy, used in other functional disorders, is a possible alternative method, although there are no controlled studies demonstrating its efficacy in FH.

Eosinophilic esophagitis

The Eosinophilic Esophagitis (EoE) is a chronic inflammatory disease, defined as a primary clinical-histological alteration of the esophagus. It presents association of the following three characteristics: esophageal and/or upper gastrointestinal symptoms; biopsy of the esophageal mucosa containing 15 or more eosinophils/field; and exclusion of GERD, suggested by normal esophageal pH monitoring or failure to respond to high doses of PPI⁽³⁶⁾.

EoE has a low prevalence of 0.02% in the general population and 1% in patients with Refractory GERD⁽³⁷⁾. In adults, it usually occurs in young males and the most common symptoms are intermittent dysphagia, food impaction and heartburn. Allergic conditions (rhinitis, rhinosinusitis, asthma, dermatitis) and hypersensitivity to environmental, food or drug allergens may be associated.

Upper endoscopy may show normal esophagus or a large spectrum of abnormalities: granular mucosa, feline esophagus or esophageal trachealization, white exudates which represent eosinophilic microabscesses, longitudinal furrows, and even extensive stenoses. Endoscopic biopsies should be performed, even in cases of normal esophagus, in the mid and distal segments. In order to rule out eosinophilic gastroenteritis, gastric and duodenal biopsies are also recommended.

Dietary orientation for EoE in adults is controversial. The treatment consists of avoiding inhalation of aeroallergens, and pharmacological therapy. The PPI is recommended prior to initiating specific medications for EoE in order to differentiate the diagnosis between GERD and EoE⁽³⁸⁾. Topical corticosteroid is the first-line drug: fluticasone 880 at 1760 µg/day, orally, divided into two to four daily doses, for six to eight weeks. Other options are viscous solution of budesonide, oral systemic corticosteroid (prednisone or methylprednisolone) and montelukast.

Lymphocytic esophagitis

Lymphocytic esophagitis (LyE) is a new clinicopathologic condition, histologically defined as peripapillary intraepithelial lymphocytosis with spongiosis (intercellular edema) of the esophagus, with no or few granulocytes (neutrophils and eosinophils)⁽³⁹⁻⁴¹⁾. This entity is rare, but the prevalence is increasing, and the natural history is still undetermined, although it seems to have a benign chronic course.

The reported symptoms of LyE are heartburn, chest pain, nausea and abdominal pain, but dysphagia is the most frequent symptom. Esophageal perforation was reported in two cases in the literature, thought to be secondary to this entity. Risk factors for LyE are old age, female gender and smoking history. LyE has potential clinical associations with GERD, pediatric inflammatory bowel disease and esophageal motility disorders.

Upper endoscopy may demonstrate normal aspect of the es-

ophagus or esophageal changes such as nodularities, linear furrows, whitish exudates, webs, rings and stenosis. These features are similar to those seen in eosinophilic esophagitis. Endoscopic biopsies, mainly obtained from the middle esophagus, are needed to make the diagnosis. Histologically, the most commonly used cut-off level of the increased number of intraepithelial lymphocytes (IEL) is ≥ 20 IEL/high power field (HPF), but this is still controversial, since it varies from ≥ 10 IEL/HPF to ≥ 50 IEL/HPF in the literature⁽³⁹⁻⁴¹⁾.

Empirical therapies use PPI and topical corticosteroids. Esophageal endoscopic dilation can be used to treat symptoms, mainly dysphagia, due to decreased esophageal diameter in webs, rings or stenoses.

Drug-induced esophagitis

Drug-induced esophagitis (DIE) is the esophageal mucosal injury caused directly by the tablet taken orally and impacts the esophagus. The incidence of DIE is estimated to be 3.9 per 100,000 population per year. The main drugs involved are antibiotics (clindamycin, doxycycline, tetracycline), ascorbic acid, bisphosphonates (alendronate), ferrous sulfate, nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen, naproxen), potassium chloride, quinidine and theophylline^(42,43).

The pathophysiology involved is that the swallowed drug adheres to the inner wall of the esophagus and causes direct damage. For example, the alendronate is highly hygroscopic (absorbs water), clindamycin, doxycycline and tetracycline have low pH, and potassium chloride is hyperosmotic. These drug features provide local irritation and may cause esophageal damage⁽⁴³⁾.

Patients often present with odynophagia, retrosternal pain, chest pain, dysphagia, heartburn, vomiting and hematemesis⁽⁴³⁾. Risk factors for DIE are older age, female gender, large tablets, decreased saliva production, altered esophageal motility and swallowing the tablet with little or no water, while lying down or right before sleep.

The endoscopic study of the esophagus can demonstrate erythema in 83% of cases, erosions in 58%, ulcers in 26% (hemorrhagic ulcers in 18% and "kissing type" ulcers in 8%) and stenoses in 8%. These lesions are mainly found in the middle third of the esophagus, which is the most common site of impaction of tablets, in 75.6% of cases, due to extrinsic compression of the esophagus by the aortic arch or the left atrium^(43,44).

Most patients have a benign course within a few days, responding well to the suspension of the harmful medication and administer PPI to prevent any GER from worsening the lesions^(42,43). Sucralfate may be useful for protection of the esophageal mucosa. Provide orientations to the patient to prevent further tablet impaction, such as taking the tablet in the orthostatic position, followed by a glass of water and not lying down for at least one hour after taking the tablet^(11, 42).

