Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

**ОКТЯБРЬ 2022 (№ 5(67))**

**УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ**
Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17
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Подписано в печать 05.10.2022 года
Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Свидетельство о регистрации
ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

**Отпечатано в типографии «Onebook.ru»**
**ООО «Сам Полиграфист»**
г. Москва, Волгоградский проспект, д. 42, корп. 5
www.onebook.ru





Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Урал-Пресс Округ» 87732

**DOI:** 10.20514/2226-6704-2022-5

Scientific and practical journal for health professionals

Included the List of the Russian reviewed scientific magazines in which the main scientific results of theses on competition of academic degrees of the doctor and candidate of science have to be published.

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE
www.medarhive.ru
**OCTOBER 2022 (№ 5(67))**

**FOUNDER AND PUBLISHER**
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107076, Moscow, Korolenko str., 3A, of. 18B
info@medarhive.ru

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**PAGE-PROOFS**
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**ADVERTISING**
Babiak Alina
reklama@medarhive.ru

Signed for printing on 05.10.2022
Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961, 26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

**Printed «Onebook.ru»**
**«Sam Poligrafist»**
Moscow, Volgograd Prospect, 42-5
www.onebook.ru





The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific Electronic Library www.elibrary.ru

Subscription index in the catalogue «Ural-Press Okrug» 87732

**DOI:** 10.20514/2226-6704-2022-5

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DOI: 10.20514/2226-6704-2022-12-5-325-329
EDN: JUVOZQ
УДК 616.5-003.871-036-07-085

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# ПАРАНЕОПЛАСТИЧЕСКИЙ СИНДРОМ ЛЕЗЕРА-ТРЕЛЯ (LESER-TRÉLAT): КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ, ДИАГНОСТИКА И ЛЕЧЕНИЕ

**T.A. Gaydina*, A.S. Dvornikov, P.A. Skripkina**

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# Paraneoplastic Leser-Trélat Syndrome: Clinical Manifestations, Diagnosis and Treatment

**Резюме**

Осмотр кожного покрова — широкодоступный и простой метод обследования пациента, который, тем не менее, позволяет диагностировать системные нарушения и заболевания на ранних стадиях. Врач любой специальности может столкнуться в клинической практике с дерматологическими паранеопластическими синдромами, которые представляют собой группу кожных заболеваний, связанных со злокачественными новообразованиями, но не имеющих прямого отношения к первичной опухоли или ее метастазам. Своевременный анализ дерматологических паранеопластических синдромов позволяет заподозрить злокачественные опухоли, и срочно направить пациента к онкологу с целью ранней диагностики и лечения потенциально излечимого онкологического заболевания. В клинической практике достаточно часто встречается паранеопластический синдром Лезера-Треля (Leser-Trélat), который проявляется внезапным появлением множественных себорейных кератом (в основном, в области спины и живота) и увеличением их числа и размеров в течение небольшого промежутка времени (недели, месяцы). Лечение данного синдрома можно проводить как одновременно, так и после лечения основного злокачественного заболевания. Дерматологические паранеопластические синдромы требуют дальнейшего углубленного изучения для понимания патогенеза, создания четкой классификации и разработки алгоритмов действия врача.

***Ключевые слова:*** *паранеопластические синдромы, дерматологические паранеопластические синдромы, синдром Лезера-Треля, кератома, множественные себорейные кератомы*

**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 31.01.2022 г.
Принята к публикации 08.06.2022 г.

**Для цитирования:** Гайдина Т.А., Дворников А.С., Скрипкина П.А. ПАРАНЕОПЛАСТИЧЕСКИЙ СИНДРОМ ЛЕЗЕРА-ТРЕЛЯ (LESER-TRÉLAT): КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ, ДИАГНОСТИКА И ЛЕЧЕНИЕ. Архивъ внутренней медицины. 2022; 12(5): 325-329. DOI: 10.20514/2226-6704-2022-12-5-325-329 EDN: JUVOZQ

**Abstract**

Examination of the skin is a widely available and simple method of examining the patient, which nevertheless allows you to diagnose systemic disorders and diseases in the human body at an early stage. A doctor of any specialty may encounter dermatological paraneoplastic syndromes in his practice, which are a group of skin diseases associated with malignant neoplasms, but not directly related to the primary tumor or its metastases.

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Timely analysis of dermatological paraneoplastic syndromes makes it possible to suspect malignant tumors that cause them and urgently refer the patient to an oncologist for the purpose of early diagnosis and treatment of a potentially curable oncological disease. In clinical practice, paraneoplastic Leser-Trélat syndrome is very common, which is manifested by the sudden appearance of multiple seborrheic keratomas (mainly in the back and abdomen) and an increase in their number and size over a short period of time (weeks, months). Treatment of this syndrome can be carried out both simultaneously and after treatment of the underlying malignant disease. Dermatological paraneoplastic syndromes require further in-depth study to understand the pathogenesis, create a clear classification and develop algorithms for the doctor's actions in case of their detection.

***Key words:*** *paraneoplastic syndromes, dermatological paraneoplastic syndromes, Leser-Trélat syndrome, keratoma, multiple seborrheic keratomas*

**Conflict of interests**

The authors declare no conflict of interests

**Sources of funding**

The authors declare no funding for this study

Article received on 31.01.2021

Accepted for publication on 08.06.2022

**For citation:** Gaydina T.A., Dvornikov A.S., Skripkina P.A. Paraneoplastic Leser-Trélat Syndrome: Clinical Manifestations, Diagnosis and Treatment. The Russian Archives of Internal Medicine. 2022; 12(5): 325-329. DOI: 10.20514/2226-6704-2022-12-5-325-329 EDN: JUVOZQ

CPSs — cutaneous paraneoplastic syndromes, LTS — Leser-Trélat syndrome

## Introduction

Skin examination is included in patient examination protocol of the vast majority medical specialties; it helps identify systemic disorders in the human body including undiagnosed malignant neoplasms. Cutaneous paraneoplastic syndromes (CPSs) are a group of skin diseases associated with malignant neoplasms, however, not directly related to the primary tumor or its metastases. It is important for any specialist to be aware of and be able to identify CPSs in order to suspect and diagnose the underlying malignant tumors as early as possible.

## Cutaneous paraneoplastic syndromes

The studies demonstrate, that CPSs develop in about 7-15 % of patients with malignancies, while the development of CPSs can both precede the diagnosis of a malignant neoplasm, or start at the late stages of oncological process or be the first sign of relapse [1]. Timely diagnosis and correct interpretation of CPSs can provide earlier detection of malignant neoplasms and higher life expectancy of patients.

F. Hebra in 1868 was one of the first to suggest the hypothesis that sudden changes in skin pigmentation may be associated with a malignant process [2].

In 1976, Helene Ollendorff Curth proposed criteria for analyzing the relationship of dermatoses with other diseases including malignant tumors of internal organs. The criteria for CPSs diagnosis proposed by Curth are presented below:

1. Onset of dermatosis should coincide with the onset of a malignant disease.
2. Both processes develop simultaneously.
3. Dermatosis is not considered to be a part of a genetic syndrome.
4. Specific dermatosis is associated with a specific tumor.
5. Dermatoses rarely occur in general population.
6. Dermatosis is highly associated with a malignant disease [3, 4].

Not all six criteria are required to suggest an association between dermatosis and malignant disease. The first two criteria are sufficient to consider dermatosis as a process related to a malignant tumor. In 2010, Ortega-Loayza A.G. et al. proposed to distinguish between main and secondary criteria for CPSs defining [5].

There is no single generally accepted classification of CPSs. Most often, CPSs are classified according to their detection rate in certain malignant neoplasms, or to the clinical and morphological principles, or to known etiological mechanisms. Using the detection rate in certain malignant neoplasms, a number of national authors distinguish mandatory CPS (almost always associated with malignant neoplasms), optional CPS (the association is statistically predictable), and occasional CPS (the incidence in patients with malignancies is higher than in the general population) [6]. According to the detection rate in certain malignant neoplasms, foreign investigators divide CPS into two large groups: obligate and facultative [7, 8]. Obligate CPSs include rare dermatoses that are always associated with a malignant neoplasm. Facultative CPSs include more common dermatoses of various etiology; their onset as a paraneoplastic process was repeatedly reported in literature sources (Table 1) [8].

## Leser-Trélat syndrome

Leser-Trélat syndrome (LTS) is a quite common obligate CPS in the practice of a general practitioner; it is manifested by the sudden onset of multiple seborrheic keratoses (mainly on back and abdomen) and by their increase in number and size during a short period of time (weeks, months) [9]. This syndrome was first described by French surgeons A. Leser and

***Table 1.*** *Relationship of obligate and facultative dermatological paraneoplastic syndromes with malignant neoplasms*

| Obligate dermatological paraneoplastic syndromes | Related malignancies |
|---|---|
| Paraneoplastic acrokeratosis (Bazex syndrome) | Squamous cell carcinoma (tongue, pharynx, larynx, esophagus, stomach, lungs) |
| Paraneoplastic pemphigus | Chronic lymphocytic leukemia, Castleman's disease, thymoma |
| Acanthosis nigricans maligna | Adenocarcinomas of the gastrointestinal tract |
| Hypertrichosis lanuginosa acquisita | Colorectal cancer, breast cancer, lung cancer |
| Necrolytic migrating erythema | Glucagonoma, small cell lung cancer |
| Leser-Trélat Syndrome | Gastric adenocarcinoma, colon cancer, lymphoproliferative diseases |
| **Facultative dermatological paraneoplastic syndromes** | **Related malignancies** |
| Erythema gyratum repens | Squamous cell carcinoma (esophagus, stomach, lungs) |
| Gangrenous pyoderma | Acute myeloid leukemia, myelodysplastic syndrome |
| Sweet-syndrome | Acute myeloid leukemia, cervical cancer |
| Dermatomyositis | Ovarian, lung and breast cancers |
| Pemphigoid of mucous membranes | Adenocarcinoma (colon, stomach, lungs) |
| Paget 's Extramammary disease | Urogenital and gastrointestinal carcinomas |
| Acquired ichthyosis | Hodgkin's lymphoma, carcinomas (lungs, ovaries, uterus) |

U. Trélat in 1880 as the appearance of multiple skin angiomas with underlying malignant visceral tumor. In 1900, Hollander was the first to find the association of the appearance of multiple seborrheic keratoses with a malignant visceral tumor, however, the eponym remained as Leser-Trélat [2]. In 1916, Balo and Koprassi concluded that malignant processes were diagnosed three times as often in the patients with multiple seborrheic keratoses. Currently, there are descriptions of LTS in various malignant diseases, however, its pathophysiology is not completely understood. It has been proven that neoplastic cells can secrete factors similar to EGF-α (epidermal growth factor) that alter extracellular matrix, stimulate the growth of keratinocytes and contribute to the development of seborrheic keratosis [10]. Higher levels of transforming growth factor TGF-α were also found in the urine of a patient with LTS and melanoma [11].

According to national and foreign literature, more than 50 % of malignant neoplasms associated with LTS include adenocarcinomas of gaster [12], colon, rectum [13] and breast [14], however, LTS was also described by researchers in association with other underlying malignant neoplasms, including cancer of lungs [15, 16], kidneys [17], skin melanoma [18], cutaneous T-cell lymphomas [19]. Literature sources contain case reports, where LTS developed with no association with any malignant neoplasm [20] which contests the pertinence of LTS to the group of obligate CPSs.

The main clinical manifestation of LTS is the explosive onset or rapid increase in the size and number of seborrheic keratoses that are verrucous well-defined plaques of brown to black color located on the skin of chest, back, limbs, face, abdomen (Figure 1).

In LTS, numerous seborrheic keratoses are usually symmetrically arranged on the back resembling a "Christmas tree", "splash" or "raindrops" [21]. Patients with LTS can be of different age, however, the average age of the onset of this syndrome is about 61 years. There are no reports of any association of LTS with sex or race [22]. Special cancer alertness should arise in cases of young patients with no senile keratosis. The main subjective complaint of patients is itching, however, it is not mandatory. Dermoscopic signs of keratoses are as follows: comedogenic holes, hairpin vessels, cerebriform structures, milia-form cysts, moth-eaten borders, fingerprint-like structures (Figure 2).

Seborrheic keratoses is treated simultaneously or after the management of a malignant disease considering the fact that the number and size of keratoses may decrease during treatment [23]. The best method for removing keratoses is determined individually considering the characteristics of each patient. The most common methods are surgical excision, electroexcision, cryotherapy, destruction with neodymium or $CO_2$ laser. $CO_2$ laser destruction of keratoses is widely used (Figure 3, 4). This method minimizes thermal damage to healthy skin and allows obtaining a satisfactory aesthetic result. Applications of chemotherapeutic agents can be considered: 30 % prospidine ointment, 5 % 5-fluorouracil ointment, solcoderm, collodion with 10 % salicylic and lactic acid. Systemic retinoids are prospective agents in multiple seborrheic keratoses in young people [24]. After the removal of keratoses, patients with LTS should be followed-up for a long time in order to exclude a malignant process (Procedure for follow-up medical care for adults with malignancies, approved by order of the Ministry of Health of the Russian Federation of June 4, 2020 N 548n.).

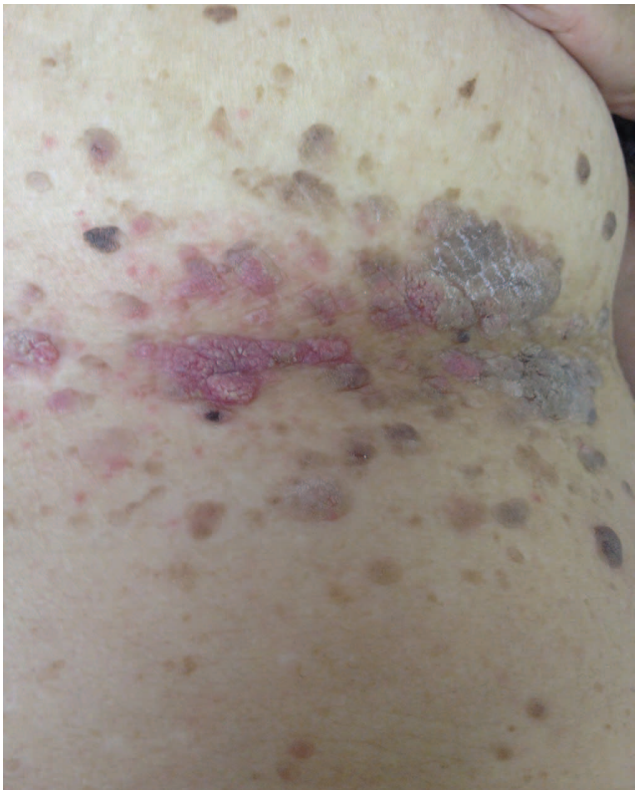

***Figure 1.*** *Multiple keratomas on the body of a 68-year-old woman with rectal adenocarcinoma. Leser-Trélat syndrome.*

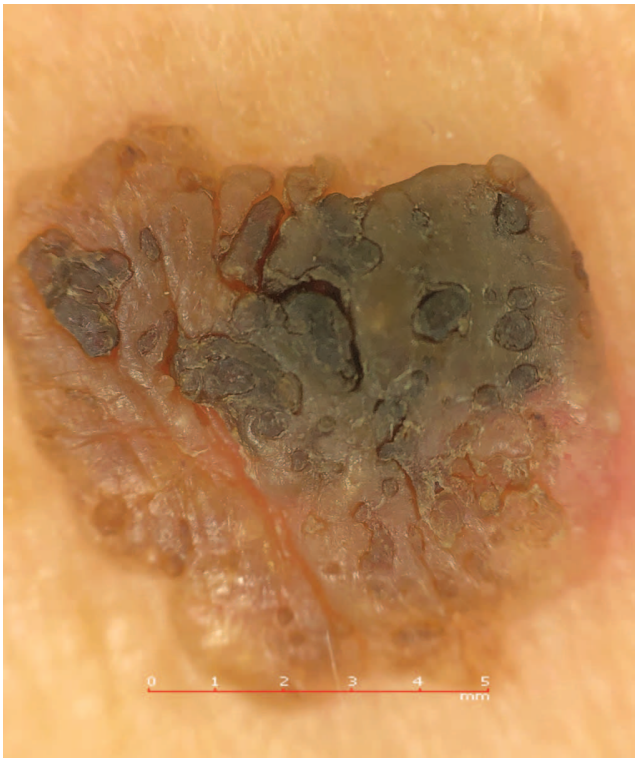


***Figure 2.*** *The dermatoscopic picture of seborrheic keratoma is represented by thick brown pigment layers of varying intensity with hyperpigmented comedon-like holes (Magnification × 20)*

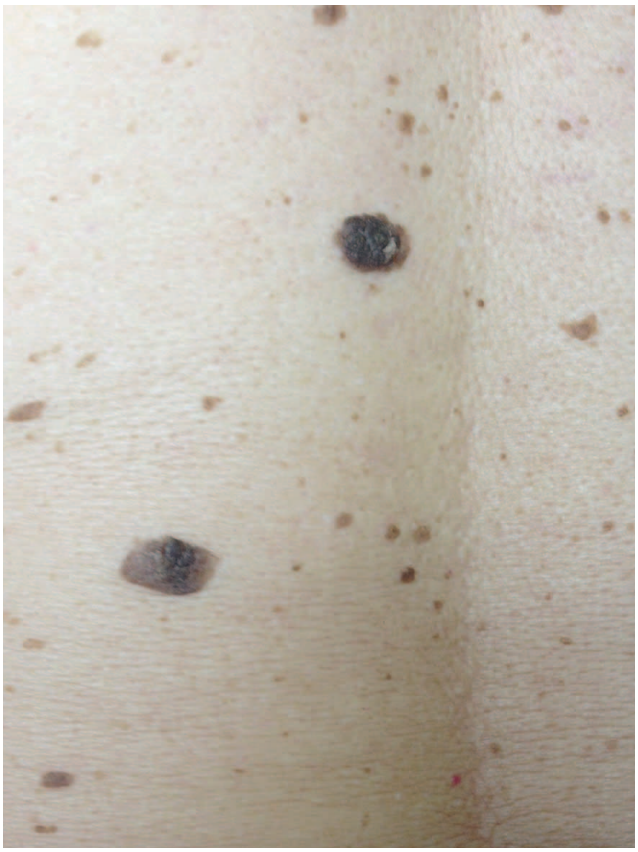

***Figure 3.*** *Macro photograph of keratomas on the skin of a woman's back*

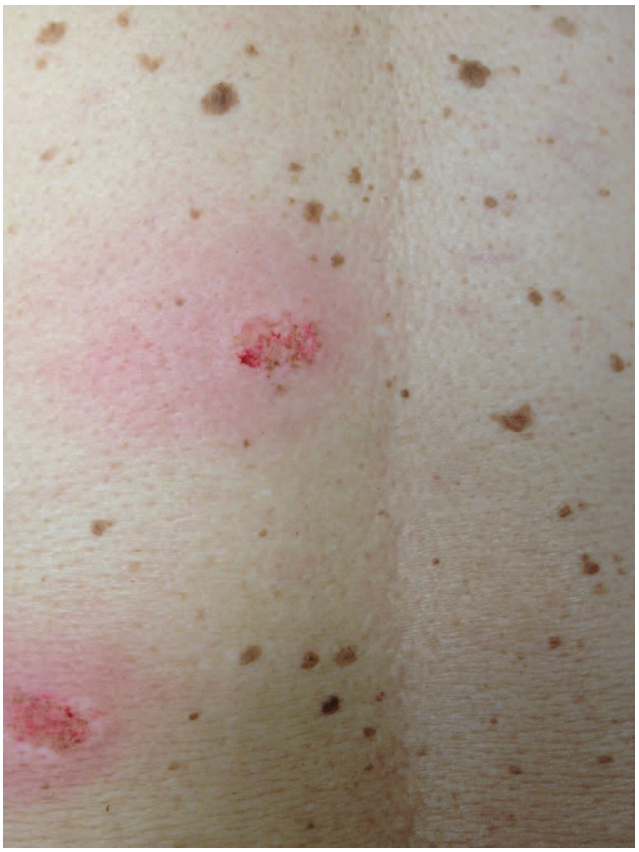

***Figure 4.*** *Micrograph of a woman's back skin immediately after removal of keratoma with a $CO_2$-laser*

## Conclusion

Multiple seborrheic keratoses may be encountered in the practice of any specialist including dermatovenerologists and general practitioners. One should consider that LTS is in most cases associated with a malignant neoplasm; therefore, a patient should be urgently referred to an oncologist for early diagnosis and treatment of a potentially curable malignancy. CPSs requires further advanced study in order to understand its pathogenesis, to create a clear classification, and to develop algorithms for physicians' actions.

### Вклад авторов

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией.

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### Список литературы / References:

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DOI: 10.20514/2226-6704-2022-12-5-330-340
EDN: CQVJCD
УДК 616.12-009.72-06:616.127-005.4-085

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# КОНСЕНСУС ЕВРОПЕЙСКИХ ЭКСПЕРТОВ ПО ВЕДЕНИЮ ПАЦИЕНТОВ С ИШЕМИЕЙ С НЕОБСТРУКТИВНЫМ ПОРАЖЕНИЕМ КОРОНАРНЫХ АРТЕРИЙ ПРИ ХРОНИЧЕСКОМ КОРОНАРНОМ СИНДРОМЕ: ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ В АМБУЛАТОРНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ В РОССИИ

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# Consensus of European Experts on the Management of Patients with Ischemia with Non-Obstructive Coronary Arteries with Chronic Coronary Syndrome: Possibilities for Use in Outpatient Clinical Practice in Russia

**Резюме**

В 2020 г вышел консенсусный документ Европейского общество кардиологов по ведению пациентов с ишемией миокарда, связанной с необструктивным поражением коронарных артерий. Основные положения нового документа ориентированы на выделение особой группы пациентов с хроническим коронарным синдромом и подозрением на вазоспастическую или микрососудистую стенокардию с целью рационализации и персонификации подхода к их ведению. Большая часть пациентов с установленной ишемией, при прохождении коронарной ангиографии не имеет гемодинамически значимой обструкции коронарных артерий. Коронарная микрососудистая дисфункция и эпикардиальный вазоспазм, отдельно или в сочетании с атеросклеротическим поражением коронарных артерий сердца, являются причинами ише-

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мии миокарда. При этом микроваскулярная дисфункция рассматривается в качестве значимого провоцирующего фактора развития рефрактерной стенокардии. Диагностика подобных состояний нередко затруднена, и поэтому для таких пациентов не назначается оптимальная терапия. Как следствие, эти пациенты имеют низкое качество жизни, что приводит к повторным госпитализациям, неблагоприятным сердечно-сосудистым исходам в краткосрочной и долгосрочной перспективе и значительной нагрузке на ресурсы здравоохранения. В статье рассматриваются возможности применения новых рекомендаций и консенсуса в диагностике и ведении таких пациентов в условиях амбулаторной клинической практики в России. На начальных этапах диагностики приоритет отдается неинвазивным методам исследования, для детального обследования проводится инвазивное обследование с фармакологической нагрузкой. При ведении пациентов используется пошаговая стратегия в зависимости от конкретной клинической ситуации. Препаратами первой линии антиишемической терапии остаются блокаторы кальциевых каналов или бета-блокаторы.

