



# Prevalence of Small Intestinal Bacterial Overgrowth Syndrome in Patients with Irritable Bowel Syndrome who Have Suffered COVID-19

Andrew V. Nalyotov<sup>1,\*</sup>, Natalya P. Guz<sup>2</sup>

<sup>1</sup> M. Gorky Donetsk National Medical University, Donetsk, Donetsk People's Republic

<sup>2</sup> Medical Centre "Gastro-line", Donetsk, Donetsk People's Republic

**Aim.** To study the prevalence of the small intestinal bacterial overgrowth syndrome in patients with irritable bowel syndrome with diarrhea who have had COVID-19 infection.

**Materials and methods.** 60 patients with irritable bowel syndrome with diarrhea were examined. In 30 patients, irritable bowel syndrome was diagnosed after COVID-19 infection (main group). The comparison group consisted of 30 patients with classical stress-induced irritable bowel syndrome. The small intestinal bacterial overgrowth syndrome was diagnosed using a hydrogen breath test with lactulose loading in all patients.

**Results.** In main group the small intestinal bacterial overgrowth syndrome was diagnosed in 93.3 % patients, which was statistically significantly higher ( $p < 0.01$ ) relative to the comparison group — 60.0 % patients

**Conclusion.** Irritable bowel syndrome in patients who have undergone COVID-19 occurs against the background of the small intestinal bacterial overgrowth syndrome development.

**Keywords:** irritable bowel syndrome, syndrome of excessive bacterial growth of the small intestine, COVID-19

**Conflict of interest:** the authors declare no conflict of interest.

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## Распространенность синдрома избыточного бактериального роста тонкой кишки у пациентов с синдромом раздраженного кишечника, перенесших COVID-19

А.В. Налетов<sup>1,\*</sup>, Е.П. Гуз<sup>2</sup>

<sup>1</sup> ГОУ ВПО «Донецкий национальный медицинский университет имени М. Горького», Донецк, Донецкая Народная Республика

<sup>2</sup> ООО «Медицинский центр "Гастро-лайн"», Донецк, Донецкая Народная Республика

**Цель исследования.** Изучить распространенность синдрома избыточного бактериального роста (СИБР) тонкой кишки у пациентов с синдромом раздраженного кишечника с преобладанием диареи (СРК-Д), перенесших инфекцию COVID-19.

**Материалы и методы.** Обследовано 60 пациентов с СРК-Д. У 30 пациентов синдром раздраженного кишечника диагностирован после перенесенной инфекции COVID-19 в сроки от 2 недель до 4 месяцев (в среднем  $68,3 \pm 2,3$  суток) (основная группа). Группу сравнения составили 30 больных с диагнозом СРК, которые не болели COVID-19. У всех пациентов была проведена диагностика СИБР тонкой кишки при помощи водородного дыхательного теста с нагрузкой лактулозой.

**Результаты.** Среди пациентов, которые перенесли COVID-19, доля больных, имеющих СИБР тонкой кишки, составила 93,3 %, что было достоверно выше группы сравнения (пациентов, имеющих «классический» СРК) — 60,0 % ( $p < 0,01$ ).

**Выводы.** Синдром раздраженного кишечника у пациентов, перенесших COVID-19, протекает на фоне развития синдрома избыточного бактериального роста тонкой кишки.

**Ключевые слова:** синдром раздраженного кишечника, синдром избыточного бактериального роста тонкой кишки, COVID-19

**Конфликт интересов:** авторы заявляют об отсутствии конфликта интересов.

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## Introduction

Irritable bowel syndrome (IBS) is one of the most common functional diseases of the gastrointestinal tract and is characterized by recurrent abdominal pain which is associated with changes of defecation pattern (constipation, diarrhea, or their combination) [1]. It is estimated that IBS affects 10–25 % of the world's population [2, 3].

The presence of IBS is not accompanied by an increased risk of colorectal cancer or inflammatory bowel disease. Despite the fact that IBS does not affect mortality, the disease can significantly impair the quality of life of patients and leads to significant costs for its treatment and diagnosis [2, 3].

