# Gastroesophageal reflux disease. Part III.

# (Etiology, diagnosis, treatment).

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## Etiology

It is known that GERD results from the damaging effect of hydrochloric acid, being thrown from the stomach into the esophagus. A systematic review demonstrated that the prevalence of GERD ranged from 18.1% to 27.8% in North America, 8.8% to 25.9% in Europe, 2.5% to 7.8% in East Asia, 8.7% to 33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America [1]. Considering that not all patients with GERD seek medical help and not all patients are correctly diagnosed with the disease, the assumption that about 40% of the population suffers from GERD seems quite probable [2]. The scientific literature only considers the total time and episodes of reflux of gastric contents to the esophagus with a pH <4 based on pH monitoring. Prior to the introduction of pH monitoring into practice, a study was made on the amount and pH of gastric juice removed from the stomach through a tube. The diagnosis of peptic disease was based on hypersecretion of hydrochloric acid [3, 4]. It is now evident that hypersecretion of gastric hydrochloric acid is an important pathogenetic element responsible to produce duodenal and gastric ulcers [5, 6, 7, 8]. Stimulation of gastric secretion of pentagastrin (4 micrograms/kg/min) together with carbachol (0.8 micrograms/kg/min) produced a 100% incidence of duodenal ulcers (DU) in male albino Wistar rats [9]. "The overproduction of acid and the associated illnesses linked to hypersecretion have a lifetime prevalence of 25-35% in the United States" [10].

Due to the hypersecretion of hydrochloric acid, all upper parts of the digestive tract are affected. Portincasa et al show that a subgroup of gallstone patients with small-mainly asymptomatic stones have impaired gallbladder and gastric motility as well as abnormal gastroesophageal pH profiles [11]. Patients with Barrett's esophagus have a more complex gastrointestinal motility disorder that involves the gallbladder, and this makes this subset of patients with GERD more prone to gallstone disease [12]. It has been shown that "biliary dyskinesia is associated with GERD and gastritis" [13].

Scientific studies have shown that hypersecretion of hydrochloric acid causes inflammation and weakening of the LES, resulting in reflux of aggressive gastric contents into the esophagus. However, in many patients, the disease progresses despite the absence or minimal manifestation of clinical symptoms.

Hypersecretion of hydrochloric acid causes an inflammatory reaction and a violation of the motor function of the stomach, which is expressed by a slowdown in evacuation from the stomach. In the duodenum, acid increases the tone of the post-bulbar sphincter, as well as the sphincters of Ochsner and Kapanji. This, firstly, causes duodeno-gastric reflux. Secondly, with the simultaneous contraction of the Ochsner and Kapanji sphincters, the pressure between them rises sharply, which leads to the reflux of microbes into the biliary tract, causing acute cholecystitis. It also leads to the sphincter of Oddi dyskinesia, increased pressure in the bile ducts, and the formation of gallstones [14]. Thus, pain in the abdomen or behind the sternum, of any nature, including heartburn, postprandial or nocturnal pain, and belching, indicated hypersecretion of hydrochloric acid. Endoscopy with biopsy could identify the site of the largest lesion to prescribe anti-acid treatment.

The introduction of pH monitoring, as well as high-resolution manometry (HRM), led to an unprecedented flourishing in the production of diagnostic equipment. Practitioners with a superficial knowledge of the physiology of the digestive system, led by engineers from firms producing apparatus, with their numerous illiterate articles advertising apparatus, drowned scientific research and gradually destroyed gastroenterological science. From a theoretical point of view, the statement that GERD is GER, which is accompanied by severe clinical symptoms, contradicts numerous studies. The claim that episodes of gastroesophageal reflux may be physiological is based on the misconception that pH monitoring is the gold standard. From a practical point of view, pH monitoring is harmful, as it detects only very severe forms of GERD. The diagnosis of hydrochloric acid hypersecretion can and should be based on clinical symptoms, and this accurate diagnosis will include fictional diagnoses: hypersensitive esophagus, duodenal dyspepsia, and irritable bowel syndrome. The practitioners using HRM, who finally destroyed science, allow themselves to publish meaningless texts, with phrases that are logically unrelated (see parts I and II).