***Ключевые слова:*** *хронический коронарный синдром, вазоспастическая стенокардия, ишемия, микрососудистая дисфункция, рефрактерная стенокардия*

## Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

## Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 02.03.2021 г.

Принята к публикации 27.04.2022 г.

**Для цитирования:** Ларина В.Н., Корчагин И.А. КОНСЕНСУС ЕВРОПЕЙСКИХ ЭКСПЕРТОВ ПО ВЕДЕНИЮ ПАЦИЕНТОВ С ИШЕМИЕЙ С НЕОБСТРУКТИВНЫМ ПОРАЖЕНИЕМ КОРОНАРНЫХ АРТЕРИЙ ПРИ ХРОНИЧЕСКОМ КОРОНАРНОМ СИНДРОМЕ: ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ В АМБУЛАТОРНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ В РОССИИ. Архивъ внутренней медицины. 2022; 12(4): 330-340. DOI: 10.20514/2226-6704-2022-12-5-330-340 EDN: CQVJCD

## Abstract

In 2020, a consensus document of the European Society of Cardiology on the management of patients with myocardial ischemia with non-obstructive coronary arteries was released. The main provisions of the new document are aimed at identifying a special group of patients with chronic coronary syndrome and suspected vasospastic or microvascular angina in order to rationalize and personalize the approach to their management. Most patients with established myocardial ischemia do not have obstructive coronary arteries when undergoing coronary angiography. Coronary microvascular dysfunction and epicardial vasospasm, alone or in combination with obstructive coronary artery atherosclerosis, are the causes of myocardial ischemia. In this case, microvascular dysfunction is considered as a significant provoking factor in the pathogenesis of refractory angina pectoris. Diagnosis of such conditions is often difficult, and therefore the correct therapy is not prescribed for such patients. As a consequence, these patients have a poor quality of life, which leads to hospital readmissions, poor cardiovascular outcomes in the short and long term, and a significant burden on health care resources. The article discusses the possibilities of applying new recommendations and consensus in the diagnosis and management of such patients in outpatient clinical practice in Russia. At the initial stages of diagnosis, priority is given to non-invasive research methods; in-depth examination, carried out using invasive methods with a pharmacological testing. Patient management uses a stepwise strategy depending on the specific clinical situation. Calcium channel blockers or beta blockers remain the first line anti-ischemic therapy.

***Key words:*** *chronic coronary syndrome, vasospastic angina, ischemia, microvascular dysfunction, refractory angina*

## Conflict of interests

The authors declare no conflict of interests

## Sources of funding

The authors declare no funding for this study

Article received on 02.03.2021

Accepted for publication on 27.04.2022

**For citation:** Larina V.N., Korchagin I.A. Consensus of European Experts on the Management of Patients with Ischemia with Non-Obstructive Coronary Arteries with Chronic Coronary Syndrome: Possibilities for Use in Outpatient Clinical Practice in Russia. The Russian Archives of Internal Medicine. 2022; 12(4): 330-340. DOI: 10.20514/2226-6704-2022-12-5-330-340 EDN: CQVJCD

ACEI — angiotensin-converting enzyme inhibitors, ACS — acute coronary syndrome, ARB — angiotensin II receptor blockers, CA — coronary arteries, CABG — coronary artery bypass grafting, CAD — coronary artery disease, CCBs — calcium channel blockers, CCS — chronic coronary syndromes, CFR –coronary flow reserve, CMD — coronary microvascular dysfunction, CVC — cardiovascular complications, ECG — electrocardiogram, ECHO-CG — echocardiography, ED — endothelial dysfunction, ESC — European Society of Cardiology, FFR — fractional flow reserve, ICAG — invasive coronary angiography, IHD — ischaemic heart disease, INOCA — ischaemia with non-obstructive coronary arteries, IOCA — ischaemia with obstructive coronary arteries, LV — left ventricle, MRI — magnetic resonance imaging, MSCT — multispiral computed tomography, PCI — percutaneous coronary intervention, PET — positron emission tomography, VSA — vasospastic angina

In 2019, the European Society of Cardiology (ESC) [1] published guidelines on the diagnosis and management of patients with "chronic coronary syndromes" (CCS), with a proposal to use this term instead of the previously used one — "stable coronary artery disease (CAD)". The discussion paper on these guidelines [2] brings up the issues that required extensive medical discussion and consensus, as well as the problems that prevented the implementation of these guidelines in Russian clinical practice. In 2020, a consensus document "An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with the European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group" [3] was published. The document is a summarized point of view of the experts of the European Association of Percutaneous Cardiovascular Interventions, the Working Group on Coronary Pathophysiology and Microcirculation supported by Coronary Vasomotor Disorders International Study Group on the importance of ischaemia with non-obstructive coronary arteries (INOCA). The document specifies that among the patients who underwent invasive coronary angiography (ICAG) for angina (or painless ischaemia), ischaemia with non-obstructive coronary arteries developed in about 70 % of patients; more often in women (50–70 %) than in men (30–50 %). INOCA (according to experts) is not a benign condition and is associated with a high incidence of adverse events and impaired quality of life. Timely diagnosis of INOCA is often complicated and is associated with an delayed choice of appropriate specific treatment.

The terms used in the consensus documents do not refer to the "secondary" ischaemia/angina caused by the following diseases: cardiomyopathy (hypertrophic, dilated), myocarditis, aortic stenosis, infiltrative cardiomyopathies, systemic inflammatory or autoimmune diseases, i.e. systemic lupus erythematosus, rheumatoid arthritis, dysfunction of platelets/impaired coagulation; management of these diseases (in the absence of concomitant atherosclerotic lesions of coronary arteries (CA)) differs from the strategy of treatment for patients with impaired blood flow in coronary arteries.

Moreover, in both consensus documents there is no clear definition of ischaemic heart disease (IHD); the term is replaced by INOCA or ischaemia with obstructive coronary arteries (IOCA) with the description of the clinical features of their course that, however, are not diagnostic criteria and allow only suggesting damage to coronary arteries and/or microvasculature.

Despite the fact that at present the functions and capabilities of a general practitioner do not allow using of the proposed provisions of two consensus documents, the objective of this article is to briefly present the main points of these ~~two~~ documents and the possibility of their implementation in outpatient clinical practice in Russia. The paper will discuss the strategy of managing patients with ischaemia with non-obstructive and obstructive atherosclerotic CAD.

The main provisions of the new document are aimed at identifying a special group of patients with chronic coronary syndrome and suspected vasospastic or microvascular angina in order to rationalize and personalize the approach to their management.

- First of all, the authors define the very concept of INOCA, as well as the examination methods that allow to diagnose it, i.e. to exclude CA obstruction and at the same time to confirm myocardial ischaemia. To that end, non-invasive examination methods are preferred.
- Secondly, the consensus document highlights INOCA "endotypes" depending on the level and nature of CAD, providing their diagnostic criteria using interventional research methods.
- Finally, based on the data on the presence of risk factors, type of coronary artery disease, comorbidities and patient characteristics, it is proposed to choose the optimal treatment strategy.

As new possibilities and instrumental methods are implemented into outpatient practice, such a scenario for identifying and managing patients with INOCA can improve patients' life quality, and slow down the further continuous progression of ischaemic heart disease (coronary artery disease). It is the primary care physician who initially faces the task of suspecting non-obstructive CAD and carrying out the correct routing of this patient for a more detailed diagnosis. Besides, the objective of a physician is to further control the symptoms and the course of the disease based on the principles of evidence-based medicine.

Myocardial ischaemia is a multifactorial process and can be either of structural or of functional nature. At the level of epicardial CA, the structural causes include atherosclerotic vascular lesions (local or diffuse) and myocardial muscle bridge; the functional ones include epicardial vasospasm. In individuals with local and/or diffuse (obstructive or non-obstructive) CAD, coronary microvascular dysfunction (CMD) and vascular epicardial dysfunction (spasm) can be independent or ancillary pathophysiological mechanism of ischaemia.

There are two "endotypes" at the microvascular level: structural remodeling of microvasculature and functional dysregulation of arterioles. Endothelial dysfunction (ED) and local inflammation of vascular wall with increased level of proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-6) and overproduction of endothelin-1 are the key factors in the CMD

pathogenesis [4]. In other words, microvascular dysfunction can result either from structural or functional changes, or from both.

Structural remodeling of coronary microvasculature is associated with decreased microcirculation and impaired oxygen delivery. It is normally caused by internal remodeling of coronary arterioles with the subsequently increased ratio of vessel wall thickness to its lumen, or reduced myocardial capillary density (capillary rarefaction), or both.

Functional dysregulation of arterioles usually develops in medium to large arterioles, with the prevalence of subsequent vasodilation mediated by blood flow.

Epicardial vasospasm usually develops as a result of hyperreactivity of epicardial vascular segment, especially associated with vasoconstrictive stimuli, including smoking, medications, increased blood pressure, exposure to cold, emotional stress, and hyperventilation. Severe coronary spasm can also be associated with allergic reactions (for example, Kounis syndrome) [5, 6].

Primary and nonspecific hyperreactivity of coronary smooth muscles is usually observed in patients with variant angina and is apparently a key element of epicardial vasospasm. The available data indicate that endothelial dysfunction contributes to the triggering of spasm in predisposed segments of coronary vessels [7].

## Clinical variants of CCS and INOCA

According to ESC experts, chronic coronary syndromes are represented by the following clinical variants ("scenarios", settings): 1) patients with suspected CAD, symptoms of stable angina and/or dyspnea; 2) patients with the development of heart failure or left ventricular (LV) dysfunction and suspected CAD; 3) patients in stable condition (with or without symptoms) less than 1 year after acute coronary syndrome (ACS) or recent revascularization; 4) patients 1 year after the initial diagnosis or revascularization (with or without symptoms); 5) patients with angina and suspected vasospasm or microvascular lesions; 6) individuals diagnosed with asymptomatic CAD during screening. Drapkina O.M. et al. [2] emphasize that there are much more such scenarios in clinical practice, and the suggested variants cannot help to appropriately consider the cases of disease, conduct registered observations and choose optimal management strategy. At the same time, one should totally agree that these "scenarios" can overlap, moving from one clinical variant into another.

In 2019 Guidelines under consideration, ESC experts associate one of CCS types with the spasm of coronary arteries and/or dysfunction of small vessels; it is likely that this particular type of CCS that is often observed in outpatient practice is highlighted in the new consensus document on INOCA.

Similar to the clinical guidelines on the management of patients with CCS as of 2019, the experts who presented INOCA consensus document also proposed to consider some its clinical variants:

- Epicardial vasospastic angina (VA, Prinzmetal angina) is a clinical sign of myocardial ischaemia that is characterized by dynamic obstruction of epicardial coronary arteries caused by vasomotor disorder;
- Microvascular angina (MVA) is a clinical sign of myocardial ischaemia caused by CMD as a result of structural remodeling of microvasculature or vasomotor disorders of arterioles;
- Microvascular and epicardial vasospastic angina.

Clinical manifestations of CCS and INOCA are nonspecific: from typical angina pain to an isolated feeling of lack of air and other symptoms (anxiety, pain between shoulder blades, gastrointestinal disorder, nausea, fatigue, weakness, vomiting, sleep disturbances) which certainly complicate timely diagnosis of these conditions. However, the INOCA document indicates that the following signs are more common in this type of ischaemia:

- chest discomfort (both at rest and after exercise; lasts more than 1 minute and is poorly controlled with nitroglycerin);
- severity of pain syndrome can vary during days or weeks: increase, then decrease ("Crescendo-decrescendo");
- stress-related symptoms;

Besides, the experts mention higher incidence of INOCA signs in women than in men.

*Thus,* ***vasospastic angina*** can be suspected in the presence of symptoms that appear mainly at rest, with preserved exercise tolerance. As a rule, patients with vasospastic angina, in contrast to patients with stable angina, are younger, have fewer cardiovascular risk factors than patients with stable angina, and the possibility of vasospastic angina increases when attacks are circadian and predominate at night or in early morning.

*The specific feature of anginal pain in* ***microvascular angina*** is its development sometime after physical activity, as well as after emotional stress; it is poorly controlled by short-acting nitrates. Pain episodes associated with exposure to cold, may occur at rest. Angina in such patients is usually of mixed nature.

Despite the widespread use of antianginal agents and/or percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG), the percentage of patients with CHD with daily or weekly angina episodes ranges from 2 % to 24 % [8].

In this aspect, it is important to consider the ***refractory angina*** presented in the 2019 ESC Guidelines on the

diagnosis and management of patients with "chronic coronary syndromes". Refractory angina is considered in the case when the symptoms of angina last more than three months, the presence of reversible myocardial ischaemia is confirmed, there are pronounced coronary bed lesions, and these symptoms cannot be controlled by intensification of drug treatment, adding second and third line antianginal agents, CABG or stenting, including PCI for chronic coronary total occlusion [1]. This definition is also specified in the current Guidelines of the Russian Society of Cardiology [9].

The concept of "***refractory angina***" was first proposed by ESC experts in 2002: a chronic condition (lasts more than three months) that is characterized by angina caused by the failure of coronary circulation (associated with the coronary artery disease); it is accompanied by pronounced clinical symptoms uncontrolled by combined drug treatment in maximum tolerable doses when myocardial revascularization (percutaneous coronary angioplasty, or CABG) is impossible [10].

In other words, any stable angina associated with adequate drug treatment can be considered refractory if myocardial revascularization is impossible. Due to the lack of clear criteria for assessing patient's clinical condition (in particular, severity — the incidence of anginal pain episodes over a certain period of time), this definition is a debatable reference. It should be mentioned that refractory angina can be diagnosed only after confirmation of the ineffectiveness of combined antianginal treatment in maximum tolerated dose [8].

Although the presence of IHD, suggested as an epicardial coronary arteries obstruction, is usually considered to be a basis for the development of refractory angina, in fact, refractory angina can also develop in microvasculare damage (microvascular dysfunction is considered as a significant precipitating factor in the development of refractory angina), hypertrophic cardiomyopathy, and diastolic dysfunction of left ventricle (LV) [3]. As a rule, the patients with refractory angina have poor life quality suffer with psychological stress, which caused significant burden on healthcare resources [11].

According to epidemiological studies, 5 to 10 % (7.7 % women, 7.3 % men) of patients with stable coronary heart disease who underwent cardiac catheterization had refractory angina; the annual incidence of refractory angina in Europe reaches 30- 50 thousand, in the USA — 75 thousand cases [12].

Thus, clinical variants of CCS and INOCA have no specific clinical manifestations that distinguish them from those in impaired blood flow in coronary arteries; they suggest higher or lower probability of structural or functional coronary artery disease, and need further clarification of diagnosis using instrumental methods, depending on individual characteristics of a patient.

It should be mentioned that the category of "patients with angina and suspected vasospasm or microvascular disease" that was identified in CCS includes the groups of patients, heterogeneous in terms of age, sex, and comorbidities, as well as in terms of degree of cardiovascular complications (CVC) risk. Such patients are quite common in outpatient practice, and only computed tomography and angiography or ICAG with additional functional tests (what is recommended by the experts) can help to finally confirm or exclude the suspected diagnosis.

## Ischaemia diagnosing methods

Functional and structural disorders of coronary microcirculation can result in decreased myocardial perfusion and ischaemia, even in the absence of large coronary artery stenosis. The role of a primary care physician (in particular, general practitioner) in diagnosing these conditions is to suspect the disease and carry out examinations adequate for this stage (complete blood count and blood biochemistry, electrocardiographic and echocardiographic examinations, 24h Holter monitoring of electrocardiogram (ECG) (24h ECG). If the symptoms persist and there are no ECG changes, the patient should be referred to a cardiologist to verify the diagnosis and undergo specific examinations.

According to the 2019 ESC Guidelines for CCS, 2020 Guidelines for INOCA, and 2020 Guidelines for stable IHD of the Russian Society of Cardiology, diagnostic examination should start with non-invasive methods: stress echocardiography (ECHO CG), stress cardiac magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET), or multispiral computed tomography (MSCT angiography). The choice of particular diagnostic method depends on the clinical presentation, however, taking into consideration the individual characteristics and preferences of a patient, as well as local resources. The clinical probability of obstructive CAD is assessed using such determinants as family history, dyslipidemia, diabetes mellitus, arterial hypertension, smoking, and other modifiable risk factors and changes on ECG.

ESC Guidelines for CCS describe a structured approach to the differential diagnosis of BCA that includes:

1. initial physical examination, diagnosis, risk assessment that should include 6 steps of diagnosis;
2. measures aimed at changing lifestyle;
3. prescription of drug products — antianginal drugs and the agents that affect on the prognosis.

Unlike the procedure for CCS diagnosing, non-invasive INOCA diagnostics includes 2 stages (steps) with the

mandatory assessment of patient's complaints, history, description of clinical symptoms, ECG, and referral to a cardiologist at the first stage of diagnosis. At the second stage of diagnosis, non-invasive examinations are recommended. Invasive examinations are carried out, first of all, in high clinical probability of CAD and if revascularization is required. At the same stage, functional tests with physical exertion, transthoracic echocardiogram, contrast stress echocardiogram, PET, imaging studies, MRI are performed.

Since non-invasive methods do not provide direct visualization of blood flow in coronary arteries and coronary microcirculation, invasive examinations are required to confirm INOCA, including CAG at the first stage, adenosine test at the second stage, and vasoreactivity test at the third stage.

To detect atherosclerosis, MSCT coronary angiography is performed; it is the preferable method in the patients with a low clinical probability of obstructive CAD. According to the 2019 Guidelines for CCS, obstructive CAD is the 50 % or higher stenosis, based on the results of MSCT coronary angiography or ICAG. In high clinical probability of coronary artery obstruction, typical and atypical angina at low level of physical activity, refractoriness to drug treatment, as well as the presence of high risk of cardiovascular events, the readiness of the patient for revascularization and the absence of somatic contraindications, if there are appropriate indications for coronary artery bypass grafting or stenting, ICAG is recommended (with supplementary functional tests).

Invasive examinations make it possible to determine the presence and degree of CAD and the nature of dysfunction (whether there is a functional impairment — vasodilation (or vasospasm) and/or impaired microcirculatory conduction with increased minimum microcirculatory resistance).

INOCA diagnosis is based on the measurement of myocardial functional state parameters, namely, myocardial blood flow and coronary reserve flow (CRF). CRF is the ratio of coronary blood flow during the maximal coronary vasodilation to the blood flow at rest.

CRF is an integrated measure of blood flow in large epicardial coronary arteries, therefore, the decreased CRF with excluded severe obstructive lesions of epicardial coronary arteries serves as a CMD marker. CRF index <2.0 or microcirculatory resistance ≥25 U are the indicators of impaired microcircular function.

CRF can be measured non-invasively: using transthoracic Doppler echocardiography of left coronary artery with the measurement of diastolic coronary blood flow after IV administration of adenosine, or magnetic resonance imaging with determination of myocardial perfusion index, or positron emission tomography.

Microcirculatory resistance can be measured using coronary artery catheterization (calculation of microcirculatory resistance index) or Doppler flow velocity (calculation of hyperemic microvascular resistance).

To exclude hemodynamically relevant CA stenosis, fractional flow reserve (FFR) is measured. FFR is an indicator of the functional relevance of stenosis; it is defined as the ratio of the pressure measured more distally from the stenosis to the pressure more proximally to stenosis (in aorta) measured at maximum vasodilation. At FFR <0.8, CA stenosis is hemodynamically insignificant.

According to ESC criteria, a combination of ICAG, pressure and flow measurements, as well as pharmacological tests should be used to determine the INOCA endotype. Following the criteria, first, it is necessary to exclude CA obstruction using one of the methods, second, mind the possible endotype with MVA+VSA combination. There is the opinion of ESC experts that requires further discussion; according to it, identification of transient ischaemia using 24h ECG is indicative of VSA (ESC I A (GR C, LE 5)[1], however, in such cases, the ESC also recommends to exclude possible CA stenosis and to perform angiographic imaging of the spasm using pharmacological loading (ESC I A (GR C, LE 4)[1] which is currently quite difficult to implement in primary health care facilities.

Diagnostic criteria for microvascular angina, vasospastic angina, their combination, and atherosclerotic lesions of CA with no blood flow restriction are presented in Table 1.

