Diagnostics and treatment of excessive bacterial contamination of the small intestine in clinical practice, our own experience

E. Y. Plotnikova[1], M. V. Krasnova[2], Y. N. Baranova[1]

[1]*Kemerovo State Medical Academy, Russia*

[2]*City clinical hospital No 3 n. a. M. A. Podgorbunsky, Kemerovo, Russia*

Key words: microbial landscape of the gastrointestinal tract, small intestinal bacterial overgrowth syndrome, malabsorption, dysbiosis, hydrogen breath tests, lactulose, intestinal decontamination, probiotics, prebiotics

From 300 to 500 different species of bacteria normally "live" in the gastrointestinal tract (GIT) of human. Microbial landscape is significantly different in the proximal and distal parts of the small intestine. If the upper small intestine is inhabited by about 10^2 CFU/ml, 10^9 CFU/ml are closer to the colon. In the proximal parts of the small intestine gram-positive aerobic bacteria species are the most abundant, while gram-negative anaerobic bacteria are frequently localized in the distal parts. In healthy people the normal intestinal flora is supported by the following basic physiological mechanisms: the pH of hydrochloric acid in the stomach, the activity of the secretory function of the pancreas and cholepoiesis, motility of the small intestine and the structural integrity of the gastrointestinal tract. Violation of any of these defense mechanisms can lead to bacterial overgrowth syndrome (BOS) in the small intestine [4].

The most important etiological factors include the following:

- dysfunction of the ileocecal valve (inflammatory, tumor processes, primary functional insufficiency);
- results of surgeries (anatomical or surgically shaped blind loop, small–large intestinal anastomosis or fistula, vagotomy, cholecystectomy, resection of the small intestine);
- gastrointestinal diseases related to motor disorders — gastrostasis, duodenostasis, stasis contents in small and large intestines (chronic constipation in patients with diabetes);

- disorders of digestion and cavity absorption (maldigestion and malabsorption), including those related with: achlorhydria of different origin (the operated stomach, with chronic atrophic gastritis, long intake of the proton pump inhibitors); exocrine pancreatic insufficiency (chronic pancreatitis); pathology of the biliary tract (cholelithiasis, chronic cholecystitis);
- enteropathy (disaccharidase insufficiency and another food intolerance);
- prolonged nutritional imbalance;
- chronic inflammatory bowel disease, diverticulitis, short bowel syndrome;
- receipt of bacteria from the extra-intestinal pouch (e.g., in cholangitis);
- local and systemic immune disorders — radiation, chemical exposure (cytostatics), AIDS;
- antibiotic therapy;
- stress of different origin;
- tumors of the intestine and mesenteric lymphatic nodes [16].
- various diets for weight loss, "cleaning" using volume enemas and especially hydrocolonotherapy, which has a certain popularity, but strongly not recommended by gastroenterologists of the world, as it roughly destroys microbial biotopes.

Upon BOS not only the number, but the spectrum of microorganisms increases with a shift towards gram-negative bacteria and anaerobes. In 30% of healthy people jejunum normally is almost sterile, the rest have a low population density, which increases in approaching the colon, and only in the distal ileum microflora of fecal type is revealed: enterobacteria, streptococci, anaerobes of Bacteroides genus, and others [6].

Symptoms of BOS don’t have specificity: flatulence, bloating, abdominal pain or discomfort, diarrhea, fatigue, weakness, weight loss — they reflect the extent of inflammation of the intestinal mucosa, "mingle" with manifestations of the underlying disease that is the cause of BOS. More severe symptoms indicate BOS complications, including malabsorption, and nutrient deficiency disorder of bone metabolism. These nonspecific symptoms often cause the diagnostic errors and

require differential diagnosis of irritable bowel syndrome (IBS), lactose or fructose intolerance.

