Main problem of the prolonged proton pump inhibitors intake

E. Y. Plotnikova

Kemerovo State Medical Academy, Kemerovo, Russia

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Under syndrome bacterial overgrowth in the small intestine (BOS) refers to a pathological condition based on the increased colonization of the small intestine or oropharyngeal faecal microflora, accompanied by chronic diarrhea and malabsorption, especially fats, and vitamin $_{B12.}$ Increasing the number of pathogenic microflora in the small intestine is detected in 70-95% of cases of chronic diseases of the intestine. With BOS increases not only the number, but I and the spectrum of microorganisms with a shift towards gram-negative bacteria and anaerobes. In 30% of healthy people jejunum normally sterile, the rest — has a low population density, which increases as we approach the colon, and only in the distal ileum revealed microflora fecal type: enterobacteria, streptococci, Bacteroides genus anaerobes, and others. [1].

The most important BOS etiological factors include:

- dysfunction of the ileocecal valve (inflammatory, tumor processes, primary functional insufficiency);
- the effects of surgery (anatomical or surgical loop formed by the blind, small intestinal or colorectal anastomosis or fistula, vagotomy, cholecystectomy, resection of the small intestine);
- gastrointestinal disease associated from motor disorders — gastrostasis, duodenostasis, stasis contents at fine and thick intestines (chronic constipation, including patients with diabetes);
- disorders of digestion and absorption cavity (maldigestion and malabsorption), including related to: achlorhydria of different origin (the operated stomach, with chronic atrophic gastritis, long reception of proton pump inhibitors (PPIs)), with exocrine insufficiency pancreatic cancer (chronic

pancreatitis), with pathology of biliary tract (cholelithiasis disease, chronic cholecystitis);

- enteropathy (disaccharidase insufficiency and other food intolerance);
- prolonged nutritional imbalance;
- chronic inflammatory bowel disease, diverticulitis, syndrome short ulcers;
- receipt of extra-intestinal bacteria from the tank (for example, cholangitis);
- local and systemic immune disorders — radiation, chemical exposure (cytostatics), AIDS;
- antibiotic therapy;
- stress of different origin;
- tumor of the intestine and mesenteric lymphatic node [23];
- different diets for weight loss, "cleansing" with enemas volume and, especially hydro, which has some popularity, but persistently not recommended by gastroenterologists of the world, as it roughly breaks microbial habitats.

Verification of bacterial overgrowth in the small intestine is carried out by means of direct and indirect methods of diagnosis of this syndrome. "Gold standard" diagnostic BOS is sown flora, it requires aspiration of the contents of the small intestine with immediate seeding aspirate in the culture medium. But bacterial overgrowth can affect more distal portions of the small intestine, which is beyond the reach of tools [22]. In 2008 it was adopted the Rome Consensus on hydrogen tests, which sets out the recommendations of international experts for clinical practice regarding the indications and methods of the H2-breath tests for diseases of the digestive tract [1]. The method is cheap, simple, but many practitioners not only do not know the basic provisions of the consensus, but still do not know with this test, do not know his diagnostic abilities, certain limitations and disadvantages. Today, many Russian clinics method breath test with lactulose (LHBT) is used for the screening diagnosis of BOS, including PPIs-induced.

After deciphering the mechanisms of regulation of acid the stomach in the first quarter of the twentieth century, the role of the major stimulants of secretion was shown — acetylcholine, histamine and gastrin. Histamine was opened by physiologist H. Dale and chemist G. Barger in the study of the physiological effects of ergot. For a series of studies in this area H. Dale was awarded the Nobel Prize in 1936. For the first time the stimulating effect of histamine on stomach cancer proved a student of I. P. Pavlov Lev Popelsky. The first revolution in the treatment of acid-related diseases, marked the Nobel Prize in Physiology or Medicine in 1988, occurred after 1972, when J. W. Black, having tried more than 700 different molecules, synthesized the first blocker H2-histamine receptors — cimetidine. This drug provided a significant reduction in gastric acid secretion of gastric parietal cells in the body by blocking the stimulating effect of histamine on them. The introduction into clinical practice of cimetidine and H2-blockers next generation of famotidine and ranitidine significantly increased the effectiveness of treatment of patients with acid-dependent diseases.

