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COVID-19 Pandemic and IBS. Results of the All-Russian Observational Non-interventional Program to Study the Effectiveness of the Drug Kolofort® in Real Clinical Practice in Patients with Irritable Bowel Syndrome After a New Coronavirus Infection (VESNA)

Vladimir T. Ivashkin[1], Rustam A. Abdulkhakov[2], Igor G. Bakulin[3], Sergey V. Zaitsev[4], Veronika I. Luchina[5], Sabir N. Mekhtiyev[6], Sergey G. Peshekhonov[7], Elena A. Poluektova[1], Tatyana I. Semenova[8], Svetlana N. Serikova[9], Galina N. Tarasova[10], Elizaveta A. Trush[1,*], Yury P. Uspenskiy[11], Igor B. Khlynov[12], Vladislav V. Tsukanov[13], Natalia P. Chernus[14]

[1] *I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation*
[2] *Kazan State Medical University, Kazan, Russian Federation*
[3] *North-Western State Medical University named after I.I. Mechnikov, Saint-Petersburg, Russian Federation*
[4] *Regional Clinical Hospital, Yaroslavl, Russian Federation*
[5] *City Clinical Hospital No. 1, Vologda, Russian Federation*
[6] *Academician I.P. Pavlov First St. Petersburg State Medical University, Saint-Petersburg, Russian Federation*
[7] *Diagnostic and Treatment Centre "Zdorov'e", Veliky Novgorod, Russian Federation*
[8] *City Hospital, Pskov, Russian Federation*
[9] *Kuban State Medical University, Krasnodar, Russian Federation*
[10] *Rostov State Medical University, Rostov-on-Don, Russian Federation*
[11] *Saint-Petersburg State Paediatric Medical University, Saint-Petersburg, Russian Federation*
[12] *Ural State Medial University, Yekaterinburg, Russian Federation*
[13] *Federal Research Center "Krasnoyarsk Science Center of the Siberian Branch of the Russian Academy of Sciences", Research Institute of Medical Problems of the North, Krasnoyarsk, Russian Federation*
[14] *Consultative and Diagnostic Center No. 4 of the Moscow Health Department, Branch No. 3, Policlinic No. 2, Moscow, Russian Federation*

Aim: to study the effectiveness and safety of using the drug Kolofort® in outpatients with irritable bowel syndrome (IBS) after a new coronavirus infection.

Materials and methods. An observational non-interventional program was conducted in patients with exacerbation of IBS symptoms after a new coronavirus infection. One hundred forty-one patients took part in the study. The final efficacy analysis included data from 127 study participants. All patients complained of increased/appearing gastrointestinal symptoms that appeared within 1–6 months after the infection (all patients had a history of COVID-19 infection). To assess the presence and severity of symptoms of the disease, the "7 × 7" questionnaire was used before the start of treatment and three months after the start of treatment.

Results. At the stage of inclusion in the program, the average total score on the "7 × 7" questionnaire was 17.36, which corresponded to a moderately severe disorder. During the treatment period, the average total score decreased to 6.14, which corresponded to borderline disorder. In addition, significant improvement was observed for each symptom separately. After three months of therapy, doctors rated the overall impression of the treatment on a 5-point Likert scale from "very effective" to "ineffective". The average score was 4.24. In addition, no serious adverse events were identified while taking the drug.

Conclusion. In real clinical practice, the drug Kolofort® demonstrated high clinical efficacy in the treatment of patients with IBS after COVID-19 infection.

Keywords: irritable bowel syndrome, post-Covid syndrome, functional diseases of the gastrointestinal tract
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Пандемия COVID-19 и СРК. Результаты Всероссийской наблюдательной неинтервенционной программы изучения эффективности препарата Колофорт® в условиях реальной клинической практики у пациентов с синдромом раздраженного кишечника после перенесенной новой коронавирусной инфекции (ВЕСНА)

В.Т. Ивашкин[1], Р.А. Абдулхаков[2], И.Г. Бакулин[3], С.В. Зайцев[4], В.И. Лучина[5], С.Н. Мехтиев[6], С.Г. Пешехонов[7], Е.А. Полуэктова[1], Т.И. Семенова[8], С.Н. Серикова[9], Г.Н. Тарасова[10], Е.А. Труш[1,*], Ю.П. Успенский[11], И.Б. Хлынов[12], В.В. Цуканов[13], Н.П. Чернусь[1,14]

[1] *ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова»» Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Российская Федерация*

[2] *ФГБОУ ВО «Казанский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Казань, Российская Федерация*

[3] *ФГБОУ ВО «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Российская Федерация*

[4] *ГБУЗ «Ярославская областная клиническая больница», Ярославль, Российская Федерация*

[5] *БУЗ ВО «Вологодская городская больница № 1», Вологда, Российская Федерация*

[6] *ФБГОУ ВО «Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Российская Федерация*

[7] *ООО «Лечебно-диагностический центр “Здоровье”», Великий Новгород, Российская Федерация*

[8] *ГБУЗ ПО «Псковская городская больница», Псков, Российская Федерация*

[9] *ФГБОУ ВО «Кубанский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Краснодар, Российская Федерация*

[10] *ФГБОУ ВО «Ростовский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Ростов-на-Дону, Российская Федерация*

[11] *ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Российская Федерация*

[12] *ФГБОУ ВО «Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Екатеринбург, Российская Федерация*

[13] *ФГБНУ «Федеральный исследовательский центр “Красноярский научный центр” СО РАН», Научно-исследовательский институт медицинских проблем Севера, Красноярск, Российская Федерация*

[14] *ГБУЗ «Консультативно-диагностический центр № 4» департамента здравоохранения г. Москвы, филиал № 3, поликлиника № 2, Москва, Российская Федерация*

Цель исследования: изучение эффективности и безопасности применения препарата Колофорт® у амбулаторных пациентов с синдромом раздраженного кишечника (СРК) после перенесенной новой коронавирусной инфекции.