To characterize BOS it is necessary not only to determine the absolute amount of bacteria and their species, but to conduct their typing that defines the display of signs and symptoms. If overgrowth of bacteria metabolizing bile salts in unconjugated or insoluble compounds prevails, the clinic of fat malabsorption or diarrhea develops due to bile acids. Deconjugated bile acids may exert toxic injurious effects on enterocytes, which not only violates the assimilation of fats, but also carbohydrates and proteins. Upon excessive growth of bacteria that mainly metabolize carbohydrates in short chain fatty acids and gas, bloating without diarrhea is predominant in the clinic, as formed metabolic products can be absorbed.

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" of BOS diagnostic is microflora inoculation, which requires aspiration of the contents of the small intestine with immediate inoculation of aspirate on a nutrient medium. But bacterial overgrowth can affect more distal parts of the small intestine, which is beyond the reach of tools [15].

Fecal inoculation that is used in our country as a method of assessing the microbial bowel biocenosis is recognized as uninformative, because, even at maximum approximation to the rules of microbiological testing, it may provide insight into the microbial composition of only 12-15 typeable species of bacteria of the distal colon [3]. Considering that most of the normal flora of the intestine is anaerobic, and the patient collects and carries his/her feces to the bacteriological laboratory in the presence of air, which includes oxygen, most of these bacteria are killed, but pathogenic aerobic flora multiplies very quickly. What will grow upon inoculation of such content? We can only guess, but it is unlikely to be related even to the microbial landscape of the rectum. Fecal study is informative for search of infectious agents or helminthic invasion.

There are other methods based on the study of indican concentration, produced by indo-positive microorganisms, phenol, paracresol, which are metabolites of

aerobic (to a lesser extent) and anaerobic (mostly) microorganisms, as well as a way to diagnose the state of microbiocenosis of different biotopes, including intestine, based on the determination of short chain fatty acids, which are mostly the metabolites of anaerobic genera of microorganisms, by gas-liquid chromatographic analysis [1].

Indirect methods include tests that are based on a study of metabolites of microorganisms. They are ^{14}C- or ^{13}C-glycocholic, ^{14}C-D- or ^{13}C-D-xylose breath tests, which require isotopes and specialized laboratory. The most used are hydrogen breath tests with lactulose, glucose, lactose and other sugars.

Hydrogen breath tests are simple, informative and non-invasive methods which were developed and studied about 25 years ago for the diagnostics of various diseases of the digestive tract, primarily — to determine the carbohydrate malabsorption and bacterial overgrowth in the small intestine. At present, this diagnostic method is implemented quickly into clinical practice all over the world. Some methodological aspects of the individual hydrogen tests are still not standardized, so the study of the effectiveness of existing tests and the development and/or improvement of new ones around the world continues [5].

In 2008 the Rome Consensus on hydrogen tests was adopted, which set out the recommendations of international experts for clinical practice regarding the indications and methods of H_2-breath tests for diseases of the digestive tract [12]. The method is cheap, simple, but many practitioners not only don’t know the basic provisions of the consensus, but don’t know about this test, don’t know its diagnostic abilities, certain limitations and disadvantages [2].

The hydrogen content in the lowest layer of the atmosphere — the troposphere — is 0.575 ppm (pmol), as its content in the breath of a healthy person is 20-30 ppm or more (with the exception of some people, whose intestinal microflora produces more methane than hydrogen, a small part of the population produces uncertain gases being non-responders to the hydrogen test). Increased hydrogen elution occurs when a part of the absorbed carbohydrates (proteins) is not absorbed or digested by the small intestine mucosa, and is used by the bacterial colonies of the colon to ferment

and produce hydrogen. Part of the hydrogen is absorbed in the intestinal mucosa and the blood, and is transported to lungs where it is excreted in expired air. Thus, the absorbed carbohydrates (glucose, fructose, lactulose, galactose, xylose, lactose, etc.) or substances similar to the molecular structure of carbohydrates (sorbitol, xylitol, mannitol, etc.) cause an increase in hydrogen concentration in the exhaled air upon malabsorption or bacterial overgrowth in the small intestine. If the gases are not recycled by bacteria, they are absorbed and then excreted in the breath or during discharge. In particular, H_2 can quickly be absorbed into the blood and excreted by lungs, which is a logical rationale for H_2-breath test that is widely used for the determination of carbohydrate malabsorption. The absorbed H_2 is almost completely removed from the blood in one passage through the lungs, thus, the level of excretion of H_2 should be equivalent to its absorption in the intestine. Approximately 14-20% of H_2 released in the colon is excreted by lungs: thus, measuring the concentration of H_2 in the exhaled air can be taken as a reflection of the intestinal production of H_2 [10, 11].