The etiopathogenesis of the disorder is complex, since a number of etiological factors are involved in its development triggering several pathophysiological mechanisms [4]. According to the modern concept of the pathogenesis of IBS, genetic predisposition and psychosocial factors play an important role in the development of the disease: stress and impaired ability to overcome it, and insufficient social support. The combination of these factors can lead to the changes in the neuroendocrine regulatory system “gut-brain”, which is realized through the development of visceral hypersensitivity and impaired intestinal motility. In recent years, the scheme the pathogenesis of IBS can be supplemented by a number of links relating to changes localized at the level of the intestinal wall, such as a violation of the cytokine profile, the expression of signaling receptors and a decrease in the synthesis of cytosolic and membrane proteins of intercellular dense contacts, which contributes to an increase in mucosal permeability, activation of the immune system and the development of nonspecific low degree inflammation of the intestinal mucosa. Against the background of these processes, there is changes in the qualitative and quantitative composition of the intestinal microbiota, which contributes to the adhesion of an increased number of different antigens [5–7].

Today the disorders of the composition of the intestinal microbiota are considered as the main factor in the development of symptoms of IBS [6, 7]. Conditionally pathogenic and pathogenic intestinal bacteria possessed adhesion factors penetrate into the lymphoid follicles and trigger a cascade of immune reactions leading to the development of nonspecific low degree inflammation, activation of the immune system and epithelial dysfunction with a change in intestinal permeability [8].

The disorders in the composition of the gut microbiota can be not only qualitative, but also quantitative, which underlies the development of small intestinal bacterial overgrowth (SIBO) that is increased colonization of the small intestine mainly by the colonic microbiota with the frequent development of abdominal pain, chronic diarrhea and malabsorption, primarily of fats and vitamin B<sub>12</sub>.

It is known that bacteria are involved in the utilization of a number of food components, and form metabolites that affect local and systemic metabolism. A number of toxic compounds (ammonia, peptidoglycans and D-lactate) formed in increased count in the gut with SIBO contribute to damage to the brush border of enterocytes, an increase the permeability of the intestinal epithelium, an activation of the intestinal immune system, which leads to the development of nonspecific inflammation and malabsorption syndrome of macro- and micronutrients [9]. A characteristic phenomenon in SIBO is the excessive production of the microbiota hydrogen, methane and carbon dioxide, which contributes to the development of symptoms of IBS, such as abdominal pain and bloating. Inflammatory infiltrate in the mucous membrane in SIBO contains a significant number of lymphocytes, mast cells, and an increased number of enterochromaffin cells. As a result, when the mediators of these cells are released, the receptors of nerve endings are stimulated, which leads to the development of visceral hypersensitivity and increased motility, that are key mechanisms in the formation of IBS [10].

Since the end of 2019, the world has been facing a rapidly spreading COVID-19 pandemic. In most clinical studies, the main attention of scientists is paid the disorders of the bronchopulmonary system, which determine the prognosis and severity of the disease in most cases [11].

The frequency of gastrointestinal symptoms (diarrhea, nausea, vomiting, anorexia, abdominal pain) in COVID-19 ranges from 3 % to 80 % of patients [11, 12].

It is proved that SARS-CoV-2 virus can have a tour-mediated penetration into the cell through the receptors of angiotensin-converting enzyme 2 (ACE2), the expression of which is found in the epithelial cells of the stomach and intestines. The effect of the virus leads to the induction of inflammation and a change in the permeability of the mucous membranes, which is realized in the development of IBS symptoms [6, 12]. The effect of SARS-CoV-2 on the composition of the intestinal microbiota is considered as one of the leading mechanisms for the development of diarrhea in COVID-19 [11].

The “gut-lung axis” in the pathogenesis of bronchopulmonary pathology in COVID-19 was formulated. This axis is bidirectional: endotoxin and microbial metabolites from gut can affect the lungs disseminating through blood and the inflammation of lungs can also affect the gut microbiota. In this regard, severe pathology of the bronchopulmonary system in COVID-19 through the “gut-lung axis” can lead to an imbalance of the gut microbiota and the development of gastroenterological symptoms [11].

It is impossible to exclude the development of gastrointestinal symptoms due to the use of drugs for the treatment of COVID-19. Massive antibiotic therapy given to patients with coronavirus infection

has a negative effect on the composition of the gut microbiota, can provoke an antibiotic-associated diarrhea. In some cases, repeated courses of may be prescribed unreasonably or be a manifestation of self-treatment [4].