A key mechanism of secretion of hydrochloric acid — H+/K+-ATPase and gastric parietal cells (proton pump) was inaugurated A. Ganser and J. Forte in 1973, G. Sachs and his team began work on the creation of the PPIs, but due to the the commercial success of H2-blockers work on the program in the UK was stopped [16, 17]. However, in a research laboratory in Mölndal (Sweden) was designed substituted benzimidazole H149/94 covalently blocking the proton pump [27]. A molecule of H149/94 was the first PPIs that has successfully passed a study in humans [6]. The drug, known as omeprazole, has been protected by the European patent SE 78-4231 dated April 14, 1978. In 1988 Omeprazole was first approved in Sweden for the treatment of duodenal ulcer, in 1989 it was inducted into the Canadian and US Pharmacopeia for treatment of duodenal ulcer, gastric ulcer, reflux esophagitis and Zollinger-Ellison syndrome. The emergence of the first PPIs opened a new era in the treatment of peptic ulcer disease, helped eliminate virtually all surgical techniques, treatment course that will provide better control of gastric acid secretion than vagotomy.

The positive effects of PPIs are undeniable, they are the main agents in the treatment of acid-related diseases, but, like all other drugs, they also have a number of side effects. The most common side effects are mild, are spontaneous and do not depend on the dose or the patient's age.

Side effects from the gastrointestinal tract: diarrhea, flatulence, abdominal pain, constipation. The appearance of gastrointestinal symptoms (hypermotility intestine) associated with inhibition of acid production, and flatulence is a consequence of occurrence of BOS. Complications of the central nervous system: headache, dizziness, drowsiness. They are rarely severe and occur spontaneously. In cases where the headache is progressive in nature, PPIs therapy is better to stop that and make some patients. Quite rare and pseudoallergy allergic reactions: itching, hives, angioedema, acute disseminated epidermal necrosis, vasculitis. Some of them require immediate discontinuation of the drug and conducting emergency medical activities with careful supervision within 10 days; pruritus and urticaria are prognostically less severe, are spontaneous and rare (<0.1%) require the abolition of PPIs. A large number of "rare" complications is described: increased transaminases (from the liver), arthralgia, asthenia syndrome, interstitial nephritis, visual impairment, hearing, digestion with weight loss, impotence, ginikomastiya, electrolyte imbalance, and others. This group of complications requires urgent discontinuation of therapy, intensive care and long-term follow-up [1].

PPIs are powerful antisecretory drugs, resulting in hypochlorhydria, which, in turn, is a risk factor for the development of BOS [30]. The presence of gastric acid is the main defense against oropharyngeal and intestinal infections. Thus, it is not surprising that the removal of natural protection inevitably leads to clinically significant disorders of the intestinal flora in some patients taking PPIs. It has long been established that PPIs can change the bacterial profiles of the stomach, duodenum and jejunum. For example, J. Thorens et al. examined 47 randomized patients with peptic ulcer disease who received 4 weeks of cimetidine or omeprazole, and then they had investigated aspirate from the small intestine to the state of the microflora. The authors found a higher level of bacterial growth after administration

of omeprazole (53% vs. 17%) [3]. This conclusion was dubbed by M. Fried et al., which showed that PPIs-induced BOS were caused not only oropharyngeal microflora and colon [5]. J. Theisen et al. We found that suppression of gastric acid omeprazole resulted in a high incidence of BOS, which in turn led to a marked increase in the concentration of non-conjugated bile acids. Furthermore, Lewis et al. documented that omeprazole-induced BOS was associated with shorter intestinal transit [28]. These studies showed that PPIs-induced BOS potentially can lead to symptoms of irritable bowel syndrome (IBS), diarrhea as a result of increased osmotic load of bile acids in combination with more rapid intestinal transit. It should be noted that the most common side effects of PPIs in all studies were abdominal pain, bloating, flatulence, constipation, diarrhea, symptoms that overlap with IBS, and occur in 5% receiving PPIs [26].