Hydrogen test is used to indicate the degree of bacterial colonization of the small intestine. This indicator is directly dependent on the concentration of hydrogen in the breath on an empty stomach. In patients with intestinal diseases, occurring with chronic diarrhea and recurrent bacterial colonization of the small intestine, the hydrogen concentration in the exhaled air greatly exceeds 15 ppm. In bacterial colonization of the small intestine, "peak" of hydrogen concentration rise in the exhaled air appears much earlier. Advantages of this test include:

- unlimited access to all the bacteria of digestive tract (unlike glucose, which allows to estimate the overgrowth only in the proximal small intestine);
- good correlation between speed of hydrogen production in digestive tract and speed of hydrogen excretion by lungs;
- distinct separation of metabolic activity of the bacteria and their host.

In using hydrogen breath tests we can diagnose:

- increase in the transit time of carbohydrates in the gastrointestinal tract;
- BOS;

- malabsorption or maldegestion of some carbohydrates;
- lactulose, sucrose, lactose intolerance.

Lactulose is artificial synthetic disaccharide consisting of galactose and fructose, in which there is no enzyme to decompose it into monosaccharides. The concentration of hydrogen (H_2) in the exhaled air upon the hydrogen breath test with lactulose may have several graphs:

- normal — in the small intestine lactulose isn't decomposed, in reaching large bowel it undergoes fermentation with hydrogen release, which is absorbed in the blood and excreted in the expired air;
- pathologhical — in bacterial overgrowth, lactulose undergoes fermentation in small intestine, hydrogen concentration reaches maximum earlier.

The test with lactulose is the most common non-invasive test to determine the intestinal transit time of various carbohydrates. After the basical expiration, the surveyed are offered to drink: children under 6 months — 3.34 g (5 ml), children older than 6 months — 6.68 g (10 ml), adults — 10 g (15 ml) of lactulose, dissolved in a small amount of water (50-150 ml). Direct recording of measurements is done by a trained nurse, the conclusion is given by a gastroenterologist, clinical evaluation and treatment are conducted by a doctor, whom the patient applied for examination to. Increase of the hydrogen concentration over 15 ppm is considered diagnostic. The early peak of H_2 concentration suggests BOS, stunting H_2 concentration points out the prolonged intestinal transit. Test is performed during 2.5-4 hours, the patient exhales into a tube or a special device, a hermetically fixed packet of a certain volume once in 15-30 minutes, depending on the phase of the study. For the accuracy of the test, it is required that the hydrogen production by colon bacteria from non-absorbed carbohydrates of the test meal led to a clearly discernible increase in the hydrogen signal in exhaled air. On the basis of the results of research it is advisable to refrain from eating the night before the test. Smoking may also change the release of hydrogen from the exhaled air. Therefore, patients are prohibited to smoke before and during the test [13].

We have had experienced with the hydrogen breath tests for five years, using the device Gastrolyzer 2 (Bedfont Scientific LTD, UK) in our practice. Here are few interesting cases from our clinical practice. All patients, except for the breath tests with lactulose, underwent standard examination: in addition to general clinical methods, a set of techniques to detect celiac disease, fecal study to detect Giardia antigen, coprogram, fecal elastase-1, CT colonoscopy or irrigoscopy, fibrocolonoscopy (by indications), psychological testing, and each patient completed questionnaires IBS Quality of Life (IBS-QOL) [14].