Материалы и методы. Наблюдательная неинтервенционная программа проводилась у пациентов с обострением симптомов СРК после перенесенной новой коронавирусной инфекции. В исследовании принял участие 141 пациент. В окончательный анализ эффективности были включены данные 127 участников исследования. Все пациенты предъявляли жалобы на усиление/появление гастроинтестинальных симптомов, появившихся в течение 1–6 месяцев после перенесенной инфекции (у всех пациентов в анамнезе была перенесенная инфекция COVID-19). Для оценки наличия и выраженности симптомов заболевания применялся опросник «7 × 7» до начала лечения и через 3 месяца после начала лечения.

Результаты. На этапе включения в программу средний суммарный балл по опроснику «7 × 7» составил 17,36, что соответствовало умеренно выраженному расстройству. За период лечения средний суммарный балл снизился до 6,14, что соответствовало пограничному расстройству. Кроме того, значимое улучшение наблюдалось по каждому симптому в отдельности. Через 3 месяца терапии врачи оценивали общее впечатление от проводимого лечения по 5-балльной шкале Ликерта от «очень эффективно» до «неэффективно». Средний балл составил 4,24. Кроме того, серьезных нежелательных явлений во время приема препарата выявлено не было.

Заключение. В условиях реальной клинической практики препарат Колофорт® продемонстрировал высокую клиническую эффективность в лечении пациентов с СРК после перенесенной инфекции COVID-19.

Ключевые слова: синдром раздраженного кишечника, постковидный синдром, функциональные заболевания желудочно-кишечного тракта
Финансирование: на проведение наблюдательной программы был получен грант от компании ООО «НПФ “Материа Медика Холдинг”».
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

According to the World Health Organization (WHO), the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus is not only dangerous for acute damage to the respiratory system, but also for complications in various organs and systems in post-infection period [1–3]. This clinical condition, known as *long COVID* or *post-COVID syndrome*, presents as persistent residual symptoms or emerging new symptoms after SARS-CoV-2 infection, including pulmonary failure, neurological and/or psychiatric disorders [4–5].

Literature data indicate that within a year after a COVID-19 infection, about 60 % of patients have at least one post-COVID symptom [6].

There is evidence that the intestinal tract is a target organ for SARS-CoV-2 virus. The virus uses angiotensin converting enzyme 2 (ACE2) receptors, expressed in epithelial cells, to invade the host. In addition, viral RNA may persist in stool samples even after nasopharyngeal samples become negative. These factors probably determine the wide prevalence of post-covid gastrointestinal symptoms, such as diarrhea, nausea, and/or abdominal pain [7, 8]. According to a systematic review, such symptoms are observed in about one fifth of patients after COVID-19 [9, 10].

Gastrointestinal symptoms may be a manifestation of functional gastrointestinal tract disorders manifested after a viral infection [11]. COVID-19 infection is also often associated with an increase in the severity of pre-existing symptoms of functional gastrointestinal tract disorders [12]. This may be due to the neurotropic effect of the virus, caused by its ability to use the trans-synaptic spreading mechanism [13], which leads to neuron damage [14]. CNS damage can be a significant pathological factor in the exacerbation of underlying somatic diseases. A direct effect of the virus on patient’s mental and neurological state has also been established [15]. CNS disorders may manifest both during the illness and after recovery. According to the literature, exacerbations of IBS after COVID-19 are based on psychoemotional stress, which aggravates the disruption of signal transmission along the brain-gut axis, causes microinflammation of the intestinal mucosa and changes in the intestinal microbiome, which leads to impaired immune response, as well as to high levels of anxiety in patients [16].

Based on the many pathogenetic factors in the post-infectious exacerbation of IBS caused by SARS-CoV-2, it is advisable to use multitarget therapy [17], which also has an effect on stress-related disorders.

Kolofort® can be considered for IBS medication. This is an original medicinal product developed and introduced into practical healthcare by the research and production company *Materia Medica Holding* (OOO “NPF Materia Medica Holding”) in 2010, for the treatment of functional disorders of gastrointestinal tract. The product includes technologically processed antibodies to the S-100 protein, tumor necrosis factor alpha (TNF-α) and histamine, which have anti-inflammatory, antispasmodic and anxiolytic effects, and have an effect on the mechanisms of IBS pathogenesis [18].

The excellent efficacy and safety of Kolofort® in the treatment of IBS, functional dyspepsia (FD), and the combination of IBS and FD, have been shown in numerous clinical trials involving more than 14,000 patients [19–21].

It is important to note that promising results as to Kolofort® effectiveness were obtained in independent researches focused on the effect of the product in the treatment of patients with functional disorders of gastrointestinal tract after a COVID-19 infection. A significant decrease in the severity of the symptoms, as well as an improvement of the mental and emotional state were observed in patients with IBS [22, 23].

However, some peculiar features of the course of IBS in patients who recovered from COVID-19 required obtaining additional data in this population, which was the goal of the All-Russian observational program VESNA.

Materials and methods

Design of the study

An observational non-interventional program was developed to study the effectiveness and safety of using Kolofort® in patients with exacerbation

of IBS symptoms after recovery from coronavirus infection.

The observational program VESNA was approved by the Independent Interdisciplinary Committee on Ethical Review of Clinical Trials.

The program was implemented in 14 trial sites in 11 cities of Russia.

The trial was conducted on the basis of outpatient records of adult patients with previously diagnosed IBS, in whom an exacerbation of IBS symptoms was observed after recovery from coronavirus infection. Patients were observed by gastroenterologists from March 20, 2022 to September 10, 2022 and took Kolofort® for 12 weeks, 2 tablets twice daily, in accordance with the instructions for medical use. As per the trial protocol, all patients had a previously established diagnosis of COVID-19 documented in their medical records (positive PCR or positive test for IgG/IgM antibodies to SARS-CoV-2).