Thus, at the outpatient level, it is difficult to make differential diagnosis of primary (IOCA and INOCA) and secondary (CMP, defects, CTD) ischemia due to the lack of adequate instrumental examination. General practitioner at a local clinic can assume myocardial ischemia of a particular nature and refer the patient to a cardiologist based on the presence of risk factors, specific complaints and symptoms, comorbidities, angina, and the presence/absence of ECG changes, and in case of vasospastic angina, judging from transient episodes of ischemia at rest identified using 24h Holter ECG. The next stage is the referral of a patient to a cardiologist to make decision on the issue of further examination, possibly — in hospital conditions. Considering new guidelines and extended indications for non-invasive studies, the issue of expanding the functions of physicians and general practitioners of the outpatient stage needs further discussion. From our point of view, this approach should be brought into accordance, since it will definitely entail: a) further increase in the incidence of ischaemic heart

[1] GR — grades of recommendations; LE — levels of evidence

***Table 1.*** *Diagnostic criteria for microvascular, vasospatic angina, their combination and atherosclerotic CAD that does not restrict blood flow*

| Condition | Pathophysiology | Diagnostic criteria |
|---|---|---|
| Microvascular angina* | CMD | Evidence of CMD:<br>Impaired coronary flow reserve (<2,0)<br>Abnormal coronary microvascular resistance indices (IMR≥25) |
| | | Adenosine test: FFR >0,8<br>CFR <2,0 IMR ≥25 HMR ≥1,9 |
| | | Acetylcholine test: no or <90 % diameter reduction + angina + ischemic ECG changes |
| Vasospastic angina | Epicardial spasm | Adenosine test: FFR >0,8; CFR ≥2,0; IMR <25; HMR <1,9 |
| | | Acetylcholine test: ≥90 % diameter reduction + angina + ischemic ECG changes |
| Both microvascular and vasospastic angina | CMD + epicardial spasm | Adenosine test: FFR>0,8 CFR<2,0 IMR ≥25 HMR≥1,9 |
| | | Acetylcholine test: no or <90 % or ≥90 % diameter reduction + angina + ischemic ECG changes |
| Atherosclerotic CAD without blood flow-liming*** | Diffuse coronary artery atherosclerosis | Adenosine test: FFR>0,8 CFR≥2,0 IMR <25 HMR<1,9 |
| | | Acetylcholine test: no or <90 % diameter reduction + no angina + no ischemic ECG changes |
| **Common criteria** | Symptoms of myocardial ischaemia: effort or rest angina or exertional dyspnoea****<br>Myocardial ischaemia: functional imaging test (reversible defect, abnormality or flow reserve) — is not necessary.<br>Coronary CTA, ICA: Absence of coronary obstruction (<50 % or FFR >0,80) | |

**Note:** CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperaemic myocardial velocity resistance; IMR, index of microvascular resistance; CMD — coronary microvascular dysfunction; CAD — coronary artery disease; ECG — electrocardiography; ICA — Invasive coronary angiography; Coronary CTA — coronary computed tomography angiography.
* Non endothelial dependent microvascular angina may be diagnosed non-invasively by the methods described
** as alternative measures of microcirculatory resistance, based on thermodilution or Doppler, respectively
*** <50 % stenosis severity by visual assessment
**** Many patients with HF with preserved LVEF have dyspnoea, absence of obstructive CAD and impaired CFR. Measurement of LV end-diastolic pressure (normal ≤10 mmHg) and NT-proBNP normal <125 pg/mL is recommended

disease (coronary artery disease) due to diagnosing of all patients with risk factors of cardiovascular complications who seek medical help; b) prescription of unreasonable treatment [2]. In future, non-invasive assessment of the signs of endothelial dysfunction based on photoplethysmography and video capillaroscopy can provide a certain prognostic value in case of suspected INOCA at the stage of outpatient treatment [4].

## Management strategy for patients with ischaemia with non-obstructive and obstructive atherosclerotic lesions of coronary arteries

It is quite possible to agree with the principle proposed in the 2019 ESC Guidelines on CCS that the patients with different risk levels of developing CVD, with different levels and grades of coronary artery disease, with or without ischemia based on the results of functional tests require different approaches to management and treatment. However, according to the conventional clinical approach, the same approach to the management of patients with suspected chronic IHD and patients with chronic IHD is justified only in certain situations, which should be clearly defined in the Russian guidelines.

General rules for the treatment of patients with CCS, INOCA and IOCA include identification and management of diseases or conditions that contribute to the development of angina or myocardial ischaemia (anemia, overweight, fever, thyroid hyperfunction, infection, rhythm disorders, etc.); change of lifestyle regardless of disease severity and drug treatment; addressing risk factors for cardiovascular complications, drug treatment and interventions.

The choice of treatment methods (including the choice of a particular drug) is based on evidence, improving quality of life and/or reducing the risk of cardiovascular complications, increasing life expectancy, considering the somatic and mental characteristics of a patient.

Risk factors such as arterial hypertension, diabetes mellitus, smoking, and dyslipidemia contribute to the progression of coronary macro-, microvascular and vasospastic dysfunction and structural remodeling of

microcirculation. The optimal choice of antianginal agents depends on the predominant mechanism of anginal symptoms (vasospastic and/or microcirculatory). Angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin II receptor blockers (ARBs) are able to improve CFR indicators in coronary microvascular dysfunction; they can be easily combined with both calcium channel blockers and beta blockers and slow down the remodeling of small vessels. ESC experts emphasize that, due to their anti-inflammatory properties, statins can also be used in patients with INOCA with reduced CFR and vascular spasm.

The management of patients with INOCA is complicated by the fact that they are a very heterogeneous population, and no randomized studies on their treatment has been performed as of now, therefore, it is recommended to adhere to the principles of stepwise antianginal therapy presented in the 2019 ESC Guidelines for CCS. The list of antianginal agents discussed in these Guidelines is presented in Table 2.

The standard antianginal drug treatment is not always effective. Short-acting nitrates have variable effectiveness and require frequent administration. Long-acting nitrates are ~~often~~, as a rule, ineffective, and can provoke an increase in symptoms in patients with MVA due to subclavian steal syndrome.

The patients with epicardial or microvascular spasm based on the results of acetylcholine test are recommended to use calcium channel blockers (CCB). In cases of MVA when calcium antagonists are ineffective, ESC experts suggest adding ranolazine to therapy. In cases of persistent anginal symptoms ivabradine should be considered, however, its effectiveness in MVA has not been adequately studied.

If microvascular angina is first diagnosed based on abnormal CFR and/or high microcirculatory resistance (suggesting microvascular remodeling), it is recommended to prescribe beta blockers as an initial therapy, followed by the addition of CCB; with persisting symptoms — nicorandil and ranolazine.

The further discussion and consensus decisions are required on several treatment-related issues. In severe forms of VSA, ESC specialists consider the use of calcium antagonists in higher doses (up to 200 mg diltiazem twice daily) and the combination of dihydropyridine calcium antagonists (amlodipine) with nondihydropyridine antagonists (diltiazem); this therapy cannot be applied to a wide population of patients, the decision should be made on an individual basis and is controversial from our point of view. If the symptoms of vasospastic angina do not resolve during treatment with calcium channel blockers followed by nitrate therapy, the use of nicorandil should be considered.

Besides, ESC experts are discussing the use of low doses of tricyclic antidepressants (imipramine and xanthine derivatives) to reduce the incidence and intensity of symptoms, considering them as second-line agents in patients with poorly controlled symptoms or with poor tolerance to antianginal drugs. Trimetazidine is also suggested to use in such cases.

***Table 2.*** *Medical therapy of INOCA*

| Diagnosis | Treatment |
|---|---|
| Microvascular angina | Beta-blockers (Nebivolol 2.5–10 mg daily) |
| | Calcium channel blockers (Amlodipine 10 mg daily) |
| | Ranolazine (375–750 mg twice daily) |
| | Trimetazidine (35 mg twice daily) |
| | ACE inhibitors (Ramipril 2,5 — 10mg), ARBs |
| Vasospastic angina | Calcium channel blockers (Amlodipine 10 mg or Verapamil 240 mg SR or Diltiazem 90 mg twice daily or 120–360 mg single or divided doses) |
| | Nitrates (Isosorbide mononitrate XL 30 mg) |
| | Nicorandil (10-20 mg twice daily) |
| Both microvascular and vasospastic angina | Calcium channel blockers (Amlodipine 10 mg or Verapamil 240 mg SR or Diltiazem 90 mg twice daily or 120–360 mg single or divided doses) |
| | Nicorandil (10-20 mg twice daily) |
| | Trimetazidine (35 mg twice daily) |
| | ACE inhibitors (Ramipril 2.5 -10mg), ARBs |
| | Statins (Rosuvastatin 10–20 mg) |

**Note:** ACE — angiotensin-converting enzyme inhibitor; ARBs angiotensin receptor blocker

The enhanced external counterpulsation can be used as an additional treatment for INOCA patients, in case of ineffectiveness of drug therapy.

Currently, the studies of the effect of Rho-kinase inhibitors (Rho-associated protein kinase (ROCK)) on the reduction of coronary vasoreactivity and contractility of vascular wall are ongoing. The results of a multicenter, randomized, double-blind, placebo-controlled trial Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR NCT03417388) that investigates the effects of statins (rosuvastatin or atorvastatin)/ACEI (lisinopril) or ARBs (losartan)/acetylsalicylic acid (aspirin) in high doses in 4,422 women aged 18 to 100 years with the symptoms of INOCA, CA stenosis <50 % and FFR >0.80 are highly expected. The hypothesis of this trial is that intensive drug treatment will reduce the risk of major cardiovascular events by 20 % compared to the conventional management strategy for this category of patients. Follow-up period will be 3 years. The expected trial completion date is December 30, 2023.

Myocardial revascularization (percutaneous coronary intervention (stenting of coronary arteries), or CABG) is used as an additional treatment method for stable angina that is refractory to drug therapy and/or hemodynamically significant atherosclerotic lesions of the left coronary artery trunk , large epicardial branches and large painless ischemia. The decision on the choice of surgical treatment is made by an X-ray endovascular surgeon, a cardiovascular surgeon and a cardiologist based on the results of CAG, non-invasive and invasive studies, and patient's clinical condition. Revascularization can contribute to reducing the amount and dose of antianginal drugs, increasing exercise tolerance and improving the life quality compared to only drug treatment. Myocardial revascularization is not performed in vasospastic angina with no hemodynamically significant atherosclerotic CAD [9].

More than half of patients (55 %) with microvascular angina are refractory to drug therapy. This situation is complicated by the fact that the choice of effective treatment for refractory angina is in fact, currently limited. Moreover, since microvascular angina is not routinely diagnosed using invasive methods (coronary angiography), it often remains undetected. Therefore, the management of refractory angina should focus not only on macro- but also on microvascular dysfunction.

Despite the growing number of patients with coronary heart disease with limitations for revascularization or "no choice", the options for refractory angina management are currently limited. Ranolazine was approved for the management of refractory angina on the basis of studies with the participation of patients with IHD, and the use of enhanced external counterpulsation demonstrated an improvement in the time before ST segment depression on the ECG, however, not the general tolerance to physical exertion in patients with refractory angina. However, the effectiveness of ranolazine with refractory angina has recently become an issue for discussion.

In RIVER-PCI trial (Ranolazine in Patients With Incomplete Revascularization After Percutaneous Coronary Intervention), 2,604 patients (average age 63.4 years) after incomplete revascularization (one or more coronary artery lesions with a stenosis diameter of 50 % or higher with a reference value of ≥2.0 mm in diameter by visual assessment) using PCI with stenting were randomized in groups to receive ranolazine 1,000 mg twice daily (n = 1,317) and placebo (n = 1,287). The results of 1.8 year median follow-up demonstrated that 26.2 % of patients in ranolazine group and 28.3 % of patients in placebo group (p = 0.48) developed the events of primary combined endpoint (revascularization as a result of myocardial ischaemia or hospitalization with no revascularization). There was a high incidence of cardiovascular events in patients with incomplete revascularization (15.3 % in ranolazine group and 15.5 % in placebo group, p = 0.14). The results of this study revealed the ineffectiveness of ranolazine in improving the prognosis in patients with IHD and incomplete revascularization [13].

In a single-center, prospective, open-label study by S. Calcagno et al., the effectiveness of treatment with ranolazine (375 mg twice daily) in addition to conventional anti-ischaemic therapy in 49 patients (age 62.6 ± 11.3 years)who underwent CAG for persistent/recurrent angina after PCI and residual ischemia of the small branches of coronary arteries that were not subject to further revascularization. In the course of the treatment with ranolazine, in 30 days, the extended duration of stress test compared with the baseline value (9'1" ± 2' vs 8'10" ± 2', p = 0.01) was observed, as well as the decreased frequency of exertional angina attacks (4.1 % vs 16.3 %, p = 0.04). Thus, the addition of low-dose ranolazine to standard anti-ischaemic drug therapy resulted in improved results of stress test and decreased frequency of angina attacks in patients with persistent/recurrent angina and residual myocardial ischaemia when revascularization is impossible. In view of the small sample of patients and short follow-up period, these results require further investigation and confirmation [14].

The 2020 Russian Guidelines for stable coronary artery disease largely coincide with European ones both at the diagnostic stage and at the stage of treatment selection. Invasive CAG is no longer the "gold standard" in the diagnosis of ischaemic lesions. The drug therapy selection is considers the mechanism and nature of CA lesions. CCB are the agents of choice for hyperreactivity of smooth muscle cells, epicardial or microcirculatory

vessels (positive acetylcholine test). Beta blockers, nitrates, CCB, and ACEI or ARBs are recommended for endothelial dysfunction (positive adenosine test).

However, the opinions of the professional communities of cardiologists in the USA, Canada, Great Britain, European countries, and Australia regarding the guidelines on separate methods of managing IHD are quite different. There is a number of drugs, "food supplements", surgical and other methods that are mentioned in some guidelines on the management of patients with chronic ischaemia caused by atherosclerotic lesions of coronary arteries, as appropriate/ with possible positive effect on the course of IHD, however, are absent in other guidelines or are indicated as "unproven" and not recommended for use [15].

Thus, the management of patients with suspected myocardial ischaemia with any pathogenetic mechanism (CMD or spasm) should be carried out with the participation of general practitioners, cardiologists, specialists in the field of interventional cardiology (if necessary, consultations with other specialists are also indicated). When symptoms of ischaemia or asymptomatic ischaemia are detected, beta blockers and/or calcium channel blockers are the first choice drugs for all patients; these agents depending on the clinical situation may be recommend by a general practitioner/general practitioner of the outpatient stage. If adjustment of treatment or additional examination is required, the patient is referred for a cardiologist' consultation.

## Conclusion

The accumulation of new knowledge and performing new studies necessitate a continuous analysis of existing solutions, implementation of new terms more precisely describing the pathological processes associated with myocardial ischaemia, for establishment of new and revision of old IHD criteria and the parameters for assessing patient's condition.

With the development of new technologies, the non-invasive examination methods that reveal certain specific features of blood flow functional state, perfusion and myocardial contractility are prioritized at the initial stage of diagnostics. The choice of methods depends on resources available, staff experience, preferences of physicians and patients. Diagnostic methods listed in the ESC Guidelines for general clinic networks can hardly be generally available in our country. This issue, of course, requires clarification and further discussion.

In view of the lack of evidence (including the management of patients with INOCA), there is no single approach to the choice of anti-ischaemic drugs and agents that affect life quality, atherosclerosis progression and the incidence of cardiovascular events. The step-by-step strategy depending on the clinical course of disease and risk factors for cardiovascular events associated with atherosclerosis remains the reference. Calcium channel blockers or beta blockers are still the first-line anti-ischaemic agents.

**Вклад авторов:**

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2022-12-5-341-351
EDN: EBLUAU
УДК 616.34:579.61]-048.25

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# ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ МОДИФИКАЦИИ КИШЕЧНОГО МИКРОБИОМА

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# Possibilities and Prospects of Modification of the Intestinal Microbiome

**Резюме**

Микробиом кишечника является вариабельной системой, которая не только адаптируется к сигналам и информации, поступающей от человека, но и влияет на своего хозяина за счет сложной системы взаимодействий живых микроорганизмов, фагов, вирусов, плазмид, мобильных генетических элементов, молекул, синтезируемых микроорганизмами, в том числе их структурных элементов (нуклеиновых кислот, белков, липидов, полисахаридов), метаболитов (сигнальных молекул, токсинов, органических и неорганических молекул) и молекул, синтезируемых организмом человека. Модификация или модулирование микробиома путем коррекции рациона питания, характера физической активности, назначения компонентов персонализированных продуктов (пребиотиков, пробиотиков, парапробиотиков, постбиотиков, аутопробиотиков) может приводить к изменению видового разнообразия, метаболического профиля микробиома кишечника и регуляции обменных процессов, локального и системного ответа на инфекционные заболевания, метаболизма лекарственных средств, деятельности многих органов и систем за счет наличия физиологических осей «микробиом кишечника–центральная нервная система», «микробиом кишечника–печень», «микробиом кишечника–почки» и некоторых других. Изучаются новые, таргетные направления модификации микробиома кишечника, которые заключаются в целенаправленном воздействии на патогенные микроорганизмы, в том числе внутриклеточные и устойчивые к антибактериальным лекарственным средствам.

Динамический характер кишечного микробиома, способность изменяться и адаптироваться под воздействием некоторых изученных факторов открывает новые перспективные направления медицинской профилактики и лечения соматических и психических заболеваний. Несомненно, модификация микробиома с клинической целью направлено на укрепление здоровья человека. Однако, индивидуальные, не всегда предсказуемые, изменения микробиома в ответ на модифицирующие факторы могут быть обусловлены уникальностью видового состава и функционального потенциала микроорганизмов у каждого человека.

***Ключевые слова:*** *микробиота, микробиом, антибиотики, пробиотики, пребиотики, трансплантация фекальной микробиоты*

**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 23.03.2022 г.
Принята к публикации 21.04.2022 г.

**Для цитирования:** Малаева Е.Г., Стома И.О. ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ МОДИФИКАЦИИ КИШЕЧНОГО МИКРОБИОМА. Архивъ внутренней медицины. 2022; 12(5): 341-351 DOI: 10.20514/2226-6704-2022-12-5-341-351 EDN: EBLUAU

**Abstract**

The gut microbiome is a variable system that not only adapts to signals and information coming from humans, but also affects its host due to a complex system of interactions of living microorganisms, phages, viruses, plasmids, mobile genetic elements, molecules synthesized by microorganisms, including their structural elements (nucleic acids, proteins, lipids, polysaccharides), metabolites (signaling molecules, toxins, organic and inorganic

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molecules) and molecules synthesized by the human body. Modification or modulation of the microbiome by correcting the diet, the intensity of physical activity, the appointment of components of personalized products (prebiotics, probiotics, paraprobiotics, postbiotics, autoprobiotics) can lead to changes in species diversity, the metabolic profile of the intestinal microbiome and the regulation of metabolic processes, local and systemic response to infectious diseases, drug metabolism, the activity of many organs and systems due to the presence of physiological axes "gut microbiome–central nervous system", "gut microbiome–liver", "gut microbiome–kidneys" and some others. New, targeted directions of modification of the intestinal microbiome are being studied, which consist in targeted exposure to pathogenic microorganisms, including intracellular and resistant to antibacterial drugs.

The dynamic nature of the intestinal microbiome, the ability to change and adapt under the influence of some of the studied factors opens up new promising areas of medical prevention and treatment of somatic and mental diseases. Undoubtedly, the modification of the microbiome for clinical purposes is aimed at improving human health. However, individual, not always predictable, changes in the microbiome in response to modifying factors may be due to the uniqueness of the species composition and functional potential of microorganisms in each person.

***Key words:*** *microbiota, microbiome, antibiotics, probiotics, prebiotics, fecal microbiota transplantation*

**For citation:** Malaeva E.G., Stoma I.O. Possibilities and Prospects of Modification of the Intestinal Microbiome. The Russian Archives of Internal Medicine. 2022; 12(5): 341-351 DOI: 10.20514/2226-6704-2022-12-5-341-351 EDN: EBLUAU

FMT — fecal microbiota transplantation, SCFAs — short-chain fatty acids

## Introduction

Human gut microbiome is a comprehensive and complex ecosystem thickly populated by species of microorganisms that interact with each other and with the human body [1, 2].

The composition of microbiota varies between individuals and depends on the host genotype host and environmental factors, including nutrition, physical activity, and the use of antibacterial agents [1–5]. It is known that the large intestine contains more microorganisms than the other GIT sections; the predominant types are *Firmicutes and Bacteroides* [1–4]. Gut microbiota synthesizes metabolites (short-chain fatty acids (SCFAs), secondary bile acids, neurotransmitters, etc.) that play an essential role in the regulation of the dynamic balance of the internal environment and the stability of basic physiological functions of human body, as well as in the pathogenesis of some diseases [2, 6]. The role of clinically significant bacterial metabolites is to maintain intestinal barrier function, to regulate food intake and energy expenditure (SCFAs), immune response (SCFAs, indole derivatives), risk of cardiovascular diseases (trimethylamine N-oxide), hepatic diseases (phenylacetate, acetaldehyde), diseases of central nervous system (4-ethylphenyl sulfate) [7].

Modification or modulation of microbiome implies the impact of any intervention aimed at successful and beneficial changes in disturbed or depleted microbiota for the benefit of human health. The objective of microbiome modification is as follows: to increase the quantitative composition of microbiota, to change the relative distribution of bacterial species or strains, their metabolic activity, virulence, bacterial antigens, ability to form biofilms, etc. However, it should be noted that it is a complex and dynamic individual ecosystem that is not fully understood yet. Simplified ideas about the potential effect of prebiotics, probiotics and other components on gut microbiome do not reflect the real matter of the issue and can have unpredictable effects [5].

## Microbial interactions and axes of interactions between gut microbiota and other biotopes

The stability of gut microbiome and its tolerance by host organism is provided by several mechanisms, in particular, the spatial separation of microorganisms from the mucous membrane itself by a layer of mucus, as well as the synthesis of antimicrobial peptides, secretory immunoglobulins A, that contribute to removal of microorganisms from intestinal epithelial surface [3]. A stable microbial community can resist the invasion of foreign bacteria and the spread of opportunistic microorganisms using the mechanisms of colonization resistance. One of the ways is the formation of gut biofilms that results in the protection of bacteria from aggressive factors and the improvement of exchange of nutrients between bacteria and the host organism. The formation of gut biofilms by beneficial bacteria is being studied, however, the development of biofilms in pathological conditions, for example, *Bacteroides fragilis* in inflammatory bowel diseases, is deemed proven [1, 3].

The interaction between microorganisms can be positive (mutualism, synergism, commensalism), negative (amensalism: predation, parasitism, antagonism, competition), and neutral [3]. A special type of interaction between gut microbes is known as cross feeding, or syntrophy, when microorganisms create highly efficient cooperative metabolic pathways and exchange nutrients or other compounds. Gut microorganisms can use each other's complementary abilities to break down nutrients and produce vitamins that support the production of metabolites for mutual exchange. For example, *Akkermansia muciniphila* degrades glycans to oligosaccharides (galactose, fructose, mannose) and SCFAs (acetate, propionate, 1,2-propanediol) that are used by other bacteria (*Faecalibacterium prausnitzii, Anaerostipes caccae, Eubacterium halii)* for the synthesis of vitamin $B_{12}$ and SCFAs (acetate, propionate, butyrate) [8]. Bifidobacteria populations can also interact with each other, as well as

with other representatives of gut microbiota, through cross-feeding when they collectively use their saccharolytic properties to metabolize carbohydrates. Interspecies hydrogen transfer is another example of a mutually beneficial process in the gut when one microorganism decomposes organic compounds such as polysaccharides and releases reducing equivalents in the form of hydrogen that are used by other microorganism as an electron donor [3]. Amensalism is expressed in the competition for nutrients, as well as the synthesis of bacteriocins and toxic metabolites. For example, microcins synthesized in the gut by *Escherichia coli*, reduce the activity of other reperesentatives of *Enterobacteriaceae* family [9]. Bacteria can use signaling molecules that function as a communication system to inform about cell density, diffusion conditions and species composition of the environment allowing microorganisms to collectively change their behavior in response to changes [10]. Such communication within and between different types of microorganisms can impact the network of interactions in the ecosystem and, therefore, change the composition of microbiota [1–3].