Patient A., 60 years. Complaints to permanent mushy feces 5-6 times a day for 2 years, recurrent abdominal pain, bloating, flatulence, intolerance to some products, weight loss of 17 kg over 2 years, worsening of health for the last 3 months. Forced to keep on a strict diet — rice porridge on the water, crackers, strong tea, etc. Examined and treated by infectious diseases specialist with some non-sustained improvement. Standard surveys — mild iron deficiency anemia, decrease of magnesium and calcium in the blood. According to the hydrogen breath test — severe bacterial contamination of the small intestine (Fig. 1, No 1). Treatment prescribed — antibiotics, then the course of prebiotics and probiotics, multivitamins. In a month patient felt better and noted weight gain of 5 kg, normalization of stool. In 6 months — the results of blood tests and breath hydrogen test without pathology (Fig. 2, No 1).

Patient U., 72 years. Complaints to nausea, bitter taste in the mouth in the morning, alternating constipation and diarrhea, recurrent abdominal pain before and after meal in some time, bloating. Lost 15 kg in the last 3 years, keeps on a strict diet with the exception of fatty, fried and dairy food, etc. The examination found: amylorrhea and steatorrhea of koprograme, fecal elastase-1 — 50 mcg/g of feces, expressed hypomotor dysfunction of the gall bladder. Hydrogen breath test data are normal (Fig. 1, No 2). Scheme of treatment of chronic pancreatitis and biliary disease prescribed with a good clinical effect in dynamics.

Patient A., 42 years. Complaints to alternating constipation and diarrhea, nervousness, weakness, fatigue. Treated repeatedly ("dysbiosis") without effect (Fig.

1, No 3). Standard examination — without pathology. According to the breath test, it can be assumed: reduced rate of transit through the small intestine, reduced levels of normal flora in the colon. According to the psychological testing — moderate somatoform anxiety disorder within IBS. Prescribed treatment — psychotropic drugs, prebiotics and probiotics. In the dynamics, the patient in 6 months has no complaints, breath test results are normal (Fig. 2, No 3).

Patient R., 64 years. Diagnosis — cirrhosis of viral etiology in the outcome of hepatitis C, class B by Child-Pugh score. Complaints to the expressed flatulence, diarrhea, pain, intensified after taking lactulose, which is a part of the treatment regimen. Breath test showed evident bacterial contamination of the small intestine (Fig. 1, No 4). In such situations the test can be used for the purpose of BOS monitoring with the aim of therapeutic antimicrobial therapy. In dynamics after a course of antibiotic treatment there is a considerable positive dynamics, but a second course with the replacement of preparation is recommended (Fig. 2, No 4).

Patient N., 32 years. Complaints to constant aching pain in the stomach, worsening during stress or after taking certain foods, periodic mushy stools 2-4 times a day, bloating, fatigue, nervousness, anhedonia. Standard examination — without pathology. For several years, visited gastroenterologists, surgeons, prescribed treatment "dysbiosis" is ineffective, the weight is stable. According to the results of the breath test, BOS is revealed (Fig. 1, No 5). Psychological questionnaires revealed severe somatoform depressive disorder within the IBS associated with BOS. Prescribed treatment — antibiotics, prebiotics, probiotics, antidepressants. After BOS treatment course (Fig. 2, No 5), there is a clinical improvement, but pain is not fully blocked, antidepressants intake is continued.

Patient M., 37 years. Complaints to periodic mushy stools since childhood, poor tolerance to milk products, over the past 3 years mushy stools 4-8 times a day has become a regular, lost 8 kg, BMI — 17.2 kg/m^2. Standard examination revealed celiac disease, mild iron deficiency anemia, according to the hydrogen breath test — BOS (Fig. 1, No 6). Prescribed treatment — gluten-free diet, antibiotics, probiotics, prebiotics, multivitamin complex with essential micronutrients. In the dynamics there

is an improvement — weight gain of 3 kg, mushy stools 2-3 times a day. Result of the hydrogen breath test is normal (Fig. 2, No 6).

Nowadays hydrogen breath tests are considered as informative methods for the diagnostics of certain physiological and pathological processes, such as malabsorption of carbohydrates (lactose, fructose, sorbitol), BOS, the timing of orocecal transit. Due to non-invasiveness and relatively low cost of the tests, they are the diagnostic tests of the first line of examination in many cases. The role and clinical indications for their conduct in gastroenterological practice are constantly refined and expanded. Practitioners should be aware of the advantages and disadvantages of these methods of examination and widely use them in the clinical practice.