The trial design did not imply additional methods of laboratory or instrumental examination to include patient data in the program. The 7 × 7 questionnaire was used to assess the presence and severity of the symptoms. The 7 × 7 questionnaire was developed by the personnel of the Department of Internal Medicine, Gastroenterology and Hepatology of I.M. Sechenov Moscow First Medical State University and was recommended for use by gastroenterologists in routine practice, to assess the presence and severity of the seven main symptoms of IBS and functional dyspepsia (FD) over the previous seven days [24]. Patients filled out a questionnaire before the start of therapy with Kolofort® and three months after the end of the course of treatment. The severity of the patient's condition was assessed by the total score and ranked by categories as follows: 0–1 — normal; 2–6 — borderline disorder; 7–12 — mild disorder; 13–18 — moderate disorder; 19–24 — severe disorder; 25 or more — extreme disorder.

The change in the total score of 7 × 7 questionnaire after three months of therapy with Kolofort® was chosen as the primary endpoint in evaluating the effectiveness.

Following parameters were additionally assessed:

— occurrence of possible complications of COVID-19 infection during the patient's observation period;

— effect of the medicinal product Kolofort® on the alleviation of the principal symptoms of IBS, i. e. abdominal pain and abnormal stool frequency and shape;

— general impression of the healthcare practitioner and of the patient regarding the use of Kolofort® (the treatment effectiveness was assessed on Likert scale, from "very effective" (score 5) to "not effective" (score 1)).

The safety of therapy was assessed by the presence and nature of adverse events, and their relationship with the study product.

Methods of statistical analysis

Statistical analysis used methods of descriptive statistics. Continuous variables are presented as estimates of the mean, standard deviation, median, the first and the third quartiles, minimum and maximum values. Categorical variables are presented as the number and proportion of patients in the respective categories. Data from patients with missing values were not included in the statistical analysis. The trends in the groups were assessed using the Wilcoxon test.

Results

Characteristics of patients

The trial involved 141 patients. The final effectiveness analysis included data from 127 participants. Data from 14 of them were not used to assess the effectiveness of the therapy, since deviations from the protocol were found, which included: loss of communication with respondents, non-compliance with the recommended medication regimen, technical errors in filling in records.

The safety analysis included data from all 141 participants. They included 91 women (71.65 %) and 36 men (28.35 %), with the average age of women 38 ± 11.3 years, and the average age of men 39 ± 9.7 years. All patients had a past history of COVID-19 infection, confirmed by medical records (a positive PCR test result for COVID-19, or an increased titer of IgG/total IgM and IgG antibodies to SARS-CoV-2). Patients sought medical advice for complaints of aggravation/appearance of symptoms such as abdominal pain, abnormal stool, and/or abdominal bloating that appeared within 1 to 6 months after the infection. On average, patients consulted a gastroenterologist in 101.2 days from the onset of coronavirus infection. One hundred and one patients were under outpatient observation for COVID-19 infection, 26 patients were hospitalized.

Lung involvement was diagnosed in 26 hospitalized patients. The average percentage of lung involvement was 40 % (41 ± 21.4 %). Five patients underwent therapy in intensive care unit; three of them required artificial lung ventilation.

It should be noted that all cases of COVID-19 in the trial occurred between August 2021 and April 2022. Based on the data from GISAID open sources, the delta variant (strains AY.122 and B.1.617.2) and the stealth omicron (strains BA.1

and BA.2) prevailed in the Russian Federation during this period. Twenty-six hospitalized patients were sick in the period from October 2021 to January 2022, which corresponded to the delta variant of SARS-CoV-2 (strain AY.122) (based on the data on the prevalence of SARS-CoV-2 strains in the Russian Federation in the period from August 2021 to April 2022, https://gisaid.org/hcov19-variants/).

Complications after COVID-19 were documented in medical records, occurred in 39 patients (30.71 %), and most commonly included asthenia, dizziness, memory impairment, and/or autoimmune urticaria. At the time of inclusion in the trial, all patients presented such complaints as abdominal pain, abnormal stool, and/or flatulence. All patients were diagnosed with IBS after ruling out organic diseases based on the results of examinations conducted in accordance with the recommendations of the Russian Gastroenterological Association and the Association of Coloproctologists of Russia (the diagnosis of IBS was established on the basis of patient complaints, and in accordance with the Rome IV criteria, after ruling out organic diseases of the gastrointestinal tract and in the absence of *red flags*).

Comorbidities were reported in 72 (56.7 %) patients. The majority of the patients had one concomitant disease (n = 44; 34.6 %) Gastrointestinal tract diseases occurred in 35 (27.6 %) patients, among whom gastroesophageal reflux disease and functional dyspepsia were most frequently recorded. Liver and biliary tract disorders represented by biliary dyskinesia, gallbladder cholesterosis, and/or non-alcoholic fatty liver disease were diagnosed in 14 (11.0 %) patients. Mental disorders were previously diagnosed in 14 (11.0 %) patients, as evidenced by the data in the patients' medical records. In almost all the cases, mental disorders were represented by anxiety disorders. Cardiovascular system disorders, including hypertension and cardiac arrhythmias, were recorded in 14 (11.02 %) patients.

Approximately 45 % of patients (n = 56; 44.1 %) took at least one drug for the treatment of comorbidities. Nineteen patients (15 %) took proton pump inhibitors, 11 (8.7 %) patients took drugs for the treatment of arterial hypertension, and 7 (5.51 %) patients took antidepressants.

The patients were distributed as follows, based on the severity of IBS: 2 (1.57 %) patients had *borderline disorder* (score 2–6), 17 (13.39 %) patients had mild disorder (score 7–12), 56 (44.09 %) patients had moderate disorder (score 13–18), 45 (35.43 %) patients had severe disorder (score 19–24), 7 (5.51 %) patients had extreme disorder (total score 25 or more).

Effectiveness assessment

At the stage of inclusion in the program, the average total score on the 7 × 7 questionnaire was 17.36, which corresponded to a moderate disorder. During the period of medication, the mean total score decreased to 6.14, meeting the criteria of borderline disorder (Fig. 1).

Since symptoms of functional dyspepsia are quite common in patients with IBS, the effect of the product on each of the symptoms of FD (pain in the stomach, burning sensation in the stomach, abdominal fullness, early satiety) was assessed in addition to the follow-up of IBS symptoms. During the three months of treatment with Kolofort®, there was a significant decrease in the severity of all the assessed symptoms (Fig. 2).