As soon as there was information about lactose intolerance as a trigger for hydrochloric acid hypersecretion [15,16,17], manufacturers of diagnostic equipment entered this area. It is believed that lactose increases the osmotic load, and increases the intestinal water content. Second, lactose is readily fermented by the colonic microbiome leading to the production of short-chain fatty acids and gas (mainly hydrogen (H2), carbon dioxide (CO2), and methane (CH4)). These biological processes are present also for other poorly-absorbed, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) that are ubiquitous in the diet [18,19], both in health and in patients with the gastrointestinal disease [20,21,22].

All articles on lactose intolerance repeat the same formula: “The clinical manifestations of lactose intolerance are due to osmotic fluid shifts into the gut, as well as the gas formation and bowel distension. This may present with abdominal pain, flatulence, and diarrhea” [18, 19, 20, 21, 22, 23]. First, if this process of lactose utilization is the norm since it is observed in healthy people and is characteristic of the utilization of any disaccharides, then why does it cause symptoms in some patients? Second, on what basis are patients with a positive breath test diagnosed with lactose intolerance? Thirdly, the described picture can only correspond to irritable bowel syndrome, while lactose intolerance is observed in a third of the world's population, including infants, in whom there can be no talk of IBS.

Instrumental confirmation of lactose intolerance is based on a false hypothesis of the pathogenesis of this problem. It is stated that "lactose digestion and the association of maldigestion with symptoms can be assessed by the H2-breath test [24] and the lactose tolerance test [25]; however, the former is confounded by fluctuations of postprandial blood sugar. The H2-breath test can be falsely positive in the presence of small intestinal bacterial overgrowth; however, a larger problem is false-negative tests due to the presence of hydrogen non-producing bacteria in the colon (2%–43%) [26]. Patients with “false positive” breath tests complain of symptoms directly after ingestion. Those with “true positive” lactose intolerance complain of symptoms only after the substrate has entered the colon (usually 50–100 min)" [19]. From this passage, it is clear that the advertised methods for diagnosing disaccharide intolerance, based on false ideas about the pathogenesis of problems in the digestive system, have no diagnostic value at all, including the diagnosis of lactose intolerance. Therefore, despite "their simplicity, reproducibility, and safety of hydrogen breath tests they are now being substituted for more uncomfortable and expensive techniques that were traditionally used in gastroenterology" [27].

## The clinical picture of lactose intolerance and its rationale

The clinical picture of lactose intolerance includes infantile colic, interrupted sleep, wet pillows and anemia in young children, abdominal or chest pain, heartburn, dysphagia, and other symptoms resulting from hypersecretion of hydrochloric acid. As a rule, all the upper parts of the digestive system are affected. If you do not take into account the etiology and pathogenesis of the disease, the disease progresses with age. But before the age of 40, it can progress despite the absence of symptoms or with minimal clinical manifestations. In old age, even coffee with milk or a jar of yogurt can cause severe heartburn or pain in the chest and/or abdomen. In order to stop the progression of the disease and

get rid of these symptoms, it is necessary to stop eating food that contains lactose. The claim that it is possible to limit the consumption of dairy products to the threshold of symptoms is scientifically unfounded and harmful, as well as the claim that the refusal of dairy products can be harmful to health [19].

As it turns out, there is a completely different route of stimulation of hydrochloric acid hypersecretion in lactose-intolerant patients. This is evidenced by numerous observations of the occurrence of heartburn 15-30 minutes after the use of dairy products, i.e. until the moment (50-100 minutes) when lactose could appear in the colon. It is strange that the authors do not take into account the fact that the process of disintegration of lactose by microorganisms in the colon is not instantaneous. It continues during the movement of feces in the large intestine for 18-24 hours. The authors call a rapid reaction to lactose a false positive since it does not correspond to generally accepted ideas about the pathogenesis of the disease. It was shown that IBS patients that had lactose intolerance on hydrogen breath testing also had heightened activity of the innate mucosal immune system with increased counts of mast cells, intraepithelial lymphocytes, and enterochromaffin cells in the terminal ileum and right colon with the release of pro-inflammatory cytokines after lactose ingestion [28]. Aguilera-Lizarraga et al found that injection of food antigens (gluten, wheat, soy, and milk) into the rectosigmoid mucosa of patients with irritable bowel syndrome induced local edema and mast cell activation. Following oral ingestion of the respective dietary antigen, an IgE- and mast-cell-dependent mechanism induced increased visceral pain. This aberrant pain signaling resulted from histamine receptor H1-mediated sensitization of visceral afferents [29].