The importance of gut microbiota in the development of pathological conditions of many organs and systems became apparent after the discovery of the following communication axes: "gut — brain", "gut — liver"", "gut — respiratory system", "gut — urogenital tract"; so, the gut became the main organ responsible for human health. Results of studies of the interconnection between gut microbiota and the microbiota of other biotopes can affect the strategy of managing patients with chronic diseases and expand the possibilities for their prevention and treatment [3, 11]. For example, in the study performed by Dubourg G. et al. (2020), it was found that 64 % of bacterial species in urine samples coincide with the identified species in gut microbiota [12]. Moreover, the reduced incidence of recurrent urinary tract infections after fecal microbiota transplantation may support the hypothesis of the interconnection between gut microbiota and urobiota [11, 13]. Modification of gut microbiota can possibly result in a change in the quantitative and qualitative composition of the microbiota of urinary tract, vagina and other localizations.

## Modification of gut microbiome

Bacteria can be described as a highly flexible and adaptive system. Lifestyle modifications and clinical interventions can alter gut microbiome (Figure 1). It should be considered that the measures aimed at one or several types of bacteria (prescription of antibacterial agents, probiotics, synbiotics) can indirectly affect other types of microorganisms due to the close relationship between them [2, 3].

When modulating the microbiome, special attention should be paid to potential negative consequences, such as the increase in the proportion of pathogenic microorganisms, transfer of antibiotic resistance, or induction of pathological host reactions.

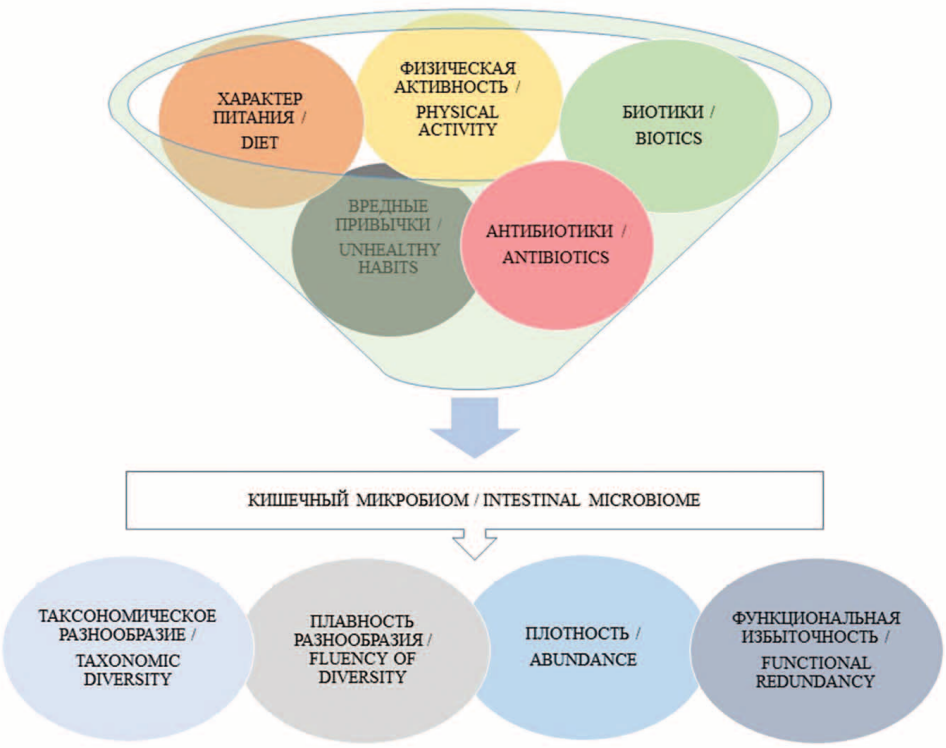


***Figure 1.*** *The main factors and parameters of modification of the intestinal microbiome*

## Lifestyle modification

The results of many studies demonstrate the relationship between nutrition, physical activity, presence of pernicious habits (smoking, alcohol consumption, drug abuse) and gut microbiome, as well as other biotopes (of skin, oral cavity, urogenital tract, etc.) [14–32].

### *Nutrition*

The interconnection between nutrition, microbiota and human health is undeniable. Diet is one of the key determinants of microbiome variability; it can be an important link between nutrition and human health. Long-term diets are associated with dynamic changes in the composition and metabolic activity of gut microbiome, while short-term diets are not enough to cause serious changes in the ecosystem [14].

General diet, intake and ratio of macro- and micronutrients affect the species diversity and metabolic profile of gut microbiome. Alongside with the macronutrients fermentation products (SCFAs, branched chain fatty acids, phenolic metabolites, etc.), there are numerous metabolites developed as a result of the bioconversion of food substrates, minor components of food, and trace elements that can potentially impact on human health [2, 3, 14].

The effect of carbohydrates, consumed with food, on microbiome is due to their characteristics and the features of human digestion. Indigestible dietary fibers, by definition, are not digested by human saccharolytic enzymes; accordingly, they subject to fermentation in large gut, and if resistant to fermentation, will be excreted with feces. Dietary fibers affect the species composition and metabolic profile of gut microbiome. Individuals with high intake of plant fiber demonstrate a predominance of phylum bacteria *Prevotella* over *Bacteroides*, high content of *Bifidobacterium spp*. and *Lactobacillus spp.* compared to those with low-fiber diets or placebo [14, 15]. When the amount of indigestible dietary fiber is reduced, bacteria can switch to alternative energy sources from the diet or can degrade host glycans in the intestinal mucus layer contributing to the development of inflammatory conditions associated with allergic, infectious and autoimmune diseases [16].

Resistant starch that is not digested in small gut can provide as much carbohydrate substrate for microbiota as dietary fiber. The changes in gut microbiome in response to the consumption of different types of resistant starch (granular, modified, etc.) may depend on the original human microbiome profile. Similarly, natural non-absorbable sugar alcohols that are added to food as low calorie sweeteners provide a substrate for intestinal fermentation. The increased amount of *Bifidobacterium spp*. is observed after the consumption of isomaltose, maltitol, lactitol, and xylitol [17]. High carbohydrate diets promote the growth of *Clostridium cluster XVIII*, *Lachnospiraceae* and *Ruminococcaceae* [5].

In individuals with high fat intake (69.5% fat as the energy source), the composition of gut microbiota is altered due to the increase in bile-resistant bacteria including *Alistipes, Bilophia, Bacteroides* and the decrease in the number of bacteria with carbohydrate substrate — *Roseburia, Eubacterium, Ruminococcus* [18]. A low-fat diet (20% fat as energy source) increases the alpha diversity of gut microbiota and the relative amount of *Blautia* and *Faecalibacterium* [14, 19].

The quantity and quality of proteins consumed (red meat protein, white meat protein, non-meat protein sources) can modulate gut microbiome. For example, high-protein diet with limited calorie intake in overweight patients results in a decreased amount of *Eubacterium rectale* and *Collinsella aerofaciens* [14]. However, the changes in the microbiome of these patients can hardly be associated with protein intake only, since other factors, in particular, decreased energy intake, could affect microbial diversity.

Despite the small number of studies on the modifying function of vitamins and minerals on gut microbiome, there is no doubt that they are important for the symbiotic relationship between the host and microorganisms, and play a certain role in the development of gut microbial composition. Vitamin K and B vitamins are usually found in the diet, however, they can be synthesized by intestinal bacteria and then distributed between species via cross-interaction [1]. Competition for minerals that are essential cofactors for a number of human and microbial metabolic processes can also determine the species that can grow and survive in gut ecosystem. For example, a high level of iron in the gut is associated with the increased growth of pathogenic microorganisms [20].

Reducing the risk of chronic disease is associated with healthy diets, such as the Mediterranean diet, and plant-based diets [21, 22].

The Western diet is characterized by high intake of meat, saturated fats, sugars, processed grains, and a low consumption of fibers. The Western diet in men living in communities is associated with a higher amount of microorganisms such as *Alistipes, Anaerotruncus, Collinsella, Coprobacillus, Desulfovibrio, Dorea, Eubacterium* and *Ruminococcus* [14, 23]. At the same time *Prevotella copri* that is aimed at the digestion of carbohydrates is much less common in the Western population individuals [24].

The Mediterranean diet is characterized by a high consumption of vegetable products such as fruits, vegetables, whole grains and legumes, moderate consumption of fish, poultry and wine, olive oil as the main source of fat, and dairy products in small amounts. The Mediterranean diet in overweight and obese people results in the increase in *Faecalibacterium prausnitzii* (taking part in the synthesis of a SCFA — butyrate) and a decrease in *Ruminococcus gnavus* (possibly producing a pro-inflammatory effect) [14, 25].

Vegetarian diets are characterized by high consumption of plant-based foods, and, correspondingly, fiber. Vegan diets are free from any animal products. Pregnant

women practicing a vegetarian diet demonstrate the increase in *Roseburia* genus *Lachnospiraceae* family bacteria and the decrease in the number of *Collinsella* and *Holdemania* [26]. Vegans and vegetarians have a higher diversity of microbial genes and proteins involved in the hydrolysis of polysaccharides, proteins and the synthesis of vitamins [14, 27].

Very low-carbohydrate ketogenic diets are characterized by high intake of fat, moderate intake of protein, and very low intake of carbohydrates that results in the development of ketosis. A ketogenic diet in children with drug-resistant epilepsy can result in modification of gut microbiome, i.e. a decrease in the number of bacteria of *Firmicutes* type, *Bifidobacterium*, *Eubacterium rectale, Dialister* families and an increase in *Bacteroides* bacteria [14, 28]. Elite athletes after ketogenic diets develop an increase in *Bacteroides* and *Dorea* bacteria of and a decrease in *Faecalibacterium* [29].

The modified Mediterranean ketogenic diet increases the amount of *Enterobacteriaceae* family bacteria, *Akkermansia, Slackia, Christensenellaceae* and *Erysipelotriaceae* genera, and results in the decreased number of *Bifidobacterium* and *Lachnobacterium* families bacteria. Interestingly, that this type of diet is associated with a decrease in Alzheimer's biomarkers in cerebrospinal fluid [14].

The Paleolithic diet is characterized by the consumption of grass-fed meat, fish, seafood, fresh fruits and vegetables, eggs, nuts and seeds, and vegetable oils. In the Paleolithic diet followers, there is an increase in the number of bile-resistant bacteria — similarly to the individuals with high fat intake [14, 18].

Thus, the type of human nutrition undoubtedly affects the species diversity and metabolic potential of intestinal microbiome. Healthy diet with much plant foods maintains favorable microbiome profiles with a higher content of species capable of fermenting carbohydrates. However, due to the high level of interindividual variability of human microbiome, no well-defined microbiome profiles that correspond to specific diets or nutrient intake have yet been established. A promising area of research is the study of the role of diets in the modification of microbiota, metabolome, aimed at the treatment and prevention of chronic diseases. To develop clinically relevant dietary recommendations for enhancing the gut microbiome stability, microbiome studies should integrate population epidemiology with narrow but in-depth clinical studies of personalized nutrition, including approaches that help in understanding the mechanisms of individual response to modulating interventions. Moreover, the future studies should go beyond the single nutrient approach and focus on the effects of the entire diet on gut microbiome [1, 14].

### *Physical activity*

Physical activity is one of the main factors that has an independent impact on the composition and metabolic activity of gut microbial communities what results in the overall increase in biodiversity, the increase in the number of bacteria that synthesize SCFAs or utilize lactate, alongside with simultaneous reducing potential pathobionts. Some of these changes are persistent and do not depend on age, weight, or food consumption [5, 30, 31].

The potential mechanisms underlying the modification of gut microbiome during physical activity are diverse: the increased gut motility, intestinal nervous system activity, mucus secretion, immunity of intestinal mucosa, integrity of the mucous barrier, availability of nutrients, changes in blood circulation, intestinal pH, enterohepatic circulation of bile acids, ability to produce biofilms [30, 32].

## Clinical interventions

Clinical interventions can produce diverse changes in gut microbiome. On the one hand, the prescription of antibacterial agents results in collateral and often negative changes in gut microbiome and the development of antibiotic-resistant strains. On the other hand, the revealed protective effect of beneficial microflora and its bioactive metabolites has resulted in the emergence of various functional biotics, such as probiotics, prebiotics, synbiotics, postbiotics, next-generation probiotics, psychobiotics, oncobiotics, pharmabiotics, smart probiotics and metabiotics that are aimed at human health benefits and found wide application in the clinical practice.

### *Antibacterial agents*

Antibiotic therapy causes one of the most serious disorders of intestinal microbiome affecting not only on the pathogens it is deigned against, but other microbiota representatives as well. For example, antibiotics with significant anti-anaerobic effect cause a long-term decrease in the relative amount of *Bifidobacterium* (ciprofloxacin, clindamycin) and *Bacteroides* (clindamycin) [33]. β-lactams and fluoroquinolones result in the increase in the ratio of *Bacteroides/Firmicutes* phylums and the decrease in microbial diversity due to the reduction of basic phylogenetic microbiota from 29 to 12 microbial taxa [34]. As a result, microbial diversity and functional potential of gut microbiota is decreased [1–4].

Oral administration of antibacterial agents directly affects the growth of microorganisms in the gut and results in the decreased thickness of parietal mucus, changes in intestinal pH, decreased synthesis of antimicrobial peptides, SCFA (butyrate), and immune tolerance [3]. For example, ampicillin is associated with a decrease in the number of acid-producing bacteria and changes in intestinal pH from slightly acidic to neutral; oral administration of vancomycin results in the decrease in the relative amount of *Coprococcus eutactus* and *Faecalibacterium prausnitzii* — butyrate producers [35]. The protective role of SCFAs and the acidic environment of

intestine is to maintain homeostasis by counteracting the massive reproduction of such dangerous bacteria as *Klebsiella* [3].

The consequence of changes in gut microbiota after the use of antibiotics may be decreased resistance to colonization by pathogens what increases the susceptibility to infections [36]. An example is the antibiotic-associated diarrhea caused by a nosocomial pathogen *Clostridioides difficile* [1]. Another problem may be the emergence of antibiotic-resistant microorganisms that can persist in the microbial community for a long time after the end of antibiotic therapy and cause difficulties in the management of bacterial infections [3, 37].

The studies of duration and nature of changes in gut microbiome after antibacterial treatment are ongoing. According to Kriss M. et al. (2018), the bacterial diversity decreases withing a week following the antibiotic therapy, after that the restoration starts, however, it does not return to its baseline state [38]. Long-term (over several years and decades) study of the species composition of gut microbiota and antibiotic resistance of bacteria in humans after administration of antibacterial agents is of interest.

The grade of damage to the representatives of gut microbiota depends on the chemical nature, the target spectrum of action, pharmacokinetic and pharmacodynamic properties, dose and duration, route of administration and excretion of a drug, microbial diversity, functional redundancy, metabolic flexibility of gut microbiome before treatment, immunological tolerance, mucus thickness, the degree of blood supply and oxygen saturation, the level of intestinal motility, and some other factors. In this regard, the degree and direction of changes in response to the treatment with antibacterial agents are highly individual [35].

Reasonable prescription of antibacterial agents and early de-escalation of antibacterial therapy can reduce the adverse effects of antibiotics on human microbiome. Moreover, alternative methods of antimicrobial therapy are currently being developed; they are aimed at the selective destruction of infectious agents with no damage to other microbiome representatives.

## *Prebiotics*

Prebiotics are the substances that cause specific changes in the composition and/or function of microbiota to benefit human health. The most important groups of prebiotics include fructooligosaccharides and galactooligosaccharides, that, when taken orally, are selectively fermented by intestinal microorganisms to SCFAs, mainly acetate, propionate and butyrate; these substances interact with free fatty acid receptors and thus modulate the metabolic activity of intestinal colonocytes and enterocytes, reinforce the integrity of gut epithelium, maintain intestinal homeostasis, affect the immune system, and change the epigenetic signature of the host [3, 6, 39].

## *Probiotics*

Probiotics are the preparations of live microorganisms that are aimed at benefiting the health of human body when used in appropriate amount [3, 39, 40].

The wholesome functions of probiotics include: maintaining colonization resistance, improving metabolism and utilization of end products of energy substrates breakdown, producing substances necessary for human body, regulating local immunity, restoring the intestinal barrier, improving the metabolism of drugs and xenobiotics, regulating the metabolism of bile acids, restoring native microbiota. Antagonistic activity of probiotics against a wide range of pathogenic microorganisms can be mediated by the synthesis of antimicrobial compounds such as organic acids, hydrogen peroxide, SCFAs, carbon dioxide, diacetyl, reuterin, acetaldehyde, phenyl lactic acid, bacteriocins and bacteriocin-like inhibiting compounds, biosurfactants, and other low molecular compounds [6].

The adhesion of probiotics that was previously considered an important beneficial property of a bacterium is now considered as a negative feature of strain, since many adhesins are considered to be pathogenic factors, and the adhesion of probiotic bacteria to gut epithelium can be carried out only in the absence of mucous layer what is typical for pathology.

Commonly used probiotics include *Lactobacillus spp., Bifidobacterium spp., Streptococcus spp., Bacillus spp.* bacteria , individual strains *Escherichia Coli* and *Saccharomyces* fungi. Probiotics have a broad spectrum of action; they can be monocomponent or multicomponent. Zendeboodi F. et al. (2020) proposed a new concept of true probiotics and pseudoprobiotics based on their metabolic activity. It lies in the fact that true probiotics include viable microorganisms that can synthesize biochemical metabolites, and pseudoprobiotics consist of spores and bacteria that have undergone any type of exposure (temperature, pH, lack of nutrients, osmotic pressure, etc.) that results in metabolic rest [39, 41].

The results of clinical trials revealed the effectiveness of the use of certain probiotic strains in most patients with irritable bowel syndrome and inflammatory bowel diseases [6, 42]. However, depending on the individual characteristics of human body and comorbidities, probiotics can, in rare cases, produce negative effect on human body, alongside with positive or neutral effects [3, 6, 42]. In this regard, the prescription of probiotics should be justified and individual-based, including the monitoring of adverse reactions.

## *Synbiotics*

The concept of synbiotics is based on a combination of prebiotics (substances) and probiotics (microorganisms) that increases the viability, survival and successful implantation or colonization of probiotic bacteria in gut. For example, the combination of bifidobacteria or

lactobacilli with fructooligosaccharides, inulin and oligofructose is currently well studied. A synbiotic combination has a synergistic effect inhibiting the growth of pathogens and enhancing the growth of beneficial microorganisms. Prebiotics, in combination with probiotics, improve the absorption of minerals, lower cholesterol levels, normalize metabolic profile and prevent the development of type 2 diabetes, obesity and inflammation. Despite the numerous positive effects of synbiotics, their development require careful selection of probiotics and prebiotics to ensure their maximum beneficial effect on human health [3, 6, 39].

## *Pharmabiotics*

Pharmabiotics are the wholesome commensal microbes, yeasts, bacteriophages, or their derivative biomolecules (vitamins, SCFAs, γ-aminobutyric acid, serotonin, catecholamines, acetylcholine, conjugated linoleic acid, antimicrobial, exopolysaccharides) clinically proven to be effective and safe [6, 39].

## *Postbiotics (meta-, paraprobiotics)*

Postbiotics are non-viable bacterial products or metabolic products of microorganisms that display biological activity in the host body. Postbiotic molecules are a mixture of metabolic products from live probiotic bacteria such as vitamins, SCFAs, extracellular-secreted biosurfactants, secreted proteins or peptides, organic acids, acellular supernatant, amino acids, and released components after bacterial lysis. Ultraviolet rays (5-30 min), heat inactivation (60-121°C /5-60 min), ionization (10 kGy), and sonication are used to obtain various postbiotic components [39].

Paraprobiotics are inactivated/non-viable microbial cells of probiotics containing teichoic acids, mucopeptides derived from peptidoglycans, surface proteins, polysaccharides such as exopolysaccharides, surface-protruding molecules such as pili, fimbriae, flagella, or crude cellular extracts that, when administered in sufficient quantities, provide benefit for human body [6, 39].

## *Fecal microbiota transplantation*

Fecal microbiota transplantation (FMT) is a medical procedure that is based on replacing the host microbiota with the microbiota of a healthy donor [3, 5, 43].

FMT can be considered as an alternative treatment for patients with *Clostridioides difficile*-associated infection, that refers to as recurrent if there were two episodes that required hospitalization, or three or more confirmed episodes of the disease, as severe — in the absence of response to standard treatment, and as fulminant — in cases when surgical interventions are impossible [44, 45].

FMT can be a high-potential method of managing many diseases and disorders associated with changes in gut microbiota, i.e. metabolic diseases, functional and inflammatory bowel diseases, hepatic diseases, autoimmune, hematological, neurodegenerative, allergic diseases, autism, malignant neoplasms, with resistance to antibacterial agents [3, 5, 44, 45]. However, FMT-associated adverse reactions should be taken into consideration (Fig. 2) [3, 6, 45].