The problem of treatment of excessive bacterial contamination is not as relevant as its diagnostics. Treatment of patients with BOS consists in removal of the excess bacterial colonization of the small intestine, restoration of the gut microbiota, normalization of digestion. Parallel symptomatic treatment is conducted aimed at the eliminating or reducing the severity of the main symptoms of the disease.

Many authors recommend the prescription of a wide spectrum of antibacterial drugs effective against anaerobic bacteria — α-rifaximin (400-600 mg 2 times a day), tetracycline (0.25 g internally 4 times a day), ampicillin (0.5 g internally 4 times a day), metronidazole (500 mg internally 3 times a day), ciprofloxacin (500 mg 2 times a day), norfloxacin (800 mg daily), vancomycin (125 mg 4 times a day) [6, 8, 16]. Sometimes repeated courses lasting from 7 to 14 days are neede. In our practice, we often use the rifaximin 400 mg 2 times a day, often only one ourse is enough to significantly improve the state of health and normalization of breath hydrogen test results. If pain and intestinal dyspepsia are saved upon normalization of the breath test, this is considered as a manifestation of IBS symptoms. In the analysis of data collected by us for 5 years, the frequency of IBS and BOS association was found in more than 60% of patients.

After a course of antibiotic therapy, we prescribe pro- and prebiotics. The choice of probiotic for the empirical correction of microbial landscape of the intestine is

rather difficult task as many of them are ineffective. Perhaps this is due to the rapid loss of the imposed strains because of the high aggressiveness of the immune system against its own microflora. It is necessary to choose only products that meet the following criteria [8]:

- contain microorganisms, which probiotic effect is proved in randomized controlled trials;
- have a stable clinical efficacy;
- are phenol- and genotype-classed;
- are preserved alive;
- are non-pathogenic and non-toxic, without causing adverse effects in long-term use;
- have a positive influence on the organism of the host (e.g., by increasing the resistance to infections);
- have a colonization potential, i.e. are preserved in the digestive tract until reaching the maximum positive effect (resistant to high acidity, organic and bile acids, anti-microbial toxins and enzymes produced by pathogenic microflora);
- are acid-fast or contained in the acid-fast capsule;
- are stable and keep viable bacteria in long-term storage [7, 9].

Thus, for BOS diagnostics in patients it is reasonable to administer breath test with lactulose, glucose, lactose and other sugars, along with other standard methods of examination. To correct this condition it is very important, in addition to selective decontamination of pathogenic and conditionally pathogenic microorganisms (if necessary), to restore the normal microbial landscape with prebiotics and probiotics, including metabolic probiotic.

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This paper is devoted to the diagnostics and treatment of the small intestinal bacterial overgrowth syndrome. Its pathogenetic mechanisms are described, as well as methods of differential diagnostics with other diseases. Part concerning the treatment of the small intestinal bacterial overgrowth syndrome reviews current data on the use of drugs with a high level of evidence and recommendations. The article also represents our own data on identification of the small intestinal bacterial overgrowth syndrome in patients and its treatment.