Based on clinical observations and studies on the response of mast cells to dietary antigens, it can be assumed that lactose intake in patients with lactose intolerance causes the release of histamine from the mast cells of the small and large intestine, which leads to the release of gastrin, which causes hypersecretion of hydrochloric acid.

## My experience in the treatment of hydrochloric acid hypersecretion

To all my patients with clinical symptoms of lactose intolerance, I recommend that they stop eating products containing lactose. I currently divide my patients into 3 groups.

**Group 1** consists of 18 patients under 30 who do not consume milk but eat butter, cheeses, and yogurts. They have no complaints and do not take medication. However, a trial of drinking milk causes heartburn in them. Only two of them

underwent an X-ray examination with an increase in pressure in the stomach. I continue to follow them.

**Group 2,** consisted of 21 patients, including 1 teenager and 20 patients over 50 years of age. They do not eat foods containing lactose. Except in rare cases (1-2 days), they do not take PPI and have no symptoms of hydrochloric acid hypersecretion. All of them were examined radiographically using high pressure in the stomach. Before they stopped taking lactose, they were repeatedly examined by gastroscopy, some underwent examination of pH monitoring and HRM. They had been taking PPI continuously for many years without much success. One of them was re-X-rayed to determine the effect of the two-year asymptomatic period on the condition of the esophagus and LES.

**Case 1.** A man of 77 years, BMI is 24.4. Rare episodes of heartburn began at age 15. At 39 years old pain behind the sternum appeared after a plentiful festive dinner. It lasted six months. The pain disappeared after gastroscopy, which did not detect pathological changes. Patient-controlled the situation by going to bed with an empty stomach. At first, he dined for 3 hours before bedtime, and recently for 6 hours. Occasionally he took one tablet of PPI before the gala dinner and for some days after it. From the age of 55, he noticed that abdominal pain and heartburn appear after drinking milk. From the age of 70, pain appeared when eating flour products prepared with milk. A sharp deterioration occurred at age 75 after eating cakes for several days while taking analgesics. An X-ray examination of the esophagogastric junction (EGJ) revealed an expansion of the esophagus to 3.8 cm and shortening of the lower esophageal sphincter (LES) to 1.4 cm with the presence of longitudinal folds at the level of the LES (Figure 1. a). Gastroscopy revealed no pathology. However, a PPI of 20 mg twice daily was prescribed. On my advice, he gradually was decreasing the dose of PPI until complete cessation while avoiding the use of all products that contain lactose.

He is currently not taking any medication and does not have any digestive symptoms. He does not eat foods containing lactose, as trying to eat a sandwich with butter and cottage cheese, even in small quantities, caused a feeling of discomfort.

2.5 years after the refusal to use products containing lactose, in the absence of any symptoms, a second x-ray examination of the EGJ was performed with an increase in pressure in the stomach (**Figure 1. b**).

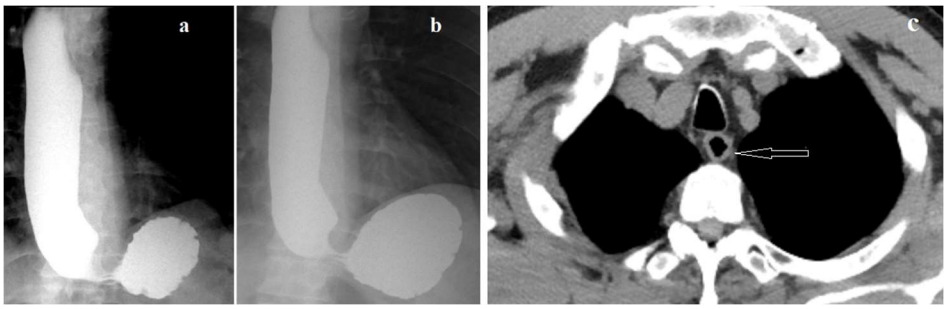


**Figure 1.** X-ray examination of EGJ during high pressure in the stomach. **(a).** Study at age 75. The esophagus is dilated (3.8 cm). The narrow segment between the esophagus and the stomach ≈ 1.4 cm long is a contracted LES, which is more than 2 times shorter than normal. **(b).** At the age of 77 years, radiographic appearance no change. XIR is 2.7. **(c).** CT scan at the level of the upper esophagus at age 74. There was gas along the entire length of the esophagus (arrow).