**The aim of the work:** to study the prevalence of SIBO in patients with irritable bowel syndrome with a predominance of diarrhea (IBS-D) who have suffered COVID-19.

## Materials and methods

In Medical Center “Gastro-line”, Donetsk, 60 patients with IBS-D aged 18 to 55 years were examined.

The diagnosis of the functional disease is established in accordance with the Clinical Guidelines of the Russian Gastroenterological Association and the Association of Coloproctologists of Russia [13]. The clinical variant of IBS is determined according to the Bristol scale.

Thirty patients were diagnosed with IBS-D after COVID-19 infection (the main group). The average age of patients in the group was  $24.3 \pm 0.4$  years.

The comparison group consisted of 30 patients who had not were infected with COVID-19 virus. They had IBS-D induced by stress. The average age of patients in the group was  $25.4 \pm 0.5$  years. Patients of the comparison group lived in areas of the Donetsk People’s Republic that were subjected to frequent shelling, the manifestation of symptoms patients noted after the intensification of hostilities in the region of residence.

There was no statistically significant difference in age and sex between the comparison groups

( $p > 0.05$ ). The women:men ratio was 3:1 in both groups.

All patients were diagnosed with SIBO using a hydrogen breath test with a load of lactulose with the digital analyzer of exhaled hydrogen “LactofaN2” (LLC “AMA”, Russia).

Permission was obtained from the Ethical Committee of the State Educational Organization of Higher Professional Education “Donetsk National Medical University named after M. Gorky” to conduct this study. Prior to the examination, all patients received an explanation about the study and were included in it after writing informed consent.

In the statistical analysis, methods of point estimation of the parameters of the general population (sample characteristics) were used. For qualitative characteristics, the value of the indicator of the frequency of SIBO development (%) and its standard error (m %) are given. Comparison of the average qualitative data was performed using a pair comparison of the share (chi-squared criterion taking into account the Yeats correction).

## Results

Studying the anamnestic data of patients of the main group, it was found that the duration of the post-COVID period before the development of IBS symptoms ranged from 2 weeks to 4 months (an average of  $68.3 \pm 2.3$  days). The manifestation of IBS-D in  $66.7 \pm 8.6$  % of patients was registered during COVID-19, and in  $33.3 \pm 8.6$  % in the post-COVID period. At the same time, we did not establish a relationship between the severity