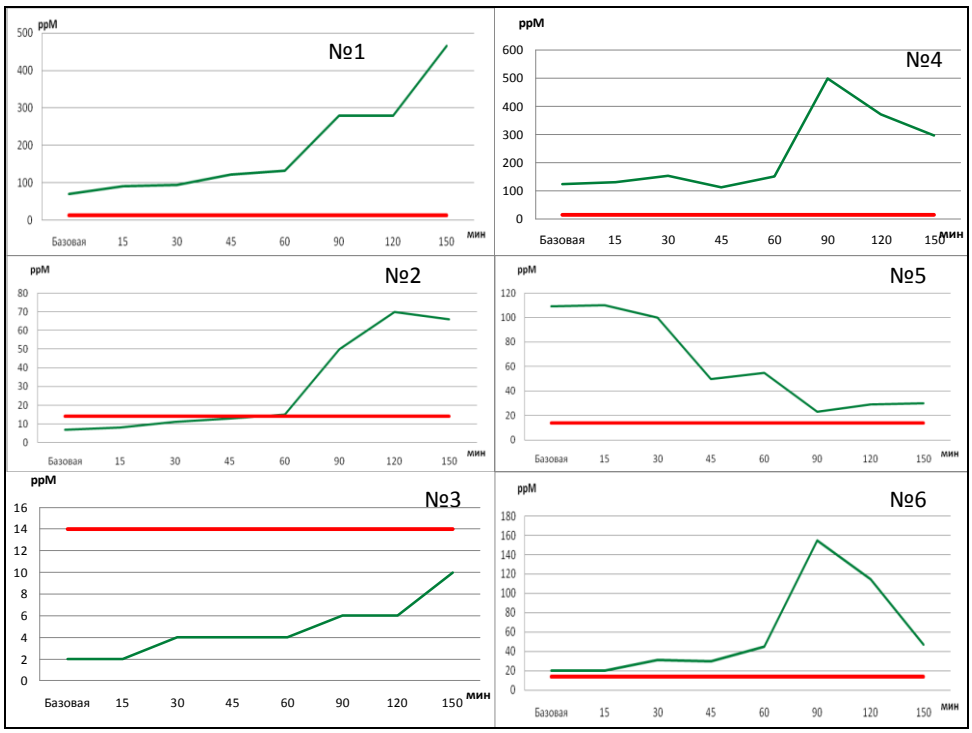

Fig. 1. Results of the breath hydrogen tests before treatment.

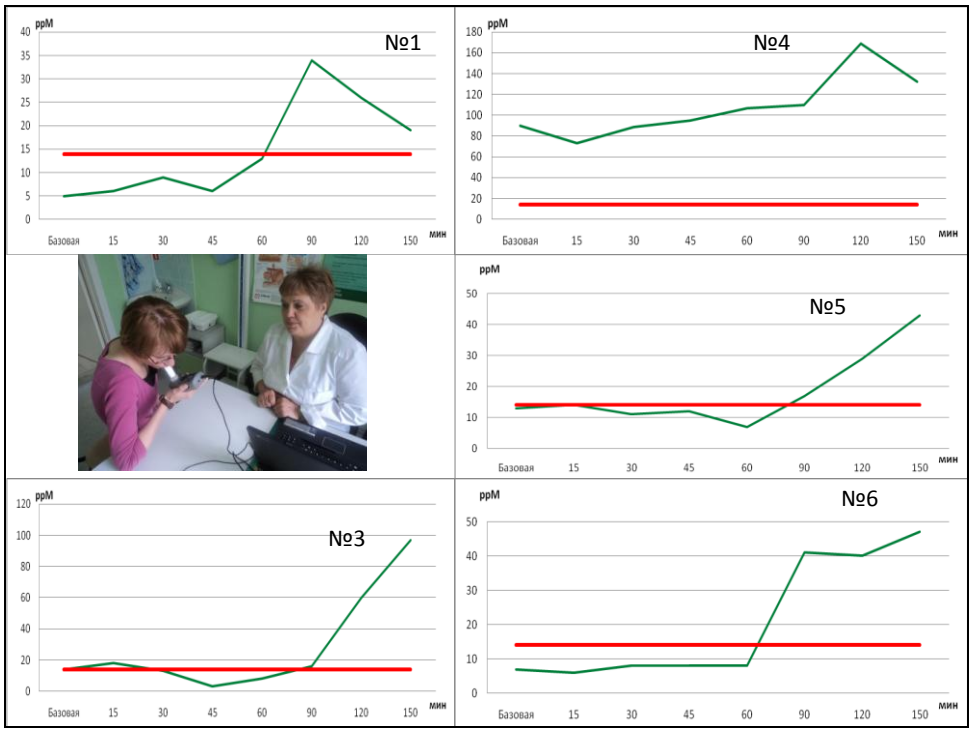

Fig. 2. Results of the breath hydrogen tests in dynamics after treatment. In the photo — conduction of the breath test.