XIR - X-ray Index Reflux is the ratio of the maximum width of the esophagus to the length of the LES. Normally, the width of the esophagus in adults is approximately 1.5 cm, and the length of the LES is 4 cm. Thus, the XIR is normally about 0.4, i.e., always less than one. The higher the XIR, the stronger the damage to the anti-reflex function of the EGJ.

In this observation, the absence of any symptoms was combined with the absence of disease progression, which is probably due to the cessation of the intake of food containing lactose. On the other hand, there are no signs of improvement in the anatomical and physiological properties of the esophagus and LES. The presence of gas along the entire length of the esophagus on CT indicates a violation of peristalsis. These data confirm that GERD is a chronic progressive process in which each exacerbation leaves irreversible fibrotic changes in both the esophageal wall and LES.

**The 3rd group**, consist of 4 patients over 60 years of age who have been taking PPI for many years. The diagnosis of GERD in them was confirmed by X-ray examination of EGL with high pressure in the stomach. They have limited the use of products containing lactose and three of them continue to take 20 mg of PPI. One of them was re-examined 2 years after the initial examination **(Figure 2).**

**Case 2.** A 65-year-old woman considers herself ill since the age of 54 when severe epigastric pains appeared. Gastroscopy revealed antral gastritis caused by Helicobacter pylori. After the course of eradication, all symptoms disappeared, and the patient considered herself healthy for 3 years. At the age of 57, when epigastric pain reappeared, gastroscopy revealed a small hernia of the esophageal opening of the diaphragm with red stripes leading to the cardia. At 61, every morning she was troubled by a painful cough and sore throat. She woke up several times during the night with attacks of suffocation and with a feeling of strong acid in her mouth.

At the same time, pain in the epigastrium and in the left hypochondrium often bothered her. 4 months after the onset of symptoms, she turned to the otolaryngologist, who discovered laryngopharyngeal inflammation, which served as the basis for the diagnosis of gastroesophageal-pharyngeal reflux. She began to take 20 mg of Esomeprasol per day. However, there was no significant effect. Gastroscopy was performed twice with an interval of 2 months. The endoscopic diagnosis was antral gastritis with the histologic conclusion: oxyntic mucosa showing mild chronic gastritis and focus erosion. Negative for H. pylori by immunostain.

X-ray examination with the provocation of high pressure in the stomach confirmed the diagnosis of GERD **(Figure 2.a).** The significant improvement came after she started taking 20 mg of Esomeprazole 2 times a day and swallowed a tablet with a barium 2.2 cm diameter. After a month, all the symptoms passed and the patient gradually began to reduce the dose of PPI, until she completely abandoned it. However, she was not sure of the stability of her recovery, as sometimes after a violation of the diet or eating regimen there was pain in the epigastrium and left hypochondrium, as well as burning and sore throat at night. She was invited to take part in a scientific study suggesting that the electrical stimulation of the lower esophageal sphincter (LES) could improve its function. She was excluded from this study since within 48 hours the pH monitoring detected a pH <4 in only 3.2% of the total time.

A repeated X-ray examination of EGJ with high pressure in the stomach was performed 2 years after the first one (**Figure 2, c)**. The patient believes she has no symptoms of GERDexcept for episodes of belching, bitterness in the mouth, and burning in the throat in the morning no more than once a month, which usually occurs after festive dinners. She considers herself practically healthy, thanks to the fact that she goes to bed with an empty stomach since she does not eat after 4 pm and for 2 years she does not take any medications. It turned out that the patient consumes products containing lactose, as she did not find on the Internet confirmation of my recommendations to discontinue them.