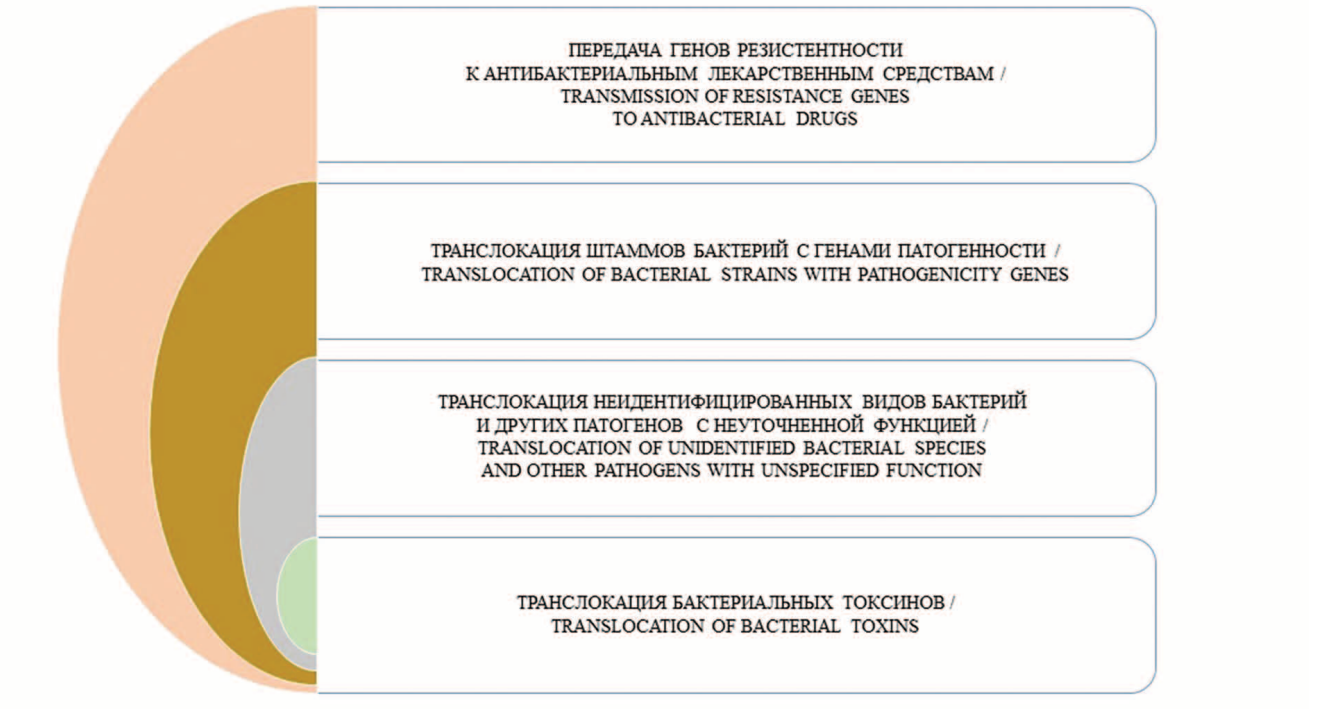


***Figure 2.*** *Potential negative consequences after fecal microbiota transplantation*

Thus, despite its proven effectiveness, FMT remains a complex and expensive procedure that carries risks of adverse collateral effects.

## High-potential trends of gut microbiome modulation

The most promising trends of gut microbiome modulation for therapeutic and prophylactic purposes are presented in Table 1 [3, 6, 46].

A promising method to reduce the adverse effects of FMT is the administration of microbial cocktails and autoprobiotics to the patient. The most appropriate microbial cocktails can include microorganisms of *Lachnospiraceae, Ruminococcaceae, Bacteroides* families [3]. Other types of microorganisms can be used depending on the final purpose. For example, the use of a microbial cocktail of three bacterial strains of fecal microbiota (genera *Escherichia, Bacillus, Enterobacter)* that metabolize urea and creatinine into amino acids, significantly decreases the concentration of urea and creatinine in the blood of animals and causes no side effects [47]. The effectiveness and safety of microbial cocktails in athletes and patients with various diseases is a promising trend to study [5, 48].

The wide use of antibacterial agents has resulted in the development of infections associated with the colonization of patients with antibiotic-resistant pathogens, for example, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, and extremely resistant enterobacteria. In connection with the high damaging potential of common antibacterial agents, alternative methods of targeted measures on pathogenic microorganisms are considered, i.e. targeted antibacterial therapy, small molecules, bacteriophages, CRISPR-CAS9 methods of genetic engineering [3].

## Practical importance of modifying gut microbiome

Rapid development of scientific knowledge and the large number of studies in the field of human microbiome, its characteristics, its role in human body, its relationship with the development of diseases will lead to the implementation into clinical practice of recommendations based on the methods of targeted effect on the patients' microbiome, for example, to prevent atherosclerosis , non-alcoholic fatty liver disease, to control the course of diabetes mellitus, to optimize the response to the treatment of cancer, to increase endurance and to accelerate recovery of athletes after exercises (Fig. 3) [3-5, 29-31].

The basic methods of affecting human microbiome will be lifestyle modification, specialized diets, administration of beneficial microbial communities, and personalized antibacterial treatment.

## Conclusion

Accumulation of new scientific knowledge has provided understanding of the role of gut microbiome as an organ that maintains and regulates the homeostasis in the human body, and participates in the pathogenesis of pathological conditions and diseases. The results of many studies revealed the relationship between the imbalance of gut microbiome and the development of somatic and mental diseases such as obesity, diabetes mellitus, asthma, allergic diseases, atopic eczema, non-alcoholic fatty liver disease, inflammatory bowel disease, multiple sclerosis, Alzheimer's disease, etc. [1-3, 11]. The role of gut microorganisms in the development of ankylosing spondylitis, systemic lupus erythematosus, psoriasis, bacterial vaginosis, and urinary tract infections is under

***Table 1.*** *Prospects of microbiome-associated interventions*

| Type of the intervention | The principle of the intervention | Potential effects of the intervention |
|---|---|---|
| Microbial cocktails | administration to the patient of a prepared and purified mixture of beneficial types of the microbiome | - alternative fecal microbiota transplantation<br>- effect on metabolic processes |
| Personalized symbiotic therapy (autoprobiotics) | isolation of pure cultures of individual types of the microbiota, their genetic analysis, cultivation outside the body and administration back into the human intestine | - alternative fecal microbiota transplantation<br>- prevention and diseases control |
| Next-generation probiotics | the use of non-traditional intestinal commensal bacteria, such as *Akkermansia muciniphila, Faecalibacterium prausnitzii, Eubaterum hallii, Bacteroides fragilis*, clusters of Clostridium IV, XIVA and XVIII, etc. and their metabolites | expanding the potential of probiotics |
| Bacterial ligands | administration of microbial ligands — agonists of Toll-like receptors — 4, 5, 7/8 | restoration of innate immunity and protection against infection |
| Small molecules | administration of thiopeptides — lactocillin, ribocil, bacteriocins (turicin CD, avidocin CD) | targeted exposure to pathogenic microorganisms |
| Targeted antibacterial therapy | administration of the conjugated complex «antibiotic-antibody against pathogen» | targeted exposure to pathogenic microorganisms, including intracellular |
| CRISPR-CAS9 methods of genetic engineering | CRISPR-CAS9 is a bacterial immune system that can be modified by molecular genetics methods | targeted exposure to pathogenic microorganisms, including those resistant to antibiotics |

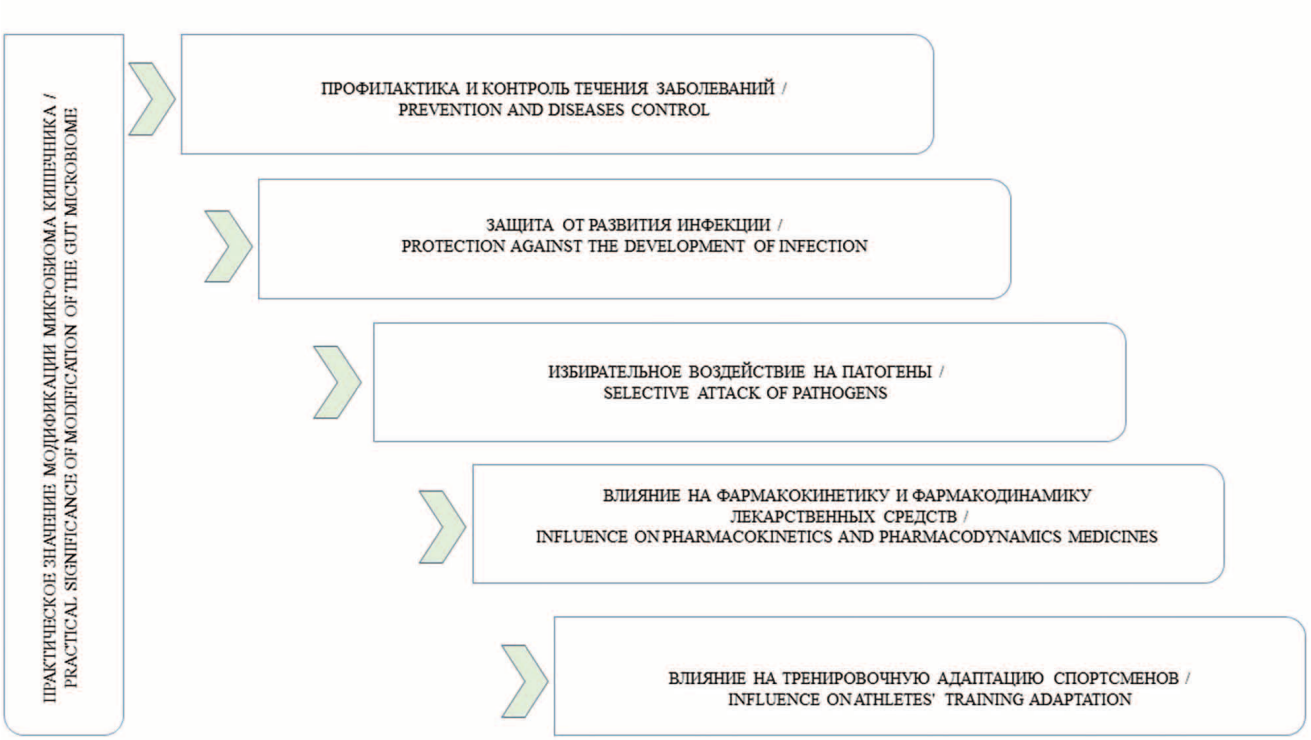


***Figure 3.*** *Potential practice-oriented prospects for modification of the gut microbiome*

discussion [3, 4]. It has been proven that gut microbiota is involved in the biotransformation of medications, increasing or, on the contrary, reducing their effectiveness [3]. Therefore, in the near future, studying the pharmacokinetics or computer modeling of new agents will require considering the characteristics of gut microbiota.

The concept of the parameters that can be used to describe a normal microbiome is currently only being developed. A large number of microorganisms and their role in human body remain unidentified. The measures aimed at modifying gut microbiome are at the core of microbiome-associated medicine that is an actively developing branch of science. However, in real practice, it is not always possible to assess the range of potential interactions between an intervention and the host's diet, genome, immune system, local commensal bacteria which can result in the lack of a proper response to the intervention or to the development of negative effects. In this regard, the unique projects aimed at studying gut microbiome and the possibilities of its programmed modulation in human diseases are the basis for new knowledge about the microbiome that will contribute to the development of personalized medicine.

**Вклад авторов:**

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2022-12-5-352-362
EDN: GYWNEQ
УДК 616.36-002.1-004.4-08:616.351-089.819.5

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# ПАТОФИЗИОЛОГИЧЕСКИЕ ПРЕДПОСЫЛКИ И ТЕРАПЕВТИЧЕСКИЙ ПОТЕНЦИАЛ ТРАНСПЛАНТАЦИИ ФЕКАЛЬНОЙ МИКРОБИОТЫ ПРИ ТЯЖЁЛОМ АЛКОГОЛЬНОМ ГЕПАТИТЕ

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# Pathophysiological Prerequisites and Therapeutic Potential of Fecal Microbiota Transplantation in Severe Alcoholic Hepatitis

**Резюме**

Из-за высокой заболеваемости и смертности проблема тяжёлого алкогольного гепатита до настоящего времени не теряет своей актуальности. При отсутствии специфической терапии, связанная с ним одномесячная выживаемость невелика, а показатели летальности достигают 30-50 %. Хотя назначение кортикостероидов является научно обоснованным лечением первой линии тяжёлого алкогольного гепатита, кратковременный ответ наблюдается примерно у 60 % пациентов, без преимуществ в долгосрочной выживаемости по сравнению с плацебо. Следует также учитывать возникновение неблагоприятных побочных реакций на их применение примерно у 50 % пациентов, а также риск осложнений, в частности, бактериальных и грибковых инфекций. Препараты второй линии, например, пентоксифиллин, этанерцепт, инфликсимаб, N-ацетилцистеин и др. при тяжелом алкогольном гепатите улучшения клинического исхода не показали. В современных руководствах обсуждается целесообразность трансплантации печени у тщательно отобранных, не отвечающих на лечение кортикостероидами больных тяжелым алкогольным гепатитом. Тем не менее, из-за многочисленных противоречий говорить о внедрении данного подхода в клиническую практику ещё рано. В последние годы были достигнуты определённые успехи в понимании патофизиологических механизмов развития алкогольного гепатита, что послужило толчком для новых направлений его патогенетической терапии. Одно из таких направлений — разработка и совершенствование методик, обеспечивающих кишечный эубиоз, в частности, посредством трансплантации фекальной микробиоты. Целью обзора было описать патофизиологические предпосылки и терапевтический потенциал трансплантации фекальной микробиоты от здоровых доноров больным тяжёлым алкогольным гепатитом. Экспериментальные исследования показали положительное влияние трансплантации фекальной микробиоты на микрофлору кишечника, которое приводило к ослаблению индуцированного алкоголем повреждения печени. У пациентов с тяжёлым алкогольным гепатитом данная методика уменьшала выраженность его симптоматики и способствовала увеличению выживаемости по сравнению с получавшими кортикостероиды. Эти предварительные результаты вселяют оптимизм и создают условия для дальнейших клинических испытаний с включением большой когорты больных тяжёлым алкогольным гепатитом для определения групп пациентов, кому трансплантация фекальной микробиоты будет наиболее эффективна с минимальным риском осложнений.

***Ключевые слова:*** *тяжёлый алкогольный гепатит, патогенез, терапия, микробиота кишечника, трансплантация фекальной микробиоты*

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**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 02.04.2022 г.

Принята к публикации 11.05.2022 г.

**Для цитирования:** Гарбузенко Д.В. ПАТОФИЗИОЛОГИЧЕСКИЕ ПРЕДПОСЫЛКИ И ТЕРАПЕВТИЧЕСКИЙ ПОТЕНЦИАЛ ТРАНСПЛАНТАЦИИ ФЕКАЛЬНОЙ МИКРОБИОТЫ ПРИ ТЯЖЁЛОМ АЛКОГОЛЬНОМ ГЕПАТИТЕ. Архивъ внутренней медицины. 2022; 12(5):352-362. DOI: 10.20514/2226-6704-2022-12-5-352-362 EDN: GYWNEQ

**Abstract**

Due to the high morbidity and mortality, the problem of severe alcoholic hepatitis has not lost its relevance to date. In the absence of specific therapy, the associated to him one-month survival rate is low, and mortality rates reach 30-50 %. Although the use of corticosteroids is a scientifically proven first-line treatment for severe alcoholic hepatitis, a short-term response is observed in approximately 60 % of patients with no long-term survival benefits compared to placebo. It should also take into account the occurrence of adverse side reactions to their use in about 50 % of patients, as well as the risk of complications, in particular, bacterial and fungal infections. The second-line drugs, for example, pentoxifylline, etanercept, infliximab, N-acetylcysteine, etc. in severe alcoholic hepatitis did not show an improvement in the clinical outcome. The modern guidelines discuss the feasibility of liver transplantation in carefully selected patients who do not respond to corticosteroid treatment with severe alcoholic hepatitis. Nevertheless, due to numerous contradictions, it is too early to talk about the introduction of this approach into clinical practice. In recent years, some progress has been made in understanding the pathophysiological mechanisms of the development of alcoholic hepatitis, which served as an impetus for new directions of its pathogenetic therapy. One of them is the techniques that provide intestinal eubiosis, in particular, through the fecal microbiota transplantation. The purpose of the review was to describe the pathophysiological prerequisites and therapeutic potential of fecal microbiota transplantation from healthy donors to patients with severe alcoholic hepatitis. Experimental studies have shown a positive effect of fecal microbiota transplantation on the intestinal microflora, which led to a weakening of alcohol-induced liver damage. In patients with severe alcoholic hepatitis, it improved the severity of its symptoms and contributed to increased survival compared to those receiving corticosteroids. These preliminary results are encouraging and create conditions for further clinical trials involving a large cohort of patients with severe alcoholic hepatitis, which will allow us to identify those for whom fecal microbiota transplantation will be most effective with minimal risk of complications.

***Key words:*** *severe alcoholic hepatitis, pathogenesis, therapy, gut microbiota, fecal microbiota transplantation*

**Conflict of interests**

The authors declare no conflict of interests

**Sources of funding**

The authors declare no funding for this study

Article received on 02.04.2022

Accepted for publication on 11.05.2022

**For citation:** Garbuzenko D.V. Pathophysiological Prerequisites and Therapeutic Potential of Fecal Microbiota Transplantation in Severe Alcoholic Hepatitis. The Russian Archives of Internal Medicine. 2022; 12(5):352-362. DOI: 10.20514/2226-6704-2022-12-5-352-362 EDN: GYWNEQ

AH — alcoholic hepatitis, ALT — alanine aminotransferase, AST — aspartate aminotransferase, CTP — Child-Turcotte-Pugh score, DAMPs — damage-associated molecular patterns, FDA — US Food and Drug Administration, FMT — fecal microbiota transplantation, IL — interleukin, LPS — lipopolysaccharides, MDF — modified Maddrey's discriminant function, MELD — model for end-stage liver disease, PAMPs — pathogen-associated molecular patterns, TLR — toll-like receptors

# Introduction

Alcoholic hepatitis (AH) is a syndrome characterized by the development of acute-on-chronic liver failure caused by long-lasting and active intake of alcohol. Its specific clinical signs include: the progressive jaundice accompanied by fever (even with no infection), malaise, weight loss and nutritional deficiency, with or without other signs of hepatic decompensation (for example, ascites and/or encephalopathy). Laboratory test results in AH usually reveal neutrophilia, hyperbilirubinemia (>50 mol/L), increased level of aspartate aminotransferase (AST) in blood serum (however, rarely >300 IU/mL), with AST/ALT (alanine aminotransferase) ratio normally exceeding 1.5–2.0. In severe cases, increased prothrombin time, hypoalbuminemia and thrombocytopenia are often observed. Such histological signs as ballooning degeneration of hepatocytes, with amorphous eosinophilic inclusions, termed Mallory-Denk bodies, surrounded by neutrophils, tubular and/or ductal cholestasis, fibrosis, and megamitochondria are considered to be independent predictors for short-term prognosis [1]. Infectious complications that develop in about a half of patients have an adverse effect on AH outcome [2]. The presence of multiple organ failure predicts one-month mortality rate 35-50 %, another 50 % of survivors also die within 12 moths [3].

Generally accepted predictive model for assessing AH severity is Maddrey's discriminant function (DF).

In its modified version (MDF), the threshold value of 32 allows the identification of patients with severe hypertension and usually is a value used to start specific therapy. If not treated, the one-month mortality rate of patients with MDF ≥32 is 30-50 %, while in MDF <32 it is below 10 %. Moreover, it was found that MELD (Model for End-stage Liver Disease) score ≥21 suggests a high risk of 90-day mortality, and patients with MDF ≥32 and Glasgow score ≥9 have a poor prognosis and 84-day survival when treated with corticosteroids. ABIC (Age — Bilirubin — International Normalized Ratio — Creatinine) score allows stratification of patients with AH into the groups of low, medium and high risk of death within 90 days [4, 5].

Corticosteroids are an evidence-based first-line therapy for severe AH, although their effectiveness is disputable [6]. A short-term response to treatment with corticosteroids is observed in about 60 % of patients with no advantages for long-term survival over placebo. The important issues associated with their use include adverse reactions (in about 50 % of patients) and the risk of complications, in particular, of bacterial and fungal infections. Second-line agents, for example, pentoxifylline, etanercept, infliximab, N-acetylcysteine, etc. in severe AH demonstrated no clinical outcome improvement [7]. Current guidelines discuss the advisability of liver transplantation in carefully selected patients with severe AH that are nonresponsive to corticosteroids. Nevertheless, due to many contradictions, it is prematurely to speak of the implementation of this approach in clinical practice [8].

Considering the urgency of this issue, new directions for the management of severe AH have been actively developed in the recent years. In particular, methods are studied that are related to the modulation of gut microbiota that is the first metabolically active site of the interaction of environmental factors with the human body and plays an important role in the development of various diseases, including AH. Hence, the provision of intestinal eubiosis, for example, with probiotics, prebiotics, or with fecal microbiota (FM) transplantation can be a pathogenetically justified method of AH management [9].

The use of fecal microbiota for medicinal purposes has been known since the ancient times: as early as the in 4th century AD, traditional Chinese medicine practitioners prescribed a suspension of human feces for the management of food poisoning or severe diarrhea. However, the successful use of fecal enemas in patients with severe pseudomembranous enterocolitis was first described in early 1950s. [10]. Since then, an active study of this technique has started. In the last decade, FMT was actively implemented into clinical practice and has already been approved by the US Food and Drug Administration (FDA) for the management of refractory *Clostridium difficile* infection [11]. Currently, good preliminary results of FMT were obtained in patients with gastrointestinal and other systems diseases (Table 1) [12].

***Table 1.*** *Experience of fecal microbiota transplantation in various diseases [12]*

| Disease | Level of Evidence | Evidence base of scientific research |
|---|---|---|
| *Clostridium difficile* infection | | |
| *Clostridium difficile*/ | | |
| Recurrent *Clostridium difficile* infection | I | Multiple meta-analyses of RCTs (benefit) |
| Severe *Clostridium difficile* infection | III-2 | Retrospective cohort study (no RCT data) |
| Primary *Clostridium difficile* infection | II | RCTs (likely equivalence to standard antibiotics) |
| Inflammatory bowel disease | | |
| Ulcerative colitis induction therapy | I | Multiple meta-analyses of RCTs (benefit) |
| Ulcerative colitis maintenance therapy | IV | Case reports |
| Crohn's disease | III-2 | Multiple meta-analyses of RCTs (benefit) |
| Pouch ileitis (pouchitis) | IV | Case series (one negative RCT) |
| Microscopic colitis | IV | Case series |
| Functional gastrointestinal disorders | | |
| Irritable bowel syndrome | II | RCTs (mixed results; systematic review negative) |
| Functional constipation | I | Systematic review of RCTs (heterogeneity) |
| Multi-drug — resistant microorganisms eradication | III-2 | Case control study (RCT negative) |
| Checkpoint inhibitor colitis | IV | Case series |
| Augmenting cancer therapeutics | IV | Case series |
| Metabolic syndrome | IV | Case series (RCTs negative for weight loss) |
| Neurologic and psychiatric disorders | | |
| Autism | II (abstract) | RCT (abstract form only) |
| Parkinson's disease | IV | Case series |
| Schizophrenia, Alzheimer's, multiple sclerosis, anxiety and depression | IV | Case series |

**Note:** The level of evidence is based on criteria developed by the National Health and Medical Research Council of Australia; RCTs — randomized controlled trials

Despite numerous unsolved challenges [13], there are many publications that describe technical and organizational issues related to it [14, 15]. It is assumed that FMT effectiveness is based on the development of a competitive environment in gut due to non-pathogenic microorganisms and their secretion of antimicrobial substances, such as bacteriocins. Furthermore, we should not exclude a positive effect of donor fecal material on the virome and gut microbiota, metabolism of short-chain fatty acids and several bile acids, as well as various immunological mechanisms [16].