Other causes

Other causes to be investigated are esophageal or gastric cancer, esophageal motor disorders (achalasia, diffuse spasm), infectious esophagitis due to bacteria, viruses or fungi (*Candida albicans*, cytomegalovirus, herpes simplex and others), caustic esophagitis, actinic esophagitis, esophageal stenosis, gastroparesis, esophagitis due to dermatological diseases (acquired bullosa epidermolysis, pemphigus vulgaris, cicatricial pemphigoid, and lichen planus), bile reflux, and Zollinger-Elisson syndrome. The treatment is specific to each of these causes.

CONCLUSION

Symptoms and other possible manifestations of GERD are heartburn, regurgitation, dysphagia, non-cardiac chest pain, chronic cough, chronic laryngitis, asthma and dental erosions. Refractory GERD was defined, by the majority of researchers, as the condition that presents a missing or partial response, after twice-daily PPI treatment. We describe a review of the current literature of the causes and treatment of PPI unresponsive symptoms. Initially, the management of PPI refractoriness consists in correcting low adherence to PPI therapy, adjusting the PPI dosage, and reinforcing the recommendations on lifestyle modification.

In the persistence of the symptoms, other causes of Refrac-

tory GERD should be investigated by clinical parameters, upper digestive endoscopy, esophageal manometry and ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring).

Several causes of refractoriness to PPI therapy may be due to the true Refractory GERD or even other non-reflux diseases, which can generate symptoms similar to GERD. The diagnosis and treatment is specific to each cause.

Author contribution

The author contributed to this paper with conception and design of the study, bibliographic review, data analysis, manuscript elaboration, revision and final approval of the manuscript.

Azzam RS. Sintomas persistentes ao tratamento com inibidor da bomba de prótons são devidos à doença do refluxo gastroesofágico refratária ou decorrentes de outras afecções? *Arq Gastroenterol*.

RESUMO – Contexto – A doença do refluxo gastroesofágico (DRGE) é a condição clínica que se desenvolve quando o refluxo do conteúdo gástrico provoca sintomas incômodos e/ou complicações. O relaxamento transitório do esfíncter inferior do esôfago é o principal mecanismo fisiopatológico da DRGE. Os sintomas e complicações podem estar relacionados ao refluxo do conteúdo gástrico para o esôfago, cavidade oral, laringe e/ou pulmão. Os sintomas e outras possíveis manifestações da DRGE são pirose, regurgitação, disfagia, dor torácica não-cardíaca, tosse crônica, laringite crônica, asma e erosões dentárias. O inibidor da bomba de prótons (IBP) é o medicamento de primeira escolha e o mais comumente utilizado para o tratamento da DRGE. A definição mais difundida de DRGE Refratária é a condição clínica que apresenta sintomas com resposta parcial ou ausente ao tratamento com IBP duas vezes ao dia. A persistência dos sintomas ocorre em 25% a 42% dos pacientes que utilizam IBP uma vez ao dia e em 10% a 20% dos que utilizam IBP duas vezes ao dia. **Objetivo** – O objetivo é apresentar uma revisão da literatura atual, salientando as causas, aspectos diagnósticos e abordagem terapêutica dos casos com sintomas suspeitos de refluxo e não responsivos ao IBP. **Conclusão** – Inicialmente, o manejo da refratariedade ao IBP consiste em corrigir a baixa aderência à terapia com IBP, ajustar a dosagem do IBP e reforçar as recomendações sobre modificação do estilo de vida, evitando alimentos e atividades que desencadeiem os sintomas. O IBP diminui o número de episódios de refluxo ácido, no entanto o número de refluxos “não-ácidos” aumenta e o paciente continua apresentando refluxo apesar do IBP. Desta forma, é possível reduzir consideravelmente a ocorrência de sintomas, especialmente aqueles dependentes da acidez do material refluído. A resposta à terapia com IBP pode ser avaliada através de parâmetros clínicos, endoscópicos e de monitorização do refluxo. Na persistência dos sintomas, outras causas de DRGE Refratária devem ser suspeitadas. Em seguida, deve ser iniciada a investigação diagnóstica, que é apoiada por parâmetros clínicos e exames complementares, como endoscopia digestiva alta, manometria esofágica e monitorização ambulatorial do refluxo (pHmetria esofágica ou impedancia-pHmetria esofágica). As causas de refratariedade à terapia com IBP podem ser devidas à DRGE Refratária verdadeira ou mesmo a outras doenças não relacionadas ao refluxo, que podem gerar sintomas semelhantes à DRGE. Existem várias causas de refratariedade ao IBP, como uso inadequado da droga (falta de aderência do paciente à terapia com IBP, dosagem inadequada de IBP), refluxo ácido residual devido à supressão ácida inadequada, escape ácido noturno, refluxo “não-ácido”, metabolismo rápido do IBP, esvaziamento gástrico lento e diagnóstico equivocado de DRGE. Este representa uma causa frequente de insucesso do tratamento clínico e neste caso, o problema não é o tratamento, mas sim o diagnóstico. As causas de diagnóstico equivocado da DRGE são pirose funcional, acalásia, megaesôfago, esofagite eosinofílica, outros tipos de esofagite e outras causas. O diagnóstico e o tratamento são específicos para cada uma dessas causas de refratariedade ao tratamento clínico com IBP.

DESCRIPTORIOS – Refluxo gastroesofágico. Inibidor da bomba de prótons. Doença do refluxo gastroesofágico refratária. Sintomas refratários.

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