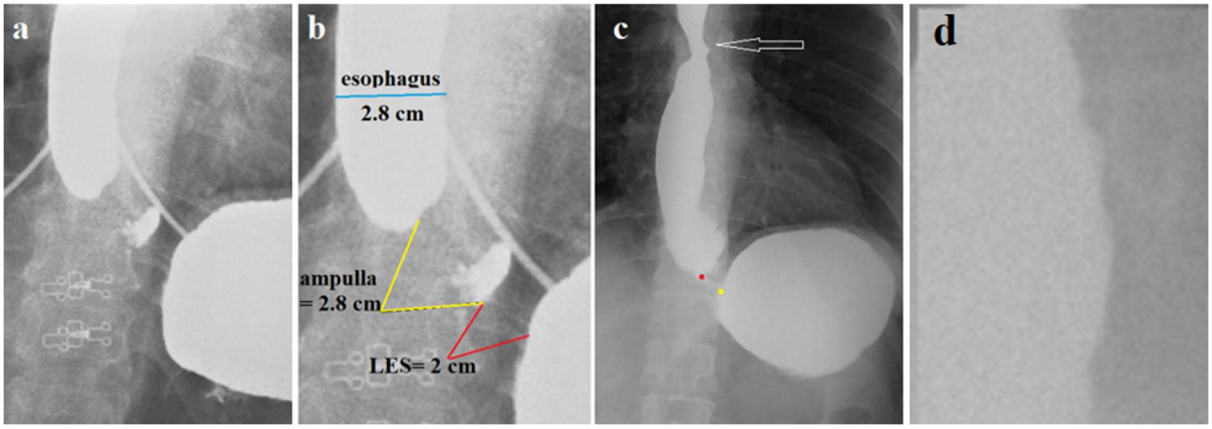

**Figure 2**. Case 2. (a) The radiograph of EGJ with high gastric pressure at age 63. (b). Scheme to figure (a). The width of the esophagus is 2.8 cm. The length of the LES is 2 cm. XIR = 1.4. (c). At the age of 65. The width of the esophagus is 3.2 cm, and the LES length (distance between colored dots) is 1.4 cm. XIR=2.3. In the upper part of the esophagus, an asymmetric narrowing is visible, suspicious of an ulcerative process (arrow). (d) The left wall of the esophagus has a finely wavy contour.

This observation is strong evidence that the progression of GERD can occur without significant symptoms. Based on an analysis of the literature, I first assumed that various disaccharides could cause hypersecretion of hydrochloric acid. However, experience with lactose exclusion has shown that lactose alone is responsible for the onset of gastrointestinal symptoms. It turned out that galactose and lactose have been detected in most honeydew honeys. The lactose content of the honeys analyzed ranged between 0.0062 and 0.0383% [30]. Such a meager amount of lactose, as well as an insignificant amount of milk in a cup of coffee, cannot cause symptoms due to the disintegration of lactose in the colon. However, it can be triggering the release of histamine from mast cells in the small and large intestines. The histamine, directly, and the secretion of gastrin caused by it result in hypersecretion of hydrochloric acid. This may explain the appearance of gastroenterological symptoms in some patients after the use of honey.

## Diagnosis

When diagnosing GERD, we must keep in mind that because of hypersecretion of hydrochloric acid, in addition to the esophagus, the stomach, duodenum, and biliary tract, including the gallbladder, are damaged. However, the stomach and duodenum have a certain degree of protection against acid attack. Meanwhile, the esophagus, together with the LES, is not adapted to repel aggression and, therefore, is damaged in the first place. Secondly, the esophagus and LES are easily accessible for examination. Both circumstances show the importance of diagnosing GERD as the initial study of patients with gastroenterological symptoms.

In the initial treatment with gastroenterological symptoms, assuming hypersecretion of hydrochloric acid, it is advisable to prescribe 20 mg of PPI with the simultaneous cessation of eating food-containing lactose. After the disappearance of symptoms, it is necessary to gradually reduce the dose of PPI until complete cessation. To make sure that it is lactose that is the trigger for hypersecretion of hydrochloric acid, it is necessary to make a provocative test. To do this, on an empty stomach, a probe is inserted into the stomach and gastric juice is aspirated one hour after taking a glass of meat broth. Re-sampling of gastric juice is carried out one hour after the introduction of a glass of milk. The significant difference in the amount of hydrochloric acid convincingly indicates that it is lactose that is the trigger for hypersecretion. As the analysis of the literature and our own research shows, the calculation of the reliability of clinical

manifestations in response to milk intake is a mistake, since the disease can progress, despite the absence or minimal manifestations of the disease.

This study is of immense importance as it determines the diet for life. The current recommendations to limit lactose intake in lactose intolerance have no scientific basis and cause harm to patients, what would be comparable to the recommendation to limit gluten intake in celiac disease.

In the presence of a long history, in addition to determining lactose as a trigger for hypersecretion, two complementary studies should be performed: esophagogastroduodenoscopy and X-ray examination with high pressure in the stomach.

**Esophagogastroduodenoscopy** allows for detecting ulcers and erosions, to determine the size of the esophageal ampulla. Histological studies can identify Barrett's esophagus, eosinophilic esophagitis, esophageal carcinoma, and other evidence of an inflammatory process in the esophageal wall (expansion of the intercellular space, metaplasia of the squamous epithelium to cardiac epithelium).