The objective of this review was to describe the pathophysiological background and therapeutic potential of FMT from healthy donors to the patients with severe AH.

## The role of gut microbiota in human physiology

Gut microbiota is a microecosystem that is often considered as a human "virtual organ". It includes 100 billion bacteria of more than 500 different species. Gut microbiota genome, defined as gut microbiome, contains about 150 times as many genes as the human genome. Microbiota colonizes the gut immediately after the birth of a baby and is present in the human body throughout their life. Its composition varies depending on age, environment, physiological or pathological status [17].

Gut microbiota plays an essential role in human physiology, specifically:

- ferments indigestible food components;
- provides the host with useful metabolites such as short-chain fatty acids that can be a source of energy and have anti-inflammatory effect;
- contributes to the synthesis of several vitamins, including vitamin K and group B vitamins;
- protects intestinal barrier, for example, by enhancing the function of mucous layer;
- regulates immune function, in particular, by stimulating the development of lymphoid structure and increasing the level of involved enzymes and transcription factors;
- prevents the toxic components from entering gastrointestinal tract;
- suppresses some types of pathogenic bacteria [18].

## The significance of ethanol-induced changes in intestinal microbiota and increased permeability of intestinal wall in the pathogenesis of alcoholic hepatitis

It has been established that liver damage in AH, alongside with the direct effect of ethanol on hepatocytes, can be caused by an inflammatory reaction due to microorganisms, associated molecular structures and products of their metabolism that enter the liver as a result of ethanol-induced changes in gut microbiota and increased permeability of intestinal wall. Actually, acetaldehyde formed during ethanol oxidation, the accumulation of reactive oxygen species and lipid peroxidation cause apoptosis of hepatocytes and the release of extracellular vesicles that, together with interleukin (IL)-1β, affect other types of cells, including polymorphonuclear leukocytes, hepatic stellate cells and sinusoidal endothelial cells, contributing to a necroinflammatory response in liver tissue [19]. At the same time, ethanol suppresses the expression of a wide range of antimicrobial proteins and peptides of the innate immune system contributing to intestinal dysbiosis, bacterial overgrowth and bacterial translocation. As a result, pathogen-associated molecular patterns (PAMPs), in particular, lipopolysaccharides (LPS) of the cell wall of gram-negative bacteria enter the liver through portal vein where, through the LPS-binding protein, they bind to the CD14 receptor located on the membrane of Kupffer cells resulting in the activation of many genes of proinflammatory cytokines and exacerbates liver damage [20] (Fig. 1).

Ethanol-induced changes in gut microbiota are characterized primarily by a decreased number of various species of *Lactobacillus spp.* and *Ruminococcaceae spp.* that attach to epithelial cells and participate in protecting the body from pathogenic and invasive bacteria. Their fermentation products are short-chain fatty acids, in particular, butyrate and propionate that serve as a key energy substrate for both enterocytes and colonocytes [21]. Besides, by producing bacteriocins, *Lactobacillus spp.* suppress microorganisms of *Enterobacteriaceae* family, for example, *Salmonella* or *Shigella* [22]. Moreover, AH-related intestinal dysbiosis is manifested by a decreased level of anti-inflammatory bacteria *Clostridium leptum* and *Faecalibacterium prausnitzii*, as well as by increased level of *Streptococcaceae spp.*, *Bifidobacterium spp., Enterobacter spp., Veillonella spp., Fusobacterium spp., Actinomyces spp.* and *Proteobacteria*; this fact, along with decreased level of *Akkermansia muciniphila*, closely correlates with the liver disease severity [23-26].

Mice that received alcohol for three weeks demonstrated an overgrowth of bacteria in small intestine, dysbiosis in cecum, suppressed expression of genes and proteins of antimicrobial lectins Reg3β and Reg3γ in small intestine, decreased number of *Firmicutes* and increased number of *Bacteroidetes* and *Verrucomicrobia* [27].

The patients with alcohol abuse have a potentially more active pro-inflammatory gut microbiota with significant amounts of endotoxemic contributors *Proteobacteria*, *Clostridium spp.*, *Holdemania spp.* (*Firmicutes*) and *Sutterella spp.* and decreased number of anti-inflammatory bacteria *Faecalibacterium spp*. [28]. Their fecal samples demonstrated about 2,700 times as many *Enterococcus faecalis* as in non-alcoholic subjects. The studies revealed harmful effect of exotoxin cytolysin secreted by these bacteria on ethanol-induced liver

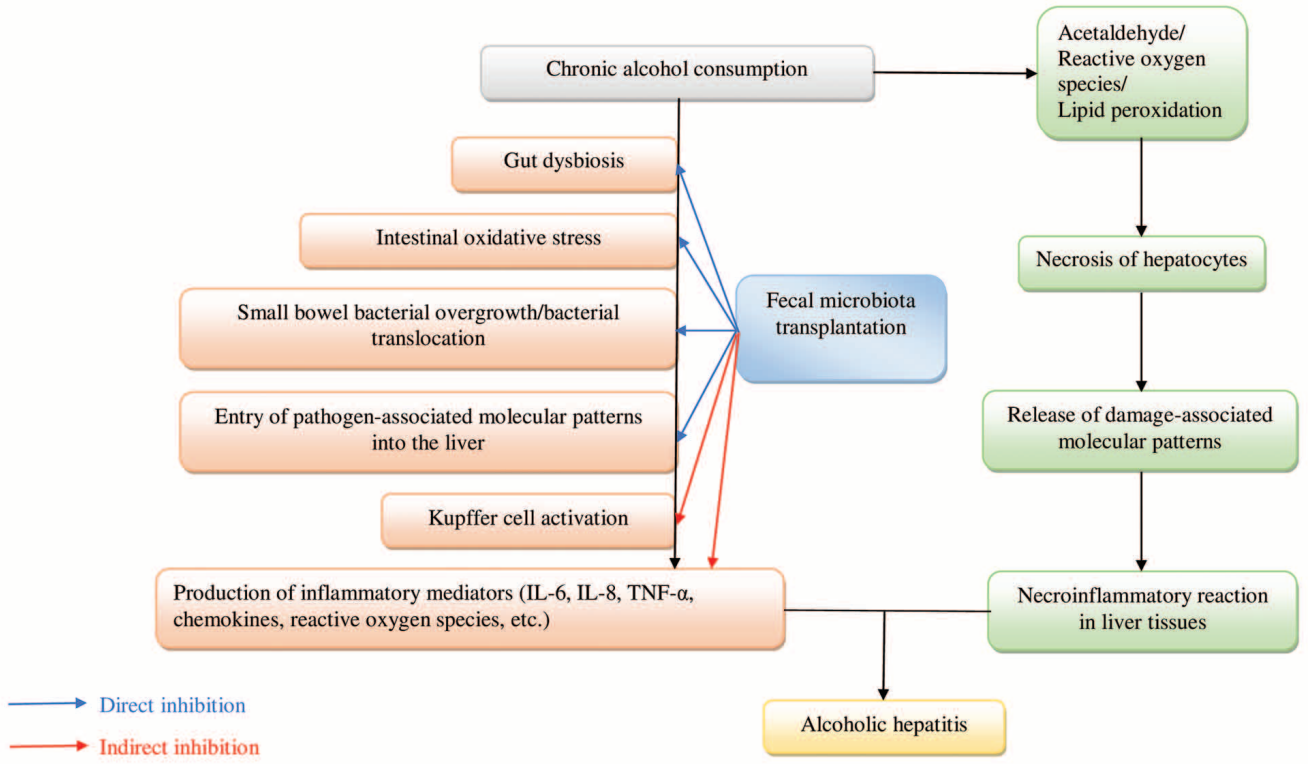


***Figure 1.*** *Potential mechanisms of the positive effect of fecal microbiota transplantation on key links in the pathogenesis of alcoholic hepatitis. IL-6 — interleukin-6; IL-8 — interleukin-8; TNF-α — tumor necrosis factor-alpha*

diseases, and found a correlation between the number of these microorganisms and the severity of AH and mortality of patients suffeting with it [29].

In the study performed by Sundaram V. et al. (2014) [30], the patients with AH and *Clostridium difficile* infection had higher hospital mortality (adjusted odds ratio (OR) 1.75; P = 0.04), longer predicted hospital stay (10.63 vs 5.75 days; P <0.001) and higher predicted treatment costs ($ 36,924.30 vs $ 29,136.58; P <0.001) compared to the patients without it.

Currently, the cause of bacterial overgrowth in alcoholics is not established. It can be due to their specific weakened peristalsis, as well as to the suppression of their innate and adaptive immune response. In healthy subjects, a wide range of antimicrobial proteins and peptides of innate immunity system secreted by intestinal epithelial cells not destroys pathogenic microorganisms and participates in the maintenance of normal gut microflora. Alcohol-induced suppression of its expression causes intestinal dysbiosis and overgrowth of bacteria which contributes to the disturbance of tryptophan metabolism and decreased indole production. Some indole derivatives are ligands for the aryl hydrocarbon receptor that, in turn, are involved in antimicrobial protection through the induction of IL-22. IL-22 increases the expression of antimicrobial Reg3 lectins derived from regenerating intestinal islets that can maintain low bacterial colonization of mucous membrane [31]. At the same time, Reg3γ deficient mice had increased bacterial colonization of the mucous membrane and the surface of epithelial cells, as well as more expressed translocation of bacteria to mesenteric lymph nodes and liver that resulted in its more pronounced ethanol-induced damage. Moreover, long-time intragastric alcohol administration to mice reduced the intestinal expression of Reg3β and Reg3γ mRNAs contributing to intestinal dysbiosis, bacterial overgrowth, and bacterial translocation [32].

Bacterial translocation is a physiological process that occurs in 5 % of healthy population and plays an important role in maintaining host immune function by delivering a small number of bacteria and their components to the reticuloendothelial system of liver. Different pathological conditions result in the steady increase in the rate and/or degree of bacterial translocation [33]. An important physical barrier that prevents the translocation is the intestinal epithelial cells closely connected with each other by tight junction proteins, primarily of claudin family. Under oxidative stress, ethanol and its metabolites can increase the permeability of intestinal wall having a direct harmful effect on adhesion junctions and on the integrity of tight junction proteins, in particular, ZO-1 (Zonula Occludens 1) [34]. Moreover, by disrupting the glycosylation of mucosal proteins, they can cause mucosa erosion and ulceration, and, possibly, change the number and composition of enteroadhesive bacterial species [35]. Dysbiosis-induced subclinical inflammation and tumor necrosis factor receptor (TNFR)1 signaling

in enterocytes may mediate the disruption of intestinal barrier and increase intestinal wall permeability [36]. Alcohol-induced modification of microbial metabolites, in particular, of short-chain fatty acids (butyrate, acetate, and propionate) is another contributive factor [37]. Thus, the decreased number of butyrate-producing bacteria weakens the strong connection between intestinal epithelial cells due to decreased expression of tight junction proteins and mucins [38]. Tight junction proteins, including ZO-1, may be adversely affected by increased intestinal expression of several microRNAs, such as miR-122 and miR-212 [39]. Finally, deoxycholic acid can also impair intestinal barrier function, while ursodeoxycholic acid prevents it [40].

Increased permeability of intestinal wall results in the situation when microorganisms, their associated molecular structures (LPS, bacterial DNA, peptidoglycans and lipopeptides), as well as the products of their metabolism cannot be adequately neutralized by local mesenteric lymph nodes and in large quantities enter the liver via mesenteric and portal circulation [41]. Here they are specifically recognized and bound by a family of Toll-like receptors (TLR) that start their clearance mechanisms and trigger the inflammatory signaling cascade. Here, TLR4 and TLR9 are the receptors of two most immunogenic bacterial products LPS and bacterial DNA, respectively [42].

TLR4 located on Kupffer cells are activated by LPS via NF-kB (nuclear factor kB) molecular signaling pathway that stimulates the expression of NLRP3 inflammasome mRNA, adapter protein ASC (apoptosis-associated speck-like protein containing a CARD), cleaved caspase 1, caspase 1, pro-IL-1β, and pro-IL-18 [43]. Morevove, with the involvement of the TIR domain-containing adapter inducing interferon-beta (TRIF) and independently of ATP/P2X7R signaling pathway, LPS stimulates NLRP3-induced caspase 1 activation and secretion of IL-1β [44]. IL-1/IL-1R signaling pathway also plays an essential role in LPS-associated liver injury [45].

TLR9 is localized in the endoplasmic reticulum of dendritic cells, macrophages, endothelial cells, and hepatocytes and mainly recognizes unmethylated CpG sequences in bacterial DNA [46].

The interaction of bacteria and their metabolic products with TLR stimulates intracellular molecular pathways contributing to the activation of NF-κB and the expression of inflammatory cytokines TNF-α, IL-1β, IL-6, IL-12, IL-18, chemokines CXCL1, CXCL2, CCL2, CCL5 , CCL3, CCL4, vasoactive substances NO, and reactive oxygen species. This local inflammatory storm results in the recruitment of systemic leukocytes such as neutrophils, CD4(+) T cells, and monocytes which contributes to liver damage [47].

Thus, ethanol-induced liver damage causes the release of damage-associated molecular patterns (DAMPs). DAMPs, in turn, activate macrophages contributing to their transdifferentiation into a pro-inflammatory phenotype and the subsequent typical inflammatory response with apoptosis and necrosis of hepatocytes as a final result. On the other hand, ethanol alters intestinal microbiota, and the associated increased permeability of intestinal wall results in the delivery of bacterial products through the portal vein to the liver with the development of a classic PAMPs-mediated inflammatory response associated with the activation of macrophages.

The main cause of death in patients with severe AH is the multiple organ failure that usually associated with underlying systemic inflammatory response syndrome. It can be caused by infectious complications, first of all, sepsis due to bacteremia as a result of bacterial translocation [48], or have a non-infectious nature due to ethanol-induced liver damage caused by PAMPs and DAMPs [49].

Excessively significant compensatory anti-inflammatory response due to corticosteroids causes immune paralysis that is characterized by decreased expression of HLA-DR antigen on the surface of macrophages, increased expression of immune inhibition markers, such as PD1 (programmed cell death 1), TIM-3 (T-cell immunoglobulin and mucin domain 3), and decreased phagocytic activity of neutrophils and monocytes which forms the basis for the susceptibility to infections [50]. Alongside with many other types of immune cells with impaired function due to severe AH, an insufficient antibacterial cytokine/cytotoxic response of MAIT cells (mucosal associated invariant T-cells) was recently revealed [51].

## The study of fecal microbiota transplantation effectiveness in severe alcoholic hepatitis

Results of preclinical experimental studies demonstrated that FMT reduced alcohol-induced liver damages, for example, those resulting from restoration of intestinal goblet cells. Mucin produced by them covers the epithelial lining of the mucous membrane surface and crypts and is the first barrier that prevents bacteria from contacting the epithelium. Moreover, FMT increased the levels of Reg3β and Reg3γ mRNA in colon which prevented intestinal dysbiosis, bacterial overgrowth and bacterial translocation, as well as reversed changes in the metabolism of some bile acids, in particular, deoxycholic acid [52].

At present, the effectiveness of FMT in severe AH was studied only in small clinical trials involving a limited number of subjects. In the first pilot study, eight patients with severe AH and contraindications to corticosteroids (MELD mean score 31 ± 5.6; MELD-Na score 33.6 ± 4.3; Child-Turcotte-Pugh (CTP) score 14 ± 0,8; serum AST level 137 ± 57 IU/mL) received the injection of 30 g of fecal material from carefully selected healthy donors, daily, for 7 days, through a nasoduodenal tube. As early as in the course of treatment, a significant improvement was observed in the severity of disease in comparison with the control group patients

who received routine treatment. The positive effect persisted all over the follow-up period (mean 355 days; range 220–368 days), with ascites resolved in 5 (57.1 %) patients and hepatic encephalopathy — in 6 (71.4 %) patients. Mean serum bilirubin level decreased from 20.5 ± 7.6 mg/dL to 2.86 ± 0.69 mg/dL (P = 0.001). CTP, MELD and MELD-Na scores decreased from 14.5 ± 0.8 to 7.7 ± 1.2, from 31.0 ± 5.6 to 12.3 ± 3.7, and from 33.6 ± 4.3 to 13.7 ± 4.6 (P <0.001), respectively. Survival rate was significantly higher in those who underwent FMT compared with the control group (87.5 % vs 33.3 %; P = 0.018). Half of them had excessive flatulence. Microbiota test one year after FMT demonstrated the dominance of *Firmicutes* species, decreased *Proteobacteria*, and increased *Actinobacteria* levels. The change in the relative number of both several pathogenic species, in particular, *Klebsiella pneumonia* (from 10 % to <1 % after 1 year) and non-pathogenic species, for example, *Enterococcus villorum* (9-23 % after 6 months), *Bifidobacterium longum* (6-50 % after 6 months), and *Megasphaera elsdenii* (10-60 % after 1 year) worth mentioning. Initially increased levels of methane metabolism, degradation of 4-fluorobenzoic acid (mediated by *Pseudomonas* and *Escherichia coli* groups), and bacterial invasion of epithelial cells decreased one year after FMT. At the same time, the initially decreased levels of bile secretion, carotenoid biosynthesis, and pantothenate biosynthesis improved almost to normal values [53].

Later, the staff of the same clinic conducted a study involving 61 patients with severe AH where the long term effectiveness of FMT (n = 35) was compared with the treatment with corticosteroids (n = 26). Ascites, hepatic encephalopathy, infectious complications and cases of long-term hospitalizations were observed more often in those who received corticosteroids (P <0.05), while a return to alcohol intake was less common (28.6 % vs 53.8 %), and the period of time associated with it was longer in those who underwent TFM (P = 0.04). Three-year survival rate was higher after FMT (65.7 % vs 38.5 %, P = 0.052), and mortality due to sepsis was significantly higher in those who received corticosteroids (N = 13/16, 81.2 %; P = 0.008). Intestinal microbiota test revealed significant increases during one to two years in relative abundance of *Bifidobacterium spp.* as well as the decrease in relative abundance of *Acinetobacter spp.* and *Porphyromonas spp.* in patients who received FMT compared with those who received corticosteroids [54].

A study performed by Dhiman R. et al. (2020) [55], included 33 patients with severe AH; 13 of them underwent FMT, while 20 received corticosteroids. The mean age (39.6 vs 40.7 years), CTP (11.5 vs 12.1) and MELD (25.2 versus 25.6) baseline scores, as well as DF (87.0 vs 83.6) demonstrated almost no differences between the groups. FMT was carried out after a five-day oral intake of antibiotics by a single injection of 30 g of freshly prepared fecal material from carefully selected healthy donors using nasojejunal tube. The patients who underwent FMT had better 1- and 3-month survival rates, as well as better resolution rate of hepatic encephalopathy and ascites, compared with those who received corticosteroids. Spontaneous bacterial peritonitis and bleeding from upper gastrointestinal tract were equally common in both groups. The most common FMT-related side effects were excessive flatulence (100 %), gastroesophageal reflux (53.8 %) and nausea (23.1 %).

Preliminary results from one of the currently ongoing randomized clinical trials (NCT03091010) involving a total of 82 patients with severe AH also showed better survival after FMT than after treatment with corticosteroids [56].

## Potential complications and risks associated with fecal microbiota

Despite the fact that FMT is a technically simple procedure, one should consider the possibility of a number of complications during its performance. For example, it is not recommended to inject large volumes of fecal material through nasoenteral tube or through upper endoscopy [57] due to the risk of aspiration; sedation should be avoided, and if appropriate, antiemetics should be used [58]. The experience has shown that FMT via LGI is safer, although there are reports on the superficial rupture of colonic mucosa when using colonoscopy [59].

A recent systematic review and meta-analysis of 61 clinical trials, including a total of 5,099 patients with *Clostridium difficile* infection, demonstrated FMT-associated severe side effects in less than 1 % of cases [60]. Some patients after FMT may develop fever, as well as transient gastrointestinal disorders, in particular, belching, nausea, vomiting, diarrhea, constipation, discomfort, stomach cramps, stomach gurgling, flatulence [61]. These are more common in young adults or in patients with previously diagnosed irritable bowel syndrome or inflammatory bowel disease [62]. There were reports on the individual cases of diverticulitis, acute appendicitis, and peritonitis, although they could be associated with both FMT and comorbidities [63]. FMT was expected to exacerbate previous inflammatory bowel diseases [64]. However, in a prospective multicenter study (NCT03106844) of 50 patients with such diseases who underwent FMT for recurrent *Clostridium difficile* infection, these concerns proved true in only 2 % of cases [65].

An important problem of FMT is the risk of the transmission of severe infection which is particularly relevant for vulnerable patients with impaired immune function [66]. For example, there were reports on two cases of cytomegalovirus infection in patients with ulcerative colitis. One of them developed it after self-administration of fecal material from the stool of the patient's child [67], and another one — after autologous FMT [68].

American authors reported on two patients with bacteremia after FMT caused by extended-spectrum beta-lactamase-producing *Escherichia coli* that was found in donor's feces using genomic sequencing [69]. It should be mentioned that faecal material was transplanted to them without testing for microorganisms with multidrug resistance, such as bacteria producing extended spectrum beta-lactamases, methicillin-resistant *Staphylococcus aureus,*carbapenem-resistant *Enterobacteriaceae,* etc., although control over their presence is a routine practice in the US state databank (OpenBiome, Cambridge, Massachusetts) since 2016 [70]. In 2019, FDA published a list of minimum requirements for screening and testing the feces donors for the presence of multidrug-resistant organisms [71].

Zellmer C. et al. (2021) [72] described four patients with self-limiting diarrhea that developed after FMT; it is associated with shiga toxin-producing *Escherichia coli*. Feces donor was found shiga toxin-negative by enzyme immunoassay, however, subsequently a more sensitive nucleic acid amplification test of fecal samples produces positive result.

Infections caused by enteropathogenic *Escherichia coli* were also reported, however, it is still unknown whether they were pathogenic or could be a part of normal gut microbiota. According to current guidelines, it is unnecessary to screen donors of fecal material for enteropathogenic *Escherichia coli* [73], however, FDA requirements stipulate the need for appropriate testing together with examination of donors, along with the examination, for shiga toxin-producing *Escherichia coli* in order to better identify these pathogens and prevent their possible transmission, especially in immunocompromised individuals [74].