It should be noted that during three months of therapy, the intensity of abdominal pain decreased from 4.43 to 1.45 (by 32.73 %), abnormalities in frequency and consistency of the stool became less pronounced, decreasing from 4.94 to 1.57 (by 32.78 %) based on 7 × 7 questionnaire.

After 12 weeks of therapy with Kolofort®, patients were distributed by severity categories as follows: 20 (15.75 %) patients were in *normal* group, 59 (46.46 %) patients had *borderline disorder*, 33 (25.98 %) — *mild disorder*, 11 (8.66 %) — *moderate disorder*, 3 (2.36 %) — significant disorder, and 1 (0.79 %) — severe disorder (Table).

After three months of therapy, physicians assessed the overall impression of the treatment rated on a 5-point Likert scale (Fig. 3) from very *effective* to *ineffective*. Based on the data obtained, 64 physicians rated the treatment with Kolofort® as very *effective* (score 5); 42 physicians — as *effective* (score 4); 13 physicians — as moderately effective (score 3); 3 doctors — as *partially effective* (score 2), and 5 physicians considered the therapy *ineffective* (score 1). The average score was 4.24.

Afterwards, variables affecting the result of reducing the average total score on the 7 × 7 questionnaire were studied. Age, gender, duration of the underlying disease, the fact of hospitalization and the presence of post-COVID complications were considered as possible factors. Analysis of variance did not show any variables that would significantly affect the result. It was found that regardless of gender, age, duration of IBS, hospitalization and/or the presence of post-COVID complications, Kolofort® equally effectively reduced the total score on the 7 × 7 questionnaire.

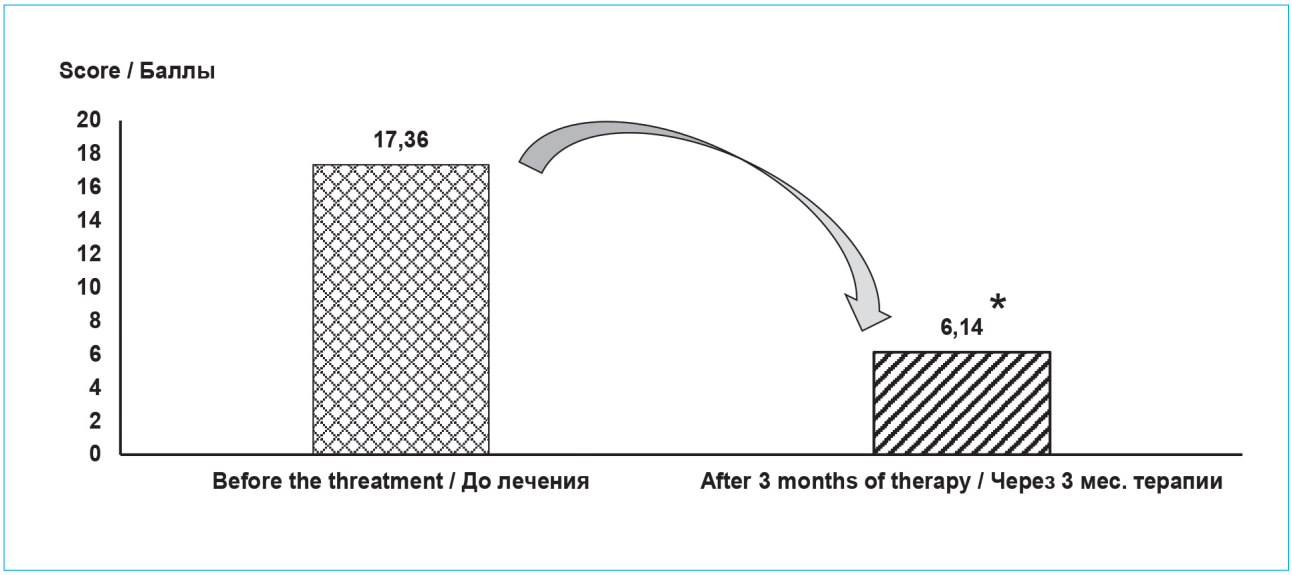

Figure 1. Dynamics of decrease in scores on the "7 × 7" scale (* — $p < 0.05$ compared to initial values)

Рисунок 1. Динамика снижения баллов по шкале «7 × 7» (* — $p < 0,05$ по сравнению с исходными значениями)