Very few studies have examined the relationship between the use of PPIs and BOS with IBS. M. Majewski et al. presented data on a cohort study of 204 patients with IBS and BOS, part of which simultaneously receives PPIs [14]. We have found that when using the PPIs was more LHBT-positive patients (48%) compared to the LHBT-negative patients (39%). Although this difference was not statistically significant ($p=0.2$), and the study did not try to account for the impact of PPIs on the results of LHBT, nor investigated the dependence "dose-response" to compare the number and duration of PPIs results LHBT. Nevertheless, the study provides the raw data with the numerical trends, which indicate the relationship of the reception and the emergence of STI-positive LHBT BOS. Moreover, the latest data show that among the LHBT-positive patients (including patients with IBS), taking rifaximin, reduces the recurrence of BOS while using PPIs [11].

It is important to identify the different types of intestinal infections associated with PPIs, although infectious complications are rare events in such a situation. A number of studies to identify the relationship between PPIs and BOS often point to infectious diseases [3, 19]. Among the pathogens encountered Shigella, Salmonella, Yersinia, and Clostridium difficile — such complications occur in less than 1% of patients with complications of type BOS while taking PPIs [29]. M. R. Brennan et al.

proposed to consider the effect of PPIs on the microbial landscape of the intestine in the form of "iceberg", where "above the waterline" are located specific bacterial agents (e.g., Clostridium difficile), leading to infections, and "below" is normal microflora, which leads to the formation of BOS at reception PPIs (Fig. 1).

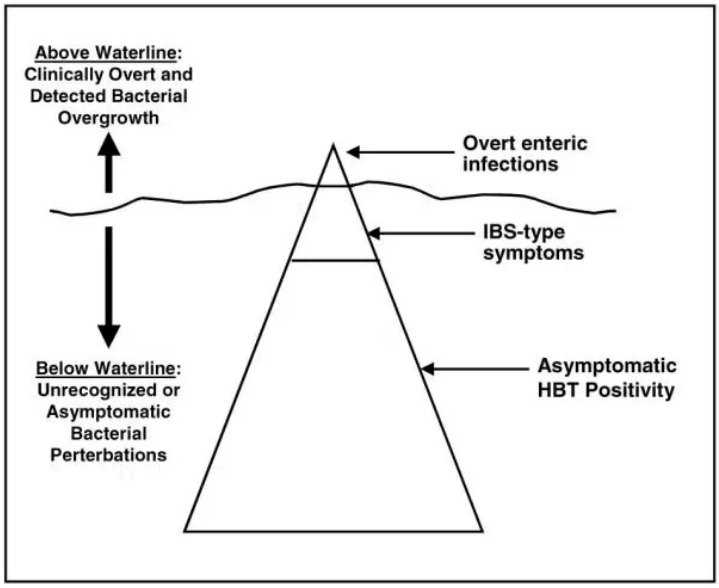

Fig. 1. The proposed "iceberg" of PPIs-induced bacterial complications in the small intestine.

Noteworthy two cohort studies carried out in m-pocket medical centers in New England. They participated in 1166 patients, and determine the cause and effect influence on the increase in PPIs the risk of C. difficile colitis etiology. In the first study, the use of PPIs during treatment infection C. difficile was associated with higher risk of relapse infection C. difficile in 42% of patients. The second study showed that an increase in effect "dose-response" with a decrease in gastric acid production in patients taking PPIs increased risk nosocomial C. difficile infection [15].

In 50% of patients taking PPIs for the treatment of gastroesophageal reflux disease (GERD), has developed BOS than a quarter of patients with IBS who were not taking PPIs, according to a study conducted by L. Lombardo et al. [12]. The study included 450 patients who were examined with the use of hydrogen breath test with glucose (GHBT) to detect the metabolic activity of enteric bacteria. 200 of the surveyed patients received one of several PPIs for a mean of 36 months about GERD. BOS was detected in 50% of patients taking PPIs, 24.5% of patients with IBS, and

only 6% healthy. In addition, the researchers found a correlation between the duration of PPIs therapy and detection of their BOS: more than 70% of those taking PPIs for more than 13 months to 3 times more likely to acquire BOS as opposed to those who took PPIs within 1 year or less. Many researchers suggest the use of hydrogen breath tests for patients to be able to monitor how BOS assess the impact of PPIs. This, they said, is "an important supervision" over the use of PPIs. L. Lombardo et al. studied in patients with PPIs-induced BOS administration of the antibiotic α-rifaximin 400 mg three times a day for 14 days. Normalization of the clinical picture and GHBT occurred in 87% of patients taking PPIs, and in 91% of patients in the IBS [25].