**X-ray method for the diagnosis of GERD using**

**high pressure in the stomach.**

In the horizontal position on the x-ray table, the patient drinks through a straw 200 ml of barium suspension from a can located near his head. When barium ends, the patient raises straightened legs. At this moment, a radiograph is produced. In some cases, to evaluate the evacuation from the esophagus, a second radiograph is produced 3-5 minutes after the first.

On radiographs, the width of the esophagus measures at the widest point, as well as the length of the distance between the esophagus and the stomach, in which there is no contrast medium. This distance is due to a contraction of the LES in response to increased pressure in the stomach. Knowing that the normal length of LES in adults ranges from 3.2 to 4.2 cm (3.60 ± 0.08 cm), we can judge the competence of the LES. If the length of the LES is less than the minimum norm, this indicates the weakness of the LES due to the disclosure of its abdominal part. The mean diameter at the cranial point of measurement was 6.75 mm at the lowest weight (2.6 kg) and 14 mm at 74 kg [31], and it is 1.5 cm in adults. The normal length of the LES in people of different ages was determined [32]. Expansion of the esophagus and shortening of the LES is convincing evidence of GERD. I calculate the radiographic index of reflux (XIR), which is the ratio of the width of the esophagus to the length of the LES. It allows you to judge the degree of damage to the anatomical structures and compare different studies with each other.

## Treatment of the hydrochloric acid hypersecretion (including GERD).

1. GERD is a chronic progressive disease. The exclusion from the diet of foods containing lactose leads to a sharp decrease in the release of hydrochloric acid. The earlier the diagnosis is made, and treatment is undertaken, the more of the anti-reflux function of the EGJ can be preserved and stop the progression of the disease.

2. When refusing to consume products containing lactose, it is desirable to consult a nutritionist to ensure the necessary needs of the body.

3. If the anti-reflux function of the EGJ is already reduced, then the reflux of gastric contents with normal amounts of hydrochloric acid also causes irritation and inflammatory response. Therefore, it is recommended to be in a horizontal position only with an empty stomach. It should not be used to use tight belts and do not bend over after eating, as in these cases, abdominal pressure rises, which provokes reflux.

4. In acute symptoms, it is necessary to prescribe PPI, the dose of which, upon reaching a clinical effect, should be gradually reduced until complete discontinuation.

**Notes**

1. The pH monitoring is based on the misconception that GERD always presents with significant clinical symptoms. Because of this error, pH monitoring detects only severe forms of the disease, which, as a rule, have a convincing clinical manifestation of GERD without any other studies. The pH monitoring does not detect more than 30% of patients with GERD, which is why they do not receive the necessary treatment, which leads to the progression of the disease. Thus, the use of pH monitoring is not only useless but very harmful.
2. The use of breath analyzers is based on the misconception that lactose intolerance symptoms result from fermented lactose by the gut microbiota, producing gases that stretch the intestines. This process occurs with all disaccharides and does not cause any symptoms. Thus, the use of gas analyzers is not only pointless but also harmful, as it misleads doctors.
3. Although lactose restriction and the use of probiotics may reduce patient complaints, these recommendations are dangerous because they contribute to the progression of GERD.
4. High-resolution manometry (HRM) is based on the same false assumptions as pH monitoring. The scientific value of HRM and pH monitoring can be judged by the recommendations of the British Society of Gastroenterology.

Here are excerpts from them. **(a)** “A systematic literature search was performed and the Grading of Recommendations Assessment, Development, and Evaluation tool was used to evaluate the quality of evidence and recommendations decide on the strength of the made” [33]. Since there are no articles in the media that contradict the concepts of the Chicago Classification, it is not surprising that its recommendations come to the fore. **(b)** "The guidelines were developed by a guideline development group of patients and representatives of all the relevant professional groups" [33]. For the first time in the history of science, patients are taking part in solving medical problems.

5. The use of PPI is not a treatment for GERD, but a way to reduce the release of hydrochloric acid to relieve symptoms. The FDA recommends no more than 3 courses of treatment for heartburn with PPIs available as OTC preparations per year, no longer than 2 weeks each [34]. With the elimination of lactose consumption as a trigger for hydrochloric acid hypersecretion, there is no need for constant use of PPI.

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