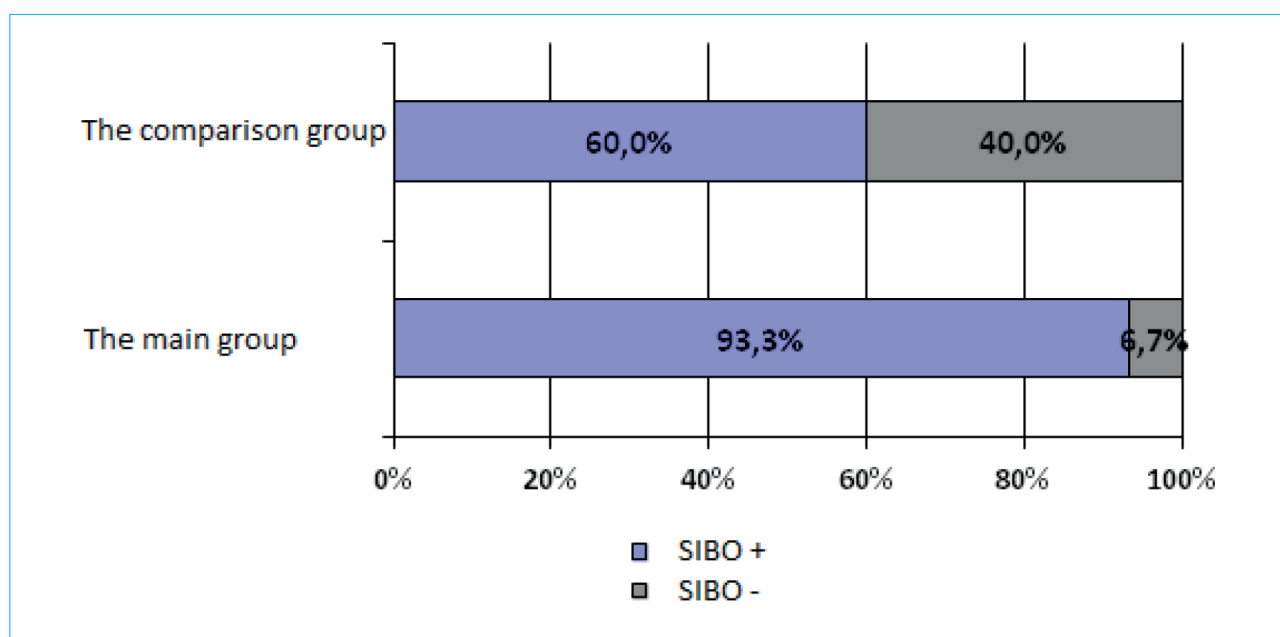


Fig. Prevalence of SIBO in patients with IBS-D who have had COVID-19 (the main group) and have not had it (the comparison group)

of bronchopulmonary pathology and the severity of IBS symptoms.

In  $16.7 \pm 6.8$  % of patients there were no bronchopulmonary symptoms, and clinical symptoms were characterized only by gastrointestinal manifestations: all patients in this group had diarrhea ( $16.7 \pm 6.8$  %),  $13.3 \pm 6.2$  % of them had nausea and  $10.0 \pm 5.5$  % had abdominal pain. In most cases, the manifestation of gastrointestinal symptoms began with diarrhea ( $56.7 \pm 8.4$  %), abdominal pain ( $23.3 \pm 7.7$  %), and with nausea and a feeling of heaviness in the epigastrium ( $20.0 \pm 7.3$  %).

Antibiotic treatment of COVID-19 was carried out in  $73.3 \pm 8.1$  % of patients of the main group. At the same time, repeated courses of antibiotic therapy were prescribed to  $46.7 \pm 9.1$  % of patients. Macrolides were most often used ( $50.0 \pm 9.1$  % of patients), cephalosporins of the II-IV generation did in  $40.0 \pm 8.9$  %, protected aminopenicillins did in  $20.0 \pm 7.3$  %, quinolones did in  $36.7 \pm 8.8$  %. There was no relationship

between the duration and number of courses of antibiotics and the severity of symptoms of IBS-D.

IBS-D in the majority of patients examined was combined with the development of SIBO. However, in patients with IBS-D who had COVID-19, the proportion of such patients was significantly greater (Fig.).

Thus, among the patients of the main group when conducting a hydrogen breath test with a load of lactulose, the proportion of patients with SIBO of the small intestine was 93.0 %, which was significantly higher than the comparison group 60.8 %;  $p < 0.01$ .

## Conclusion

Thus, for patients who have had COVID-19, the development of IBS-D almost always accompanied the development of SIBO. At the same time, among patients with classical IBS-D induced by stress, the incidence of SIBO is significantly less common.

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**Information about the authors**

**Andrew V. Nalyotov\*** — Dr. Sci. (Med.), Prof., Head of Department of Pediatrics No. 2, M. Gorky Donetsk National Medical University.  
Contact information: nalyotov-a@mail.ru;  
83003, Donetsk People's Republic, Donetsk, Illich ave., 16.  
ORCID: <https://orcid.org/0000-0001-5070-9606>

**Natalya P. Guz** — director of Medical Centre “Gastro-Line”, gastroenterologist.  
Contact information: gastrodoc@mail.ru;  
83003, Donetsk People's Republic, Donetsk, Illich ave., 14E.  
ORCID: <https://orcid.org/0000-0003-0828-7045>

**Сведения об авторах**

**Налетов Андрей Васильевич\*** — доктор медицинских наук, профессор, заведующий кафедрой педиатрии № 2 ГОУ ВПО «Донецкий национальный медицинский университет имени М. Горького».  
Контактная информация: nalyotov-a@mail.ru;  
83003, Донецкая Народная Республика, г. Донецк, пр. Ильича, 16.  
ORCID: <https://orcid.org/0000-0001-5070-9606>

**Гуз Наталья Петровна** — директор ООО «Медицинский центр “Гастро-лайн”» г. Донецка, врач-гастроэнтеролог.  
Контактная информация: gastrodoc@mail.ru;  
83003, Донецкая Народная Республика, г. Донецк, пр. Ильича, 14е.  
ORCID: <https://orcid.org/0000-0003-0828-7045>

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\* Corresponding author / Автор, ответственный за переписку