COVID-19 pandemic raises concerns over potential transmission of SARS-CoV-2 coronavirus with FMT. Although the genetic material of SARS-CoV-2, including live virus, was found in the feces of individuals after a novel coronavirus infection even after the respiratory symptoms resolution [75], no actual cases of infection through donor fecal material were reported. Performing of SARS-CoV-2 RT-PCR test on fecal samples is currently not widely available. However, experts stand for screening donors for symptoms of novel coronavirus infection with quarantine of their stool and further monitoring of the disease [76].

## Conclusion

Severe AH is often associated with the development of multiple organ failure which determines an unfavorable prognosis and is accompanied by high mortality rate. In accordance with current guidelines, corticosteroids are the first-line treatment for severe AH, however, their effectiveness is not observed in every patient. Moreover, none of the second-line therapeutic approaches demonstrated reduced one-month mortality. Considering this challenging issue, a number of high-potential methods are currently undergoing clinical trials; one of them is FMT. The preliminary results of its use produce optimism and create conditions for further studies with the inclusion of a large cohort of patients with severe AH in order to determine the groups of patients to enjoy the maximal effectiveness of FMT and suffer the minimal risk of complications.

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DOI: 10.20514/2226-6704-2022-12-5-363-369
EDN: JLCFYK
УДК 616-085

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# ГЕННАЯ ТЕРАПИЯ БОЛЕЗНЕЙ ЧЕЛОВЕКА: ПОСЛЕДНИЕ ДОСТИЖЕНИЯ И БЛИЖАЙШИЕ ПЕРСПЕКТИВЫ РАЗВИТИЯ

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# Gene Therapy for Human Diseases: Recent Achievements and Near-Term Development Prospects

**Резюме**

В статье кратко изложены недавние успехи в генетической медицине, которые проложили путь для дальнейшего развития генной терапии и заложили основу для разработки технологий следующего поколения. Рассмотрены вопросы, связанные с основным препятствием для более широкого применения методов генной терапии, в частности, с иммунным ответом на векторы доставки генов и продукты чужеродных трансгенов. В этом контексте обсуждается роль новых технологий, позволяющих обойти иммунное препятствие, таких как разработка модифицированных капсидов адено-ассоциированых вирусов (AAV) и методов временного удаления антител из кровотока, а также переноса гена в ткани с помощью наночастиц. Наряду с технологиями первого поколения генной терапии, ориентированных на доставку трансгенов в ткани-мишени, резюмируются последние достижения в разработке совершенно нового подхода к генной терапии, основанного на точной модификации последовательностей генома человека — технологии редактирования генов. И наконец, обозначены перспективные технологии редактирования генов следующего поколения, такие как технологии редактирования, нацеленные на РНК и технологии редактирования эпигенома, которые являются более специфичными и точными, эффективными и применимыми к различным группам заболеваний. В заключение делается вывод, что генная терапия является на сегодняшний день самой захватывающей и революционной биотехнологией современности как из-за недавнего прогресса, так и из-за возможностей, которые она может обеспечить в ближайшем будущем.

***Ключевые слова:*** *генная терапия, аденоассоциированный вирус (AAV), капсиды, наночастицы, редактирование генов, эпигенетика*

**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 26.12.2021 г.

Принята к публикации 01.06.2022 г.

**Для цитирования:** Айтбаев К.А., Муркамилов И.Т., Муркамилова Ж.А., Юсупов Ф.А. ГЕННАЯ ТЕРАПИЯ БОЛЕЗНЕЙ ЧЕЛОВЕКА: ПОСЛЕДНИЕ ДОСТИЖЕНИЯ И БЛИЖАЙШИЕ ПЕРСПЕКТИВЫ РАЗВИТИЯ. Архивъ внутренней медицины. 2022; 12(5): 363-369. DOI: 10.20514/2226-6704-2022-12-5-363-369 EDN: JLCFYK

**Abstract**

The article briefly summarizes recent advances in genetic medicine that paved the way for the further development of gene therapy and set the stage for the development of next generation technology. Issues related to the main obstacle for wider application of gene therapy methods, in particular, with the immune response to gene delivery vectors and transgene products are considered. In this context, the role of new technology allowing to bypass the immune obstacle, such as development of modified capsids of adeno-associated viruses (AAV) and methods for temporary removal of antibodies from the bloodstream, as well as gene transfer into tissues using nanoparticles, is discussed. Along with the technology of the first generation gene therapy focused on the delivery of transgenes into target tissues, latest advances in the development of a completely new approach to gene therapy which is based on precise modification of the human genome sequence, gene editing technology, are summarized. Finally, promising next-generation gene editing technology is outlined, such as RNA-targeted editing technology and epigenome editing technology, which are more specific, precise, efficient and applicable to different groups of diseases. The article concludes that gene therapy and, in particular, human genome editing is perhaps the most exciting and revolutionary biotechnology of our time, due to both recent developments and opportunities it might provide in the nearest future.

***Key words:*** *gene therapy, adeno-associated virus (AAV), capsids, nanoparticles, gene editing, epigenetics*

**Conflict of interests**

The authors declare no conflict of interests

**Sources of funding**

The authors declare no funding for this study

Article received on 26.12.2021

Accepted for publication on 01.06.2022

**For citation:** Aitbaev K.A., Murkamilov I.T., Murkamilova Zh.A., Yusupov F.A. Gene Therapy for Human Diseases: Recent Achievements and Near-Term Development Prospects. The Russian Archives of Internal Medicine. 2022; 12(5): 363-369. DOI: 10.20514/2226-6704-2022-12-5-363-369 EDN: JLCFYK

## Introduction

As far back as 1970s, gene therapy, replacing or complementing disease-causative defective DNA with exogenous healthy or beneficial DNA, was recognized as providing viable treatment options for genetic disorders in human [1]. In 1980s, the concept of using a viral vector to transfer genes into mammalian cells was developed [2], and in 1990, and the first approval for testing gene therapy using a viral gene transfer vector encoding adenosine deaminase (ADA) enzyme in a 4-year-old patient suffering from X-linked severe combined immunodeficiency (SCID-X1 ) due to ADA deficiency of (adenosine deaminase) [3] was obtained in 1990. This was followed by a decade of new trials; however, two of them failed, so, the further gene therapy trials were suspended. In the first case, gene therapy for ornithine transcarbamylase deficiency using an adenovirus (Ad)-mediated delivery vector unexpectedly led to severe vector toxicity, multiple organ failure, and death of an 18-year-old man [4]. In the second case, gene therapy of six patients with SCID-X1, mediated by gamma-retroviral vector (γRV) encoding interleukin-2 receptor gamma chain, was associated with uncontrolled exponential proliferation of clonal mature T cells and integration of retroviral vector in the immediate vicinity of LMO2 proto-oncogene promoter (The LIM only protein 2) which resulted in aberrant transcription and expression of LMO2 [5]. These events were followed by a period of closed clinical trials. However, in the following years, new and safer viral vectors were discovered, including a large number of adeno-associated viral (AAV) vectors [6]. The use of these vectors in new genetic medicine development programs promoted the further progress in the methods of gene therapy of human diseases; their summary and prospects for development in the years to come are presented in this review.

## GENE THERAPY FOR HUMAN DISEASES

### Viral transgene delivery vector therapy

Over the past five years, gene and cell therapy for human diseases enjoyed renaissance; after decades of efforts in this direction, the first treatment methods approved for clinical practice have emerged (see figure). These include oligonucleotide-based therapy methods (Spinraza for spinal muscular atrophy, Exondys 51 and

Vyondys 53 for Duchenne muscular dystrophy), three cell therapy methods (Kymriah for acute lymphoblastic leukemia, Yescarta for large B-cell lymphoma, Tescartus for recurrent or refractory mantle cell lymphoma in adults), and two gene therapy methods *in vivo* (Luxturna for hereditary retinal dystrophy, Zolgensma for the treatment of patients with proximal spinal muscular atrophy). These treatment methods have different clinical indications and target tissues including neuromuscular diseases, hereditary blindness, and cancer. The importance of these approved treatment methods can hardly be overestimated: they drastically change the life of patients with severe hereditary pathologies and create a foundation for the development of treatment methods for many other human diseases. For example, a successful *in vivo* transfer of a normal copy of the defective gene into human retina and central nervous system with the help of Luxturna and Zolgensma drugs, using AAV-virus as a vector, in Leber congenital amaurosis and spinal muscular atrophy, respectively, facilitated the development of (AAV-based) of hemophilia [7] and Duchenne muscular dystrophy [8] treatment methods, respectively. Likewise, the early development of the method of *ex vivo* lentiviral and retroviral genes transfer to T cells that resulted in the development of adoptive cell immunotherapy (a personalized type of nonspecific cell immunotherapy with activated lymphocytes) was expanded to cover the modification of hematopoietic stem cells that allowed managing hereditary diseases such as sickle cell anemia and beta thalassemia [9]. This early success of gene therapy and the possibility of their extrapolation to other pathologies and patient populations cannot but win admiration. However, the next generation methods are even more impressive, as they can significantly expand the use of these agents for the management of many other human diseases. For example, the main obstacle to a wider implementation of gene therapy methods is still the immune response to gene delivery vectors and alien transgene products. Therefore, the control of human immune system is the trend of research where one of the most effective "breakthroughs" in the field of gene therapy can be made in the near future. Thus, despite the remarkable success of many AAV-based gene therapy methods, up to 50 % of patients are currently excluded from such treatment due to pre-existing immunity to viral capsids [10]. The recent investigations in the field of immune system control were successful and resulted in the development of methods (that are currently undergoing clinical trials) capable of bypassing this immune barrier. These methods use modified AAV capsids that evade the pre-existing neutralizing antibodies [11, 12] and the methods for temporary removal of antibodies from bloodstream [13]. Immunosuppression regimens can also provide both bypassing the pre-existing immunity and prevention of the adaptive immunity to the vector, which, where necessary, can enable subsequent repeated dosing [14, 15].

## Non-viral delivery vector (nanoparticle-based) therapy

Furthermore, a significant progress was achieved in the development and profiling the non-viral vectors (nanoparticles) of gene delivery which increased the applicability of used treatment methods [16]. Given the clinical success of miRNA delivery by nanoparticles and the first approval of an miRNA-based drug (Onpattro) for hereditary transthyretin amyloidosis (ATTR) treatment in 2018, it can be assumed that in the future these technologies will have a huge impact on gene therapy [17]. One of the advantages of using nanoparticles as gene delivery vectors is their ability to avoid detection by immune system, which restricts gene delivery by viruses. Furthermore, the chemically defined compositions of nanoparticles provide unique opportunities for their functionalization and tissue targeting, which can finally be critical for the success of gene transfer *in vivo* outside retina and liver.

## Genome editing technology

In contrast to first generation gene therapy methods that were focused on the delivery of transgenes, the genome editing technology provides a completely new approach to treatment based on the precise modification of human genome sequences (see figure). There are four basic methods of genome editing — using meganuclease, zinc finger nuclease (ZFN), TALE nuclease (TALEN), and CRISPR/Cas9 nuclease. While genome editing treatment methods were first included into clinical trials as early as in 2010 as a T cells HIV (human immunodeficiency virus) prevention method [18], the first example of disease modifying efficacy was demonstrated only in 2019 in the clinical trials based on CRISPR editing of the genes for sickle cell anemia and beta thalassemia (CTX001) [19]. This pathbreaking success combined with promising safety parameters for the edited T-cell genes and hematopoietic stem cells in human trials [19-21] laid the foundation for the long-awaited results of current and forthcoming clinical trials on genome editing *in vivo* including the current trial of AAV-based retina genome editing (EDIT-101) [22] and the scheduled trial of CRISPR delivery to the liver based on non-viral nanoparticles (NTLA-2001) [19, 23].

Despite this progress, it should still be recognized that the expansion of genome editing technology to target tissues outside retina and liver is associated with numerous issues. In order to encourage and promote research in the field of cell and genome therapy (CGT), including the development of genome editing technologies, the corresponding consortia and government programs were established in the United States, China, Russia and some countries of the European Union. Thus, in the United States, the financing of the regenerative medicine sector that includes gene therapy increased sharply from USD 6 billion in 2019 to USD 19.9 billion in 2020 [24]. Due

to the political support of the country's leadership, CGT research in China have reached unprecedentedly high level. Currently, China, featuring with rapidly growing biotechnology sector with more than 45 national and 4 joint companies with foreign partners, ranks second after the United States in terms of the number of submitted patent applications and registered clinical trials in the field of genetic medicine and is considered to be one of the most advanced world centers of cell and gene therapy. Russia has also established a state program for the development of genetic technologies for 2019–2027; its total funding is 127 billion rubles [24]. Efforts made in this area of scientific research by the leading countries of the world should undoubtedly significantly accelerate the development of treatment methods based on genome editing, in the following ten years or more.

Actual gene editing technologies use nuclease-based systems to cut DNA strands and stimulate DNA repair pathways to make the required sequence changes. Although the clinical trials of these technologies have just started, the numerous, more specific and accurate, effective and applicable to various groups of diseases next generation editing technologies are ready for clinical trials [25, 26]. For example, the invention of basic editing and primary editing allowed precise changing of genome sequences in the absence of DNA breaks and regardless the endogenous DNA repair pathways activity [25]. RNA-targeted editing technologies allow temporary and reversible gene expression modification with no need for permanent changes in genome sequences (see figure) which potentially results in higher efficiency and safety [26]. Finally, the advantages of epigenome editing technologies are the customization, reversibility, and the potential for sustainable results after short-term editor activity that are inherited through cell division [27]. In parallel with these advanced editing modalities, the list of possible DNA targeting systems continues to expand, especially with the exponentially increasing variety of CRISPR-Cas (Clustered regularly interspaced short palindromic repeat sequences/CRISPR-associated protein) systems obtained from the modified variants of various bacteria species and various classes of CRISPR targeting mechanisms [26]. The rapid pace of technological innovation in these areas of editing, according to the researchers, will change our current understanding of gene therapy and significantly expand the range of human diseases to which these approaches can be applied.

## Gene regulatory elements editing technology

Another innovation area that will significantly impact the field of gene therapy in the near future is the functional genomics and our understanding of the human genome regulation, that is, epigenetics. For example, the functions of ~ 6000 of ~ 20,000 human genes are currently not known [28]. Therefore, simultaneously with the possibility of treatment using gene editing, CRISPR technologies can also facilitate the functional decomposition of these genome sequences [29]. It should be mentioned that previously scientific investigations and therapeutic interventions were conventionally almost exclusively focused on genes, although 98 % of our genome consists of non-coding DNA, containing epigenetic regulators responsible for >90 % of susceptibility to common diseases [30]. In fact, the first example of the therapeutic efficacy of a gene editing approach based on CRISPR technology (CTX001) as a strategy for compensating for lost beta-globin in hemoglobinopathies involves editing a distal gene regulatory element to alter gene expression rather than editing the underlying genetic mutation [31]. Due to the efforts of ENCODE (The Encyclopedia of DNA elements) international consortium, more than two million of these regulatory gene elements were mapped in hundreds of human cell types and tissue samples; however, the function of very few of these sites is known [32]. Therefore, annotating this "dark matter" of genome can lead to the development of completely new areas in the biology of diseases and classes of therapeutic targets that will allow the use of fundamentally new treatment methods, i.e. gene therapy, genome editing, etc.

## Universal cellular therapy methods technology

Interestingly, that the rate of development of technological innovations in gene and cellular therapy is significantly ahead of the rate of their approval and safe implementation in clinical practice. In some cases, this is due to the inadequacy of the existing safety and efficacy requirements to some new therapeutic technologies. For example, the current regulatory models that require a large number of patients to establish safety and efficacy are not applicable to therapeutic technologies aimed at eliminating a mutation found in one patient or in a very small number of patients. Therefore, one of the most promising strategies in this direction is the development of a single composition that will allow to treat a much larger population of patients. Universal cellular therapy methods, created by applying gene editing to obtain allogeneic donor invisible cells that can elude detection by the host's immune system (see figure), can be used both in regenerative medicine and in adoptive cell immunotherapy [33]. Several clinical trials are currently underway to study treatment methods using this design [19], and the conclusions of these trials will significantly affect the future of gene and cellular therapy. However, despite the high-potential prospects of this approach, it is not aimed at correcting genetic mutations *in vivo* and has no effect on the development of transformative technologies such as basic editing and primary editing that can correct individual particular mutations. Similarly, the recent report on oligonucleotide-based therapy targeting a particular genetic mutation and the successful treatment of

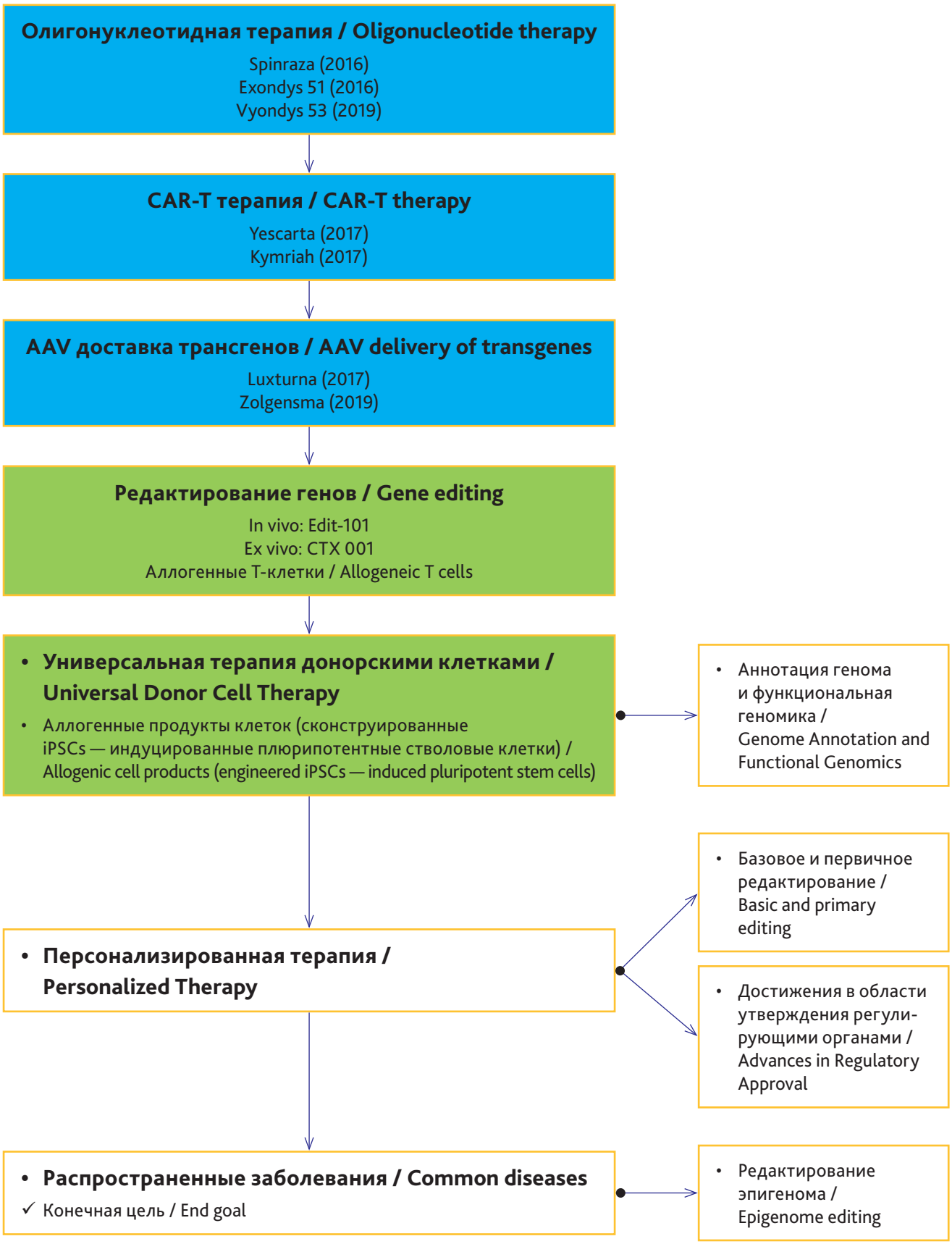


***Figure.*** *Milestones in the development of gene therapy for common diseases.*
**Note:** Approved treatments and their year of approval are represented by blue boxes, while experimental treatments are represented by green boxes. To reach later milestones, further research is needed to develop alternative therapeutic approaches and address fundamental scientific questions (shown as markers)

a patient with Batten disease can only be considered as a potential program and motivation for such efforts [34]. Consequently, the significant advances in cellular and gene therapy are expected to emerge in the near future in the field of regulatory sciences, as well as the solution of unique challenges using innovative personalized technologies, as we move towards the therapy.

## Conclusion

The development of genetic technologies is prioritized in the world's leading countries, and gene therapy, in particular, human genome editing is currently the most exciting and revolutionary biotechnology of the present day [35]. The unrivaled level of control over the delivery of nucleic acids, modulation of immune system, and the precise manipulation of human genome are the technologies that could not have been imagined ten years ago; they will undoubtedly give an impetus to the formation and development of new fields of medicine during the decade to come. At the same time, this emerging glimpse of a new world of technical possibilities has been inspiring the development of new research fields, such as synthetic biology, cell reprogramming and high-performance functional genomics that will undoubtedly continue to transform the concept of biomedical studies.

**Вклад авторов:**

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2022-12-5-370-379
EDN: NHWVPC
УДК 616.98:578.834.1-06:616.24-002.17

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# НЕОБРАТИМЫЕ ИЗМЕНЕНИЯ ЛЁГКИХ В ИСХОДЕ ПОВРЕЖДЕНИЯ ПРИ COVID-19 — РАЗМЫШЛЕНИЯ НА ТЕМУ И ПРИМЕРЫ ЛУЧЕВЫХ ИЗОБРАЖЕНИЙ

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# Irreversible Lung Transformation Resulting from Damage In COVID-19 — Discourses and Examples of CT Images

**Резюме**

Проблема формирования необратимых остаточных изменений после перенесенного вирусного повреждения легких при COVID-19 (COronaVIrus Disease 2019, новая коронавирусная инфекция) по прошествии двух лет пандемии остается важной и обсуждаемой. Это связано с большим числом пациентов, перенесших коронавирусную инфекцию (в т.ч. со значимым объемом поражения легких) и возможным неблагоприятным прогнозом с уменьшением качества и продолжительности жизни. С учетом того, что в последнее время активно применяется антифибротическая терапия ряда интерстициальных заболеваний легких (при идиопатическом легочном фиброзе и системных заболеваниях), рассматривается вопрос о возможном использовании этих средств и при неблагоприятном исходе COVID-19. Однако до сих пор точно неизвестно, насколько часто развивается фиброз в исходе новой коронавирусной инфекции, а также четко не выделены группы пациентов, которые могут иметь неблагоприятный прогноз в виде исхода в фиброз.