A large retrospective analysis of more than 2,000 hydrogen test with glucose or lactulose has found that the use of proton pump inhibitors was an independent predictor of positive hydrogen test relating to BOS, in patients with diabetes, liver cirrhosis, cardiovascular, rheumatological diseases and gastrointestinal interventions (odds ratio (OR) 1 27, p=0.028) [4].

Another study by D. Compare et al. of 554 patients selected 42 patients with NERD. After 8 weeks of treatment the patients complained of PPIs bloating (43%), flatulence (17%), abdominal pain (7%) and diarrhea (2%). After 6 months BOS was detected in 26% of patients using GHBT [7].

A year ago, the American Gastroenterological Journal published an article, which reduced the role of PPIs influence on the formation according to the BOS results GHBT and LHBT. This article analyzes the results of 10 studies conducted from 2004 to 2010. The data of 1191 patients (70% female), of whom 566 (48%) were on PPIs therapy. Positive GHBT was associated with age (OR, 1.03; 95% confidence interval (CI) 1.01-1.04) and diarrhea (OR, 1.99; 95% CI 1.15-3.44), where the level of H2> 20; with older age (OR, 1.01; 95% CI 1.00-1.02), and diarrhea (OR, 1.53; 95% CI 1.13-2.09), where the level of H2> 10; with older age (OR, 1.01; 95% CI, 1.00-1.02), which marks the level of H2>20 or CH_4>15. Use of PPIs was not associated with a positive GHBT when using any of these criteria [18]. L. Lombardo replied to this article comments, pointing out that the work has not been

evaluated duration of use of PPIs, which directly influences the formation of BOS in patients using proton pump inhibitors [13].

The greatest experience in the world of the treatment of BOS was acquired using α-rifaximin. α-rifaximin (Alpha Normiks, production Alfa Wassermann SpA, Italy) is a non-systemic antibiotic semisynthetic rifampicin very low gastrointestinal resorptive and good bactericidal activity. Antibacterial action it includes gram-positive and gram-negative microorganisms, such as aerobic and anaerobic bacteria [21]. According to various studies, α-rifaximin improves symptoms in 33-92% and eliminates bacterial overgrowth in the BOS 80% of patients [20, 24]. Most authors recommend the use of α-rifaximin for 7-10 days as one course of treatment or as a cyclic therapy. High doses of α-rifaximin (1200 or 1600 mg / day) were more effective than the standard dose (600 or 800 mg/day) [10, 16]. α-rifaximin perhaps the only antibiotic that can achieve long-term clinical benefit in patients with irritable bowel syndrome associated with BOS[8].

Thus, the above article in our findings and conclusions need further investigation and confirmation. But it is important to consider that the prolonged use of proton pump inhibitors may lead to the formation of BOS, especially in patients of older age groups, so you need to develop a strategy for the use of PPIs in GERD with minimal dose or "on demand". It is necessary to study the impact on the microbial landscape of the small intestine with the prolonged use of NSAID-PPIs gastropathies, chronic pancreatitis and other acid-related diseases. In order to control and monitor the development of BOS in these patients should be applied LHBT. The drug of choice for the correction of BOS can serve as α-rifaximin.

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E. Y. Plotnikova

Kemerovo State Medical Academy, Kemerovo, Russia

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Bacterial overgrowth syndrome has many etiological factors, one of which is a prolonged intake of the proton pump inhibitors. The article represents an analysis of the proton pump inhibitors use upon acid-dependent diseases and their role in the rise of small intestinal bacterial overgrowth syndrome. Modern methods of diagnostics, monitoring and treatment of PPIs-induced bacterial overgrowth syndrome are described.