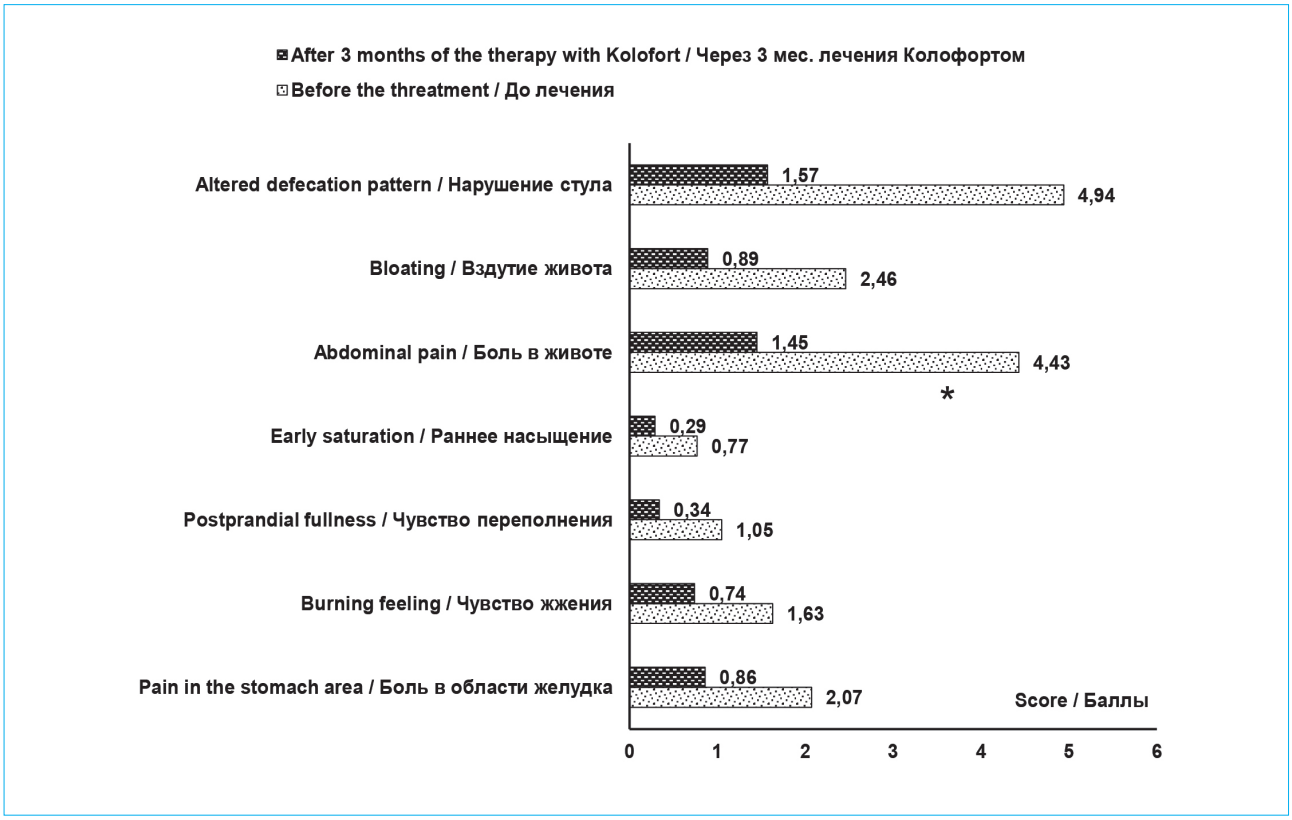

Figure 2. Dynamics of the severity of gastrointestinal symptoms on the "7 × 7" scale

Рисунок 2. Динамика выраженности гастроинтестинальных симптомов по шкале «7 × 7»

Safety assessment

During the observation period, 7 adverse events (AEs) were recorded in 5 (3.5 %) patients; these AEs were common according to the WHO classification, i.e., more than 1 case in 100 patients but less than 1 case in 10 patients (more than 1 % but less than 10 %) [25].

Three AEs were associated with the state of the gastrointestinal tract (2.1 % of all the AEs) and included 1 case of dry mouth (0.7 %), and 2 cases of

Table. Distribution of patients by severity categories according to the "7 × 7" questionnaire after three months of therapy with Kolofort®

Таблица. Распределение пациентов по категориям тяжести согласно данным опросника «7 × 7» через 3 месяца терапии препаратом Колофорт®

Degree of severity ***Категория тяжести***	**Before treatment, *n* (%)** ***До лечения, n (%)***	**After 3 months of treatment, *n* (%)** ***Через 3 месяца лечения, n (%)***
Healthy *Здоров*	0	20 (15.75 %)
Borderline disorder *Пограничное расстройство*	2 (1.57 %)	59 (46.46 %)
Mild disorder *Легкое расстройство*	17 (13.39 %)	33 (25.98 %)
Moderate disorder *Умеренно выраженное расстройство*	56 (44.09 %)	11 (8.66 %)
Significant disorder *Выраженное расстройство*	45 (35.43 %)	3 (2.36 %)
Severe disorder *Тяжелое расстройство*	7 (5.51 %)	1 (0.79 %)

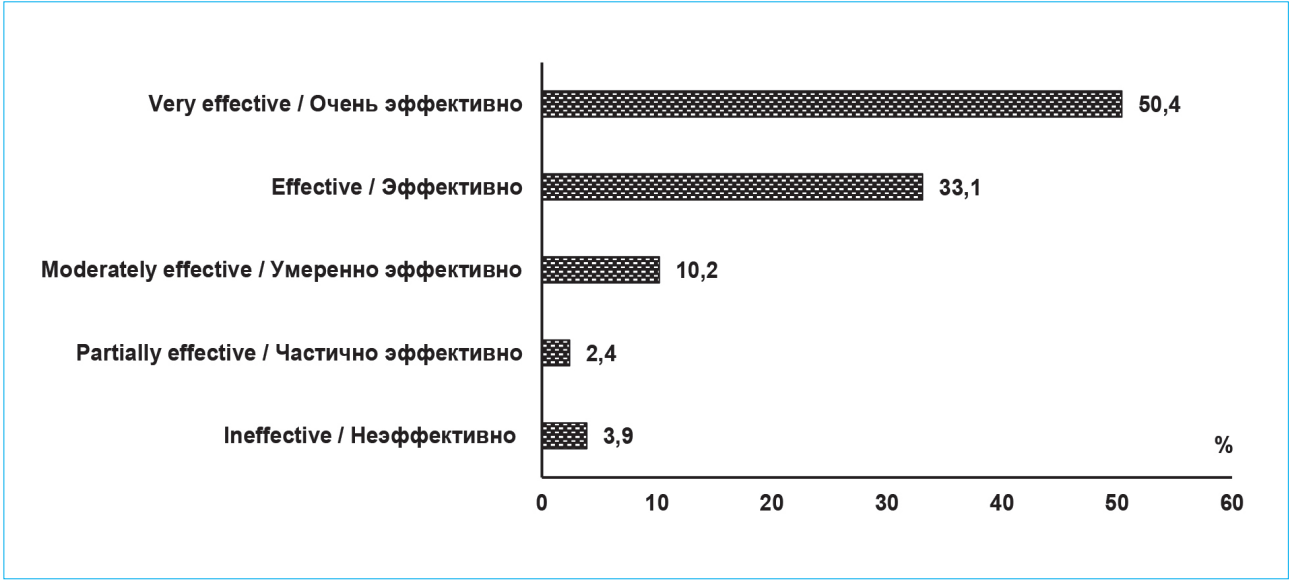

Figure 3. Distribution of physician assessments of treatment results (%)

Рисунок 3. Распределение врачебных оценок результатов лечения (%)

nausea (1.4 %). There was 1 case of nasopharyngitis (0.7 % of all AEs). One patient had a headache three times during the observational program (0.7 % of all identified AEs).