В обзоре рассмотрены патогенетические аспекты возможного развития необратимых изменений у пациентов с COVID-19, предрасполагающие факторы, а также особенности диагностики с акцентом на КТ-визуализацию с собственными наблюдениями авторов.

***Ключевые слова:*** *коронавирус, COVID-19, фиброз, интерстициальное заболевание легких, компьютерная томография, бронхоэктазы, «матовое стекло»*

**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 18.02.2022 г.
Принята к публикации 25.05.2022 г.

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**Для цитирования:** Винокуров А.С., Юдин А.Л. НЕОБРАТИМЫЕ ИЗМЕНЕНИЯ ЛЁГКИХ В ИСХОДЕ ПОВРЕЖДЕНИЯ ПРИ COVID-19 — РАЗМЫШЛЕНИЯ НА ТЕМУ И ПРИМЕРЫ ЛУЧЕВЫХ ИЗОБРАЖЕНИЙ. Архивъ внутренней медицины. 2022; 12(5): 370-379. DOI: 10.20514/2226-6704-2022-12-5-370-379 EDN: NHWVPC

## Abstract

The problem of the formation of irreversible residual changes after suffering viral lung damage with COVID-19 (COronaVIrus Disease 2019) after two years of the pandemic remains important and discussed. This is due to a large number of patients who have had a coronavirus infection (including those with a large amount of lung damage) and a possible unfavorable prognosis with a decrease in the quality and life expectancy. Given the fact that antifibrotic therapy has recently been actively used for a number of interstitial lung diseases (with idiopathic pulmonary fibrosis and systemic diseases), the question of the possible use of these drugs in case of an unfavorable outcome of COVID-19 is being considered. However, it is still not known exactly how often fibrosis develops in the outcome of a new coronavirus infection, and groups of patients who may have a poor prognosis in the form of an outcome in fibrosis have not been clearly identified.

The review considers the pathogenetic aspects of the possible development of irreversible changes in patients with COVID-19, predisposing factors, as well as diagnostic features with an emphasis on CT scan with the authors' own observations.

***Key words:*** *coronavirus, COVID-19, fibrosis, interstitial lung disease, CT scan, bronchiectasis, ground glass opacities*

## Conflict of interests

The authors declare no conflict of interests

## Sources of funding

The authors declare no funding for this study

Article received on 18.02.2022

Accepted for publication on 25.05.2022

**For citation:** Vinokurov A.S., Yudin A.L. Irreversible Lung Transformation Resulting from Damage In COVID-19 — Discourses and Examples of CT Images. The Russian Archives of Internal Medicine. 2022; 12(5): 370-379. DOI: 10.20514/2226-6704-2022-12-5-370-379 EDN: NHWVPC

ACE — angiotensin-converting enzyme, ARDS — acute respiratory distress syndrome, AV — artificial ventilation, COPD — chronic obstructive pulmonary disease, CT — computed tomography, DAD — diffuse alveolar damage, DLCO — diffusing capacity of the lungs, ECMO — extracorporeal membrane oxygenation, GCs — glucocorticoids, ILD — interstitial lung disease, OP — organizing pneumonia, PF — pulmonary fibrosis, RF — respiratory function, SARS — severe acute respiratory syndrome

Lung lesion during the acute phase of COVID-19 (COronaVIrus Disease 2019, a novel coronavirus infection) is not a specific condition. SARS-COV-2 virus in lung tissue causes the development of diffuse alveolar damage (DAD) in combination with the signs of vasculitis [1]; their stage and prevalence correlate with the clinical presentation. The same changes are observed in patients with acute respiratory distress syndrome (ARDS), as well as with diseases caused by other viruses — the most illustrative example of them is H1N1 flu. Due to the fact that DAD develops through typical phases (exudative, proliferative), its possible outcome is the pulmonary fibrosis (PF) that is observed in patients after ARDS and is registered in patients as the outcome of severe influenza. For example, in ARDS, not associated with a virus, PF is detected during autopsy in 4 % after one week of ARDS manifestations, in 24 % — between week 1 and week 3, and in 61 % after 3 weeks [2]. Therefore, PF can also develop in patients with COVID-19. However, not all patients with coronavirus infection develop clinical signs of ARDS which is significant for prognostic evaluation. Based on literature, SARS-COV2-associated ARDS is diagnosed in 5-40 % of cases [3, 4], and it is this particular group of patients that can potentially have a negative prognosis in terms of development of an irreversible process. To compare, PF development in patients with SARS (Severe Acute Respiratory Syndrome) was observed in up to 8 % of cases, in those with H7N9 influenza — in up to 20 % [5].

Notably that the definitions regarding long-term changes in lungs after coronavirus infection are quite diverse. Alongside with the term “fibrosis”, the literature sources contain the references to post-COVID interstitial lung disease (ILD), organizing pneumonia (OP), and fibrotic lesions [6, 7]. Generally, it seems to be a more correct approach, since not every type of post-COVID ILD innevitably results in PF. According to Aronson K.I. et al., the true prevalence, as well as the feasibility of management of these conditions with glucocorticoids (GCs) should be established in large studies; besides, the computed tomography (CT) findings should be confirmed by morphological studies [8].

The prevalence of post-COVID PF is predicted to constitute 10-15 cases per 10,000 people which is ten times as high as the risk of idiopathic pulmonary fibrosis development [7]. However, we can hardly say that this phenomenon is widespread in current pandemic. Neither pulmonologists nor radiologists observe a high incidence of fibrosis as an outcome of pulmonary lesions in their practice. This fact may be attributed both to certain SARS-COV-2 features and to the changes in the therapeutic approach — the use of biological agents (IL-6 inhibitors) to stop the excessive immune response, widespread use of GCs in both acute and delayed periods of infection. All these facts may result in lower severity of nonspecific inflammation in lung tissue and is the prevention of fibrotic process, and promotes positive changes in OP with no gross structural changes.

It was found that the SARS-COV-2 virus itself, when combined with an angiotensin-converting enzyme (ACE), increases angiotensin II level to activate the connective tissue growth factor (CTGF), involved in the development of fibrosis [9]. In the review by Ademola S. Ojo et al. (2020), the pathogenesis of PF as the outcome of a severe or long-term process is associated with the damage to the basement membrane of cells and the transformation of sites of organization into fixed or progressive tissue with fibroblasts with further impairment of lung architecture [10].

In the early days of this novel coronavirus infection, physicians often had erroneous opinion about the development of PF in patients that was based on the analysis of CT results in 2-3 weeks after the acute period and one dynamic CT examination; it is definitely not a reliable conclusion. The intermediate changes that from morphological viewpoint are the areas of organization and atelectasis of various lengths (both lobular and typical discoid) were misdiagnosed as PF; on CT images, they are visualized as linear and radial consolidation strips with clear contours (Figure 1).

The frequent development of reversible atelectases may be associated with the viral damage of type II alveolar cells (in the course of DAD) that produce a surfactant [11]. Subsequently, it was observed that such atelectases were completely resolved [12] which is most likely due to the gradual regeneration of type II alveolar cells and improved microcirculation. We can also assume the presence of the impairments of pulmonary ventilation associated with a musculoskeletal system imbalance, i.e. the weakness of intercostal muscles, diaphragm, their impaired innervation, etc. Theoretically, all these factors can result in the development of atelectases. It should be taken into consideration that lung tissue can stay collapsed for a relatively long time with no structural changes (up to two months) [11]. Later, an irreversible process of interstitial structures, bronchi and vessels deformation will develop in this atelectasized area, and PF-equivalent changes will be observed. The complete resolution of post-COVID-19 changes in lungs is observed 6 months after hospitalization in 50 % of patients, and 9 months — in 75 % [13].

The comprehensive monitoring of PF-suspected patients as the outcome of COVID-19 remains an important issue. First of all, one should assess the persistence of clinical signs or their aggravation. Special attention should be paid to long-term dyspnea or its aggravation after the acute stage of viral process, weakness and tachycardia [14], as well as the possible oxygen dependence. The useful functional methods include respiratory function (RF) tests and the measurement of diffusing capacity of the lungs (DLCO). For example, according to Zaitsev A.A. et al. (2020), 3 weeks after discharge from the hospital, dyspnea persists in 50 % of patients, restrictive impairments of respiratory function are detected in 15.6 %, and DCL of different grades decreases in 56 % of cases. The authors observed the greatest decrease in DCL in patients with massive persistent changes on CT [15]. Qin W. et al. (2021) also mentioned a correlation between the presence of traction bronchiectases, reticular changes and subpleural thickening with decreased DCL parameters [14].

It is reasonable to identify clinical and radiological groups that later may be prone to PF. As a rule, in patients with small and medium lung lesions (up to 50 %), the changes gradually resolve completely, except for the residual areas of ground-glass opacity with no reticular striation that can persist for quite a long time and are not reliable indicators of fibrosis onset. Special attention should be paid to the patients with a severe clinical course of the disease and large lung damage (more than 50 %) who stayed in hospital for a long time and/or were treated in intensive care units (the highest correlation with a decrease in DCL parameters is observed in connection with artificial ventilation) [9,16,17]. Smoking and previous alcohol consumption (as additional factors of respiratory symptoms aggravation), age (a tendency to fibrosis development with age) are also distinguished as risk factors [18]. The patients with a "frozen" ground glass pattern, despite ongoing therapy, should subject to follow-up for PF development; this sign may indicate

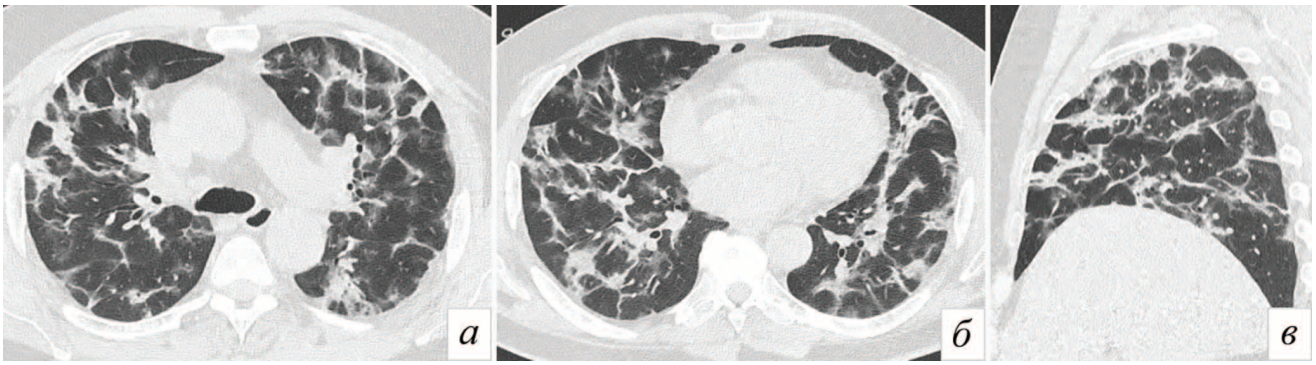


***Figure 1.*** *Patient K, 55 years old. The early resolution phase of lung injury in COVID-19. Thoracic CT scans in axial (а, б) and sagittal (в) projections. Multiple band-like strips of consolidation, perilobular hardenings. This CT picture is presented by the pattern of OP in combination with discoid atelectasis, which can be mistaken for fibrotic changes*

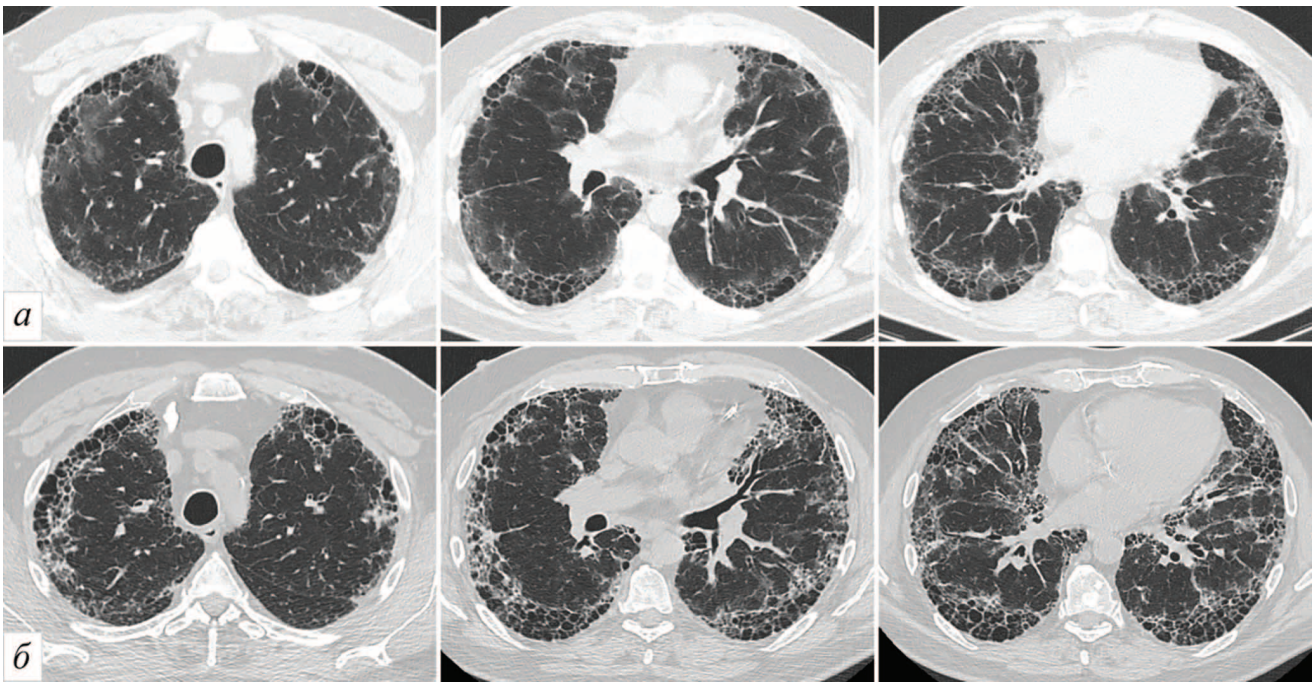


***Figure 2.*** *Patient N., 58 years old. COVID-19 (PCR+) on the background of usual interstitial pneumonia. Axial chest CT scans at appropriate levels. Row A — the study dated 07.03 2021, row Б — the study dated 21.04.2021. In dynamics, in place of areas of "ground glass" the appearance of pronounced reticular changes and structural realignment in the form of a "honeycomb lung", the progression of "honeycombs" in the already existing areas, the appearance of their additional rows*

a persistent morphological DAD pattern in lungs. The pre-existing premorbid background represented by a fibrous process associated with various ILDs or systemic diseases can contribute to the progression of fibrosis in previously intact areas in the presence of viral damage; otherwise, it can change the CT presentation (for example, the development of a "honeycomb lung" associated with the pre-existing isolated reticular changes) (Fig. 2). One can find the examples of such transformations in the papers of Speranskaya A.A. et. al. [19]. With an extensive CT pattern of OP at the end of acute phase, one can expect a gradual development of PF with no adequate GCs treatment. It is these groups of patients that will require special pulmonologist's attention during the follow-up, including regular CT examinations — in 3-6-12 months, etc., if necessary.

## Radiation diagnostics

CT is helpful for assessment of the possible development of irreversible changes due to its high sensitivity, especially when it comes to small pathological areas localized in the basal sections of lungs. Conventional X-ray is globally used as a primary diagnostic method, however, for long-term structural consequences, CT is the method of choice [17].

Visualization of changes in lungs is crucial for registration the signs of PF or its equivalents. It is related to the fact that a morphological study is not quite common in such cases and can worsen the current pulmonary symptoms, resulting in complications (pneumothorax, bleeding) associated with the compromised lung tissue at the stage of convalescence after the damage. Considering the development of the "post-COVID" syndrome, clinical presentation can also persist for quite a long time, or even aggravate for reasons that are not related to lung damage (one of the important mechanisms is extensive vasculitis, coagulopathy) [1]. Therefore, it is visualization that will allow identifying definite criteria for the development of a fibrotic process in patients and to objectify them.

The most important factor for a radiologist's conclusion will be the monitoring the changes over time: the continuance of visualization of the changes identified or their progression. The results of one isolated CT examination, or the results obtained shortly after the acute stage are not relevant to make a conclusion on PF. In other diseases (for example, tuberculosis), morphologists have previously highlighted the resolution of several seemingly irreversible changes. Strukov A. I. indicates that such reverse development of atelectases, retention bronchiectases and carnification areas (which are actually OP) is admissible [20]. For example, the decreased diameter of bronchial lumen over time with no structural changes of the wall, in case of resolution of the adjacent infiltration, illustrates the reversibility of the process rather than the development of true bronchiectasis. The dilatation of bronchial lumen, especially in the lower lobes, is often observed in patients with viral lung damage at the stage of resolution and even in the acute

phase; it is associated with de-airing and infiltration of lung tissue that results in temporary decrease of its volume. The same is true for the functional lung tests — the importance of follow-up over time and comparison with previous results. It is also important to observe the typical changes associated with the previous areas of ground-glass opacity/consolidations over time [17].

When can a radiologist suspect irreversible changes in lungs as the outcome of COVID-19 according to CT results? Based on our own clinical experience, the most significant signs are as follows:

- the decreased volume of the anatomical region of lung (segment, lobe) which is especially distinctive by the location of the of interlobar pleura layers. One can also pay attention to the overall decrease in lung volume associated with the normal depth of inhale (Fig. 3). When visualizing such changes, one should exclude other causes of the volume decrease associated with bronchial patency, that is, bronchial tumors, mucopurulent and hemorrhagic clots, secondary destructive processes, etc.
- Deformation and dilatation of the lumen of bronchi/bronchioles with the development of traction broncho/bronchiolectasis (Fig. 3e, Fig. 4). Alongside with the deformation, one can also observe the convergence of bronchovascular bundles in the affected lung part. According to Huang W. et al. (2021), dilated bronchial lumen, as a manifestation of PF, is the most common sign — it is presented in up to 80 % of cases [21]. If this is the case, one should evaluate the results of all previous x-ray examinations, since bronchial dilatation could have developed in a patient long before the viral infection, among others, due to the chronic obstructive disease (COPD) which is often characterized by cylindrical bronchiectasis. It should be remembered that the bronchial lumen dilatation in the areas of OP can be potentially reversible after the intraalveolar granulations reduction. Radiologist should be especially careful in the interpretation of such detected changes. The changes in the shape of the bronchi represented by varicose bronchiectases and bronchioectases with typical wave-shaped wall are more suspicious of an irreversible process.
- Intrapulmonary and pleural-pulmonary strands that persist over time and are often located in the area of deformed bronchi and surround them. The large amount of such strands spreading in different directions can produce an impression of background ground-glass opacity that indicates either a certain averaging of the surrounding density, or fine-structure fibrosis (Figure 5).

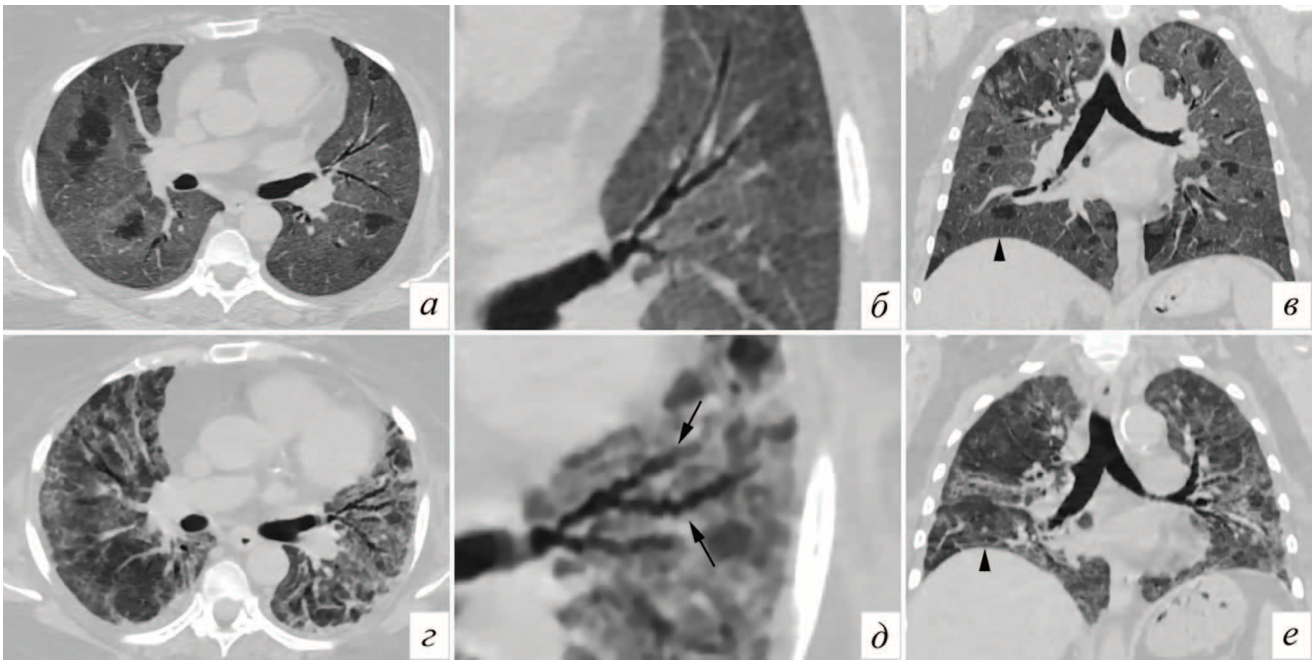


***Figure 3.*** *Patient F., 60 years old. COVID-19 (PCR+). Thoracic CT scans in axial projection (а, г), coronal projection (в, е) and enlarged fragments (б, д) at appropriate levels. The upper row — the study dated 23.11.2020, the lower row — the study dated 25.12.2020. Against the background of heterogeneous hardenings in both lungs, the appearance of traction (varicose) bronchiectase in the upper lobe on the left (arrows) are clearly visible, which were absent before. In other parts of the lungs there is no such deformation. Also, in the dynamics there is a general decrease in lung volume at the same depth of inspiration