Among the above adverse events, 5 AEs were mild (dry mouth, nasopharyngitis, 3 cases of headache) and 2 AEs were moderate (2 cases of nausea). No serious adverse events were identified. There were no cases of discontinuation of medication with Kolofort®. No associations of AEs with the product were recorded in any of the cases.

Discussion

VESNA was the first observational program in the Russian Federation to evaluate the effectiveness of monotherapy with the medicinal product Kolofort® in

the treatment of patients with IBS, with the intensity of symptoms increasing significantly in patients who had previously recovered from COVID-19 infection.

According to the literature data, the likelihood of exacerbation of IBS symptoms increases by 6 times within a few months after recovery from COVID-19 infection [26].

Great importance is attached to psychological stress as a trigger causing a cascade of pathophysiological processes leading to gastrointestinal post-covid syndrome. Based on a meta-analysis of 17 studies that included 63,439 people, the incidence of increased anxiety during the pandemic was 31.9 % [29]. According to T. Oshima et al., symptoms worsened in the context of psychological discomfort caused by self-isolation, increased levels of anxiety, and fear of infection in 11.9 % of patients with IBS who did not have COVID-19 [30], while an increase in IBS symptoms was observed in 36 % of patients who recovered from COVID-19 [17].

In the study, patients consulted a doctor for their complaints about 3 months after the infection, which makes it possible for us to consider the exacerbation of IBS as a manifestation of the post-COVID syndrome. A review of 35 studies involving more than 1 million patients showed that the likelihood of developing post-COVID syndrome, including the occurrence of complaints from the gastrointestinal tract, is higher in women than in men [27, 28].

The results of the trial demonstrate the characteristics of an average patient with an exacerbation of IBS after a previous infection with COVID-19: it is a woman of about 38 years of age, who underwent outpatient treatment for COVID-19, consulted a gastroenterologist with complaints of gastrointestinal symptoms, the intensity of which increased within several months after the viral infection. The patients' main complaints included abdominal pain, and abnormal stool frequency and shape. The symptoms of IBS were moderately severe.

The obtained results demonstrated that the medicinal product Kolofort® had a pronounced therapeutic effect, reducing the intensity of IBS symptoms from the score of 17.36 to 6.14 over 3 months of therapy, with the resulting symptoms severity assessed as borderline. During the period of observation, the therapy with Kolofort® resulted in an increase in the number of patients in the normal and borderline categories.

These results are consistent with the results obtained earlier in the large-scale trial COMFORT, in which more than half of patients with IBS, FD and/or their combination moved from moderately severe category into borderline category after 3 months on medication [20].

The trial showed that Kolofort® had a significant effect on the principal symptoms of IBS, i.e., abdominal pain and abnormal stool. This was expressed as a decrease in scores on the 7 × 7 scale by about one third. It is interesting to note that a double-blind, placebo-controlled trial of the efficacy and safety of Kolofort® in the treatment of patients with IBS showed similar results: in 1/3 of the participants, the pain syndrome was completely eliminated by the end of the treatment [21]. This confirmed the effectiveness of IBS therapy with Kolofort®, whether or not patients had a history of COVID-19.

It should also be noted that in this trial, Kolofort® showed approximately the same effectiveness in reducing the total score on the 7 × 7 questionnaire in different categories of patients, regardless of gender, age, and presence of complications after the past infection.

There is no doubt that IBS therapy after COVID-19 should influence a multitude of pathogenetic factors, including psycho-emotional aspects. Taking into account the multifactorial mechanism of damage to the nervous system by SARS-CoV-2 virus, the IBS medication that would affect the pathogenetic mechanisms of CNS damage is advisable. The high effectiveness of the medicinal product Kolofort® is associated with its comprehensive effect on the "CNS — intestine" axis. Special features of the product include its effect on the gastrointestinal manifestations of IBS, as well as effective alleviation of anxiety and depression symptoms, which can significantly improve the prognosis in patients with IBS who recovered from COVID-19 infection. It should be noted that IBS is often observed with underlying mental disorders. The prevalence of mental disorders in patients with IBS is confirmed by the 2021 meta-analysis: about 28 % of patients with IBS suffer from a depressive disorder, while 29 % of the patients suffer from an anxiety disorder [29]. By influencing the ligand-receptor interactions of the brain-specific S-100 protein with serotonin receptors and σ1-receptors in the central nervous system, Kolofort® provides a pronounced anxiolytic effect [31]. A previous trial showed that therapy with Kolofort® leads to a significant decrease in the levels of distress, depression, anxiety, and somatoform disorders [32].

Psycho-emotional changes and stress disorders cause immune activation of stress-responsive systems [33]. It has been established that Kolofort® is able to restore the balance of cytokines, in particular, interleukin-10, interleukin-1β and tumor necrosis factor alpha, the level of which changes as a result of the immune system's response to infection [34].

Stress also has a negative impact on the intestinal microbiome. In particular, an increase in the permeability of the intestinal mucosa and changes in the microbiome have been shown in patients who had recovered from COVID-19 [35]. Accordingly, the gastrointestinal tract microbiome should be one of the targets for the therapy in patients with post-COVID syndrome. One of the trials focused on the effectiveness of Kolofort® demonstrated a positive effect on the parameters of the colon biocenosis in patients with diarrheal IBS [36].

Thus, the treatment of patients with IBS after COVID-19 should not only focus on the elimination of the leading symptoms, such as abdominal pain and stool disorders, but also on the effect on pathogenetic causes of IBS.

Among probable limitations of this trial, it is worth noting that patients were not divided into IBS subtypes, medical records did not contain information about the patients' past medication for coronavirus infection COVID-19, microbiological composition of feces was not assessed, and groups were not compared. However, this trial had the advantage of observing the administration of the product in real-life clinical setting, which made it possible to study the effectiveness of therapy in a heterogeneous group of patients.

Conclusion

Our observational multicenter trial in real-life clinical setting demonstrated high clinical effectiveness of Kolofort® in the treatment of patients with IBS after a COVID-19 infection. Over a 3-month period of therapy, a significant decrease in the principal symptoms of IBS was demonstrated. At the end of the course of medication, most physicians concluded that the medication was effective. In general, good effectiveness and tolerability of the product ensured good compliance to treatment.

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Information about the authors

Vladimir T. Ivashkin — Dr. Sci. (Med.), Professor, Member of the Russian Academy of Sciences, Head of the Department of Internal Diseases Propedeutics, Gastroenterology and Hepatology, Director of the Clinic of Internal Diseases Propedeutics, Gastroenterology and Hepatology named after V.Kh. Vasilenko, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: 2135833@mail.ru;
19435, Moscow, Pogodinskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0002-6815-6015

Rustam A. Abdulkhakov — Dr. Sci. (Med.), Professor, Honored Doctor of the Republic of Tatarstan, Professor of the Department of Hospital Therapy of the Faculty of Medicine, Kazan State Medical University.
Contact information: rustemabdul@mail.ru;
420012, Kazan, Butlerova str., 49.
ORCID: https://orcid.org/0000-0002-1509-6776

Igor G. Bakulin — Dr. Sci. (Med.), Professor, Head of the Department of Internal Diseases Propedeutics, Gastroenterology and Dietetics, North-Western State Medical University named after I.I. Mechnikov.
Contact information: igbakulin@yandex.ru;
191015, Saint-Petersburg, Kirochnaya str., 41.
ORCID: https://orcid.org/0000-0002-6151-2021

Sergey V. Zaitsev — Head of the Regional Gastroenterological Center, Yaroslavl Regional Clinical Hospital, Chief Gastroenterologist of Yaroslavl Region.
Contact information: svzaytsev203071@yandex.ru;
150062, Yaroslavl, Yakovlevskaya str., 7.
ORCID: https://orcid.org/0009-0002-1423-8338

Veronika I. Luchina — Gastroenterologist, Vologda City Hospital No. 1.
Contact information: nika011967@rambler.ru;
160012, Vologda, Sovetskiy ave., 94.
ORCID: https://orcid.org/0009-0002-1222-8048

Sabir N. Mekhtiyev — Dr. Sci. (Med.), Professor of the Department of Internal Diseases, Academician I.P. Pavlov First St. Petersburg State Medical University.
Contact information: kosov_p@me.com;
197022, Saint-Petersburg, L'va Tolstogo str., 6–8.
ORCID: https://orcid.org/0000-0001-7367-9219

Сведения об авторах

Ивашкин Владимир Трофимович — доктор медицинских наук, профессор, академик РАН, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и гепатологии, директор Клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: ivashkin_v_t@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, 1, стр. 1.
ORCID: https://orcid.org/0000-0002-6815-6015

Абдулхаков Рустем Аббасович — доктор медицинских наук, профессор, заслуженный врач Республики Татарстан, профессор кафедры госпитальной терапии лечебного факультета ФГБОУ ВО «Казанский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: rustemabdul@mail.ru;
420012, г. Казань, ул. Бутлерова, 49.
ORCID: https://orcid.org/0000-0002-1509-6776

Бакулин Игорь Геннадьевич — доктор медицинских наук, профессор, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и диетологии ФГБОУ ВО «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации.
Контактная информация: igbakulin@yandex.ru;
191015, г. Санкт-Петербург, ул. Кирочная, 41.
ORCID: https://orcid.org/0000-0002-6151-2021

Зайцев Сергей Вячеславович — заведующий Областным гастроэнтерологическим центром ГБУЗ «Ярославская областная клиническая больница», главный гастроэнтеролог Ярославской области.
Контактная информация: svzaytsev203071@yandex.ru;
150062, г. Ярославль, ул. Яковлевская, 7.
ORCID: https://orcid.org/0009-0002-1423-8338

Лучина Вероника Игоревна — врач-гастроэнтеролог БУЗ ВО «Вологодская городская больница № 1».
Контактная информация: nika011967@rambler.ru;
160012, г. Вологда, Советский просп., 94.
ORCID: https://orcid.org/0009-0002-1222-8048

Мехтиев Сабир Насрединович — доктор медицинских наук, профессор кафедры внутренних болезней ФБГОУ ВО «Первый Санкт-Петербургский государственный медицинский университет им. И.П. Павлова» Министерства здравоохранения Российской Федерации.
Контактная информация: kosov_p@me.com;
197022, г. Санкт-Петербург, ул. Льва Толстого, 6–8.
ORCID: https://orcid.org/0000-0001-7367-9219

Sergey G. Peshekhonov — Cand. Sci. (Med.), Gastroenterologist, Diagnostic and Treatment Centre "Zdorov'e".
Contact information: sgpesh@mail.ru;
173021, Veliki Novgorod, Mira ave., 44/20.
ORCID: https://orcid.org/0009-0003-1614-8413

Пешехонов Сергей Георгиевич — кандидат медицинских наук, врач-гастроэнтеролог, ООО «Лечебно-диагностический центр "Здоровье"».
Контактная информация: sgpesh@mail.ru;
173021, г. Великий Новгород, просп. Мира, 44/20.
ORCID: https://orcid.org/0009-0003-1614-8413

Elena A. Poluektova — Dr. Sci. (Med.), Professor of the Department of Internal Diseases Propedeutics, Gastroenterology and Hepatology, Gastroenterologist, Department of Chronic Intestinal and Pancreatic Diseases of the Clinic of Internal Diseases Propedeutics, Gastroenterology and Hepatology named after V.Kh. Vasilenko, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: poluektova_e_a@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0002-9038-3732

Полуэктова Елена Александровна — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии, врач-гастроэнтеролог отделения хронических заболеваний кишечника и поджелудочной железы Клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: poluektova_e_a@staff.sechenov.ru;
119435, г. Москва, ул. Погодинская, 1, стр. 1.
ORCID: https://orcid.org/0000-0002-9038-3732

Tatyana I. Semenova — Head of the Gastroenterology Department, Pskov City Hospital, Chief Freelance Gastroenterologist of the Pskov Region State Committee for Health and Pharmacy.
Contact information: doksemenova@yandex.ru;
180016, Pskov, Kommunalnaya str., 23.
ORCID: https://orcid.org/0009-0001-5843-7913

Семенова Татьяна Ивановна — заведующая гастроэнтерологическим отделением ГБУЗ ПО «Псковская городская больница», главный внештатный гастроэнтеролог Государственного комитета Псковской области по здравоохранению и фармации.
Контактная информация: doksemenova@yandex.ru;
180016, г. Псков, ул. Коммунальная, 23.
ORCID: https://orcid.org/0009-0001-5843-7913

Svetlana N. Serikova — Dr. Sci. (Med.), Professor of the Department of Surgery No 3 of Faculty of Advanced Training and Professional Retraining of Specialists, Kuban State Medical University.
Contact information: serikovasn@mail.ru;
350063, Krasnodar, Mitrofana Sedina str., 4.
ORCID: https://orcid.org/0000-0003-2397-4839

Серикова Светлана Николаевна — доктор медицинских наук, профессор кафедры хирургии № 3 ФПК и ППС ФГБОУ ВО «Кубанский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: serikovasn@mail.ru;
350063, г. Краснодар, ул. Митрофана Седина, 4.
ORCID: https://orcid.org/0000-0003-2397-4839

Galina N. Tarasova — Dr. Sci. (Med.), Professor, Rostov State Medical University.
Contact information: doctor-gastro@yandex.ru;
344022, Rostov-on-Don, Nakhichevanskiy lane, 29.
ORCID: https://orcid.org/0000-0003-4054-9180

Тарасова Галина Николаевна — доктор медицинских наук, профессор ФГБОУ ВО «Ростовский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: doctor-gastro@yandex.ru;
344022, г. Ростов-на-Дону, Нахичеванский пер., 29.
ORCID: https://orcid.org/0000-0003-4054-9180

Elizaveta A. Trush* — Postgraduate at the Department of of Internal Diseases Propedeutics, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: trush_e_a@student.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, build. 1.
ORCID: https://orcid.org/0000-0003-2449-6912

Труш Елизавета Александровна* — аспирант кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: trush_e_a@student.sechenov.ru;
119435, г. Москва, ул. Погодинская, 1, стр. 1.
ORCID: https://orcid.org/0000-0003-2449-6912

Yury P. Uspenskiy — Dr. Sci. (Med.), Professor, Chief Gastroenterologist of Saint-Peterburg, Head of the Department of Intermediate Level Therapy named after Professor V.A. Valdman, Saint-Petersburg State Paediatric Medical University.
Contact information: Uspenskiy65@mail.ru;
194100, Saint-Peterburg, Litovskaya str., 2.
ORCID: https://orcid.org/0000-0001-6434-1267

Успенский Юрий Павлович — доктор медицинских наук, профессор, главный гастроэнтеролог Санкт-Петербурга, заведующий кафедрой факультетской терапии им. профессора В.А. Вальдмана ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: Uspenskiy65@mail.ru;
194100, г. Санкт-Петербург, ул. Литовская, 2.
ORCID: https://orcid.org/0000-0001-6434-1267

* Corresponding author / Автор, ответственный за переписку

Хлынов Игорь Борисович — доктор медицинских наук, доцент кафедры факультетской терапии стоматологического факультета ФГБОУ ВО «Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: hlinov.doc@yandex.ru;
620028, г. Екатеринбург, ул. Репина, 3.
ORCID: https://orcid.org/0000-0002-0944-9811

Igor B. Khlynov — Dr. Sci. (Med.), Associate Professor of the Department of Intermediate Level Therapy, Faculty of Dentistry, Ural State Medial University.
Contact information: hlinov.doc@yandex.ru;
620028, Yekaterinburg, Repina str., 3.
ORCID: https://orcid.org/0000-0002-0944-9811

Цуканов Владислав Владимирович — доктор медицинских наук, профессор, заведующий клиническим отделением патологии пищеварительной системы у взрослых и детей ФГБНУ «Федеральный исследовательский центр "Красноярский научный центр" СО РАН» Научно-исследовательского института медицинских проблем Севера.
Контактная информация: gastro@impn.ru;
660022, г. Красноярск, ул. Партизана Железняка, 3г.
ORCID: https://orcid.org/0000-0002-9980-2294

Vladislav V. Tsukanov — Dr. Sci.(Med.), Professor, Head of the Clinical Department of Pathology of the Digestive System in Adults and Children, Federal Research Center "Krasnoyarsk Science Center of the Siberian Branch of the Russian Academy of Sciences", Research Institute of Medical Problems of the North.
Contact information: gastro@impn.ru;
660022, Krasnoyarsk, Partizana Zheleznyaka str., 3g.
ORCID: https://orcid.org/0000-0002-9980-2294

Чернусь Наталья Павловна — кандидат медицинских наук, ассистент кафедры поликлинической терапии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет); врач-гастроэнтеролог ГБУЗ «Консультативно-диагностический центр № 4» департамента здравоохранения г. Москвы, филиал № 3, поликлиника № 2.
Контактная информация: chernusnp@mail.ru;
121165, г. Москва, ул. Киевская, 24.
ORCID: https://orcid.org/0000-0002-3272-9600

Natalia P. Chernus — Cand. Sci. (Med.), Teaching Assistant at the Department of Polyclinic Therapy, I.M. Sechenov First Moscow State Medical University (Sechenov University); Consultative and Diagnostic Center No. 4 of the Moscow Health Department, Branch No. 3, Policlinic No. 2.
Contact information: chernusnp@mail.ru;
121165, Moscow, Kievskaya str., 24.
ORCID: https://orcid.org/0000-0002-3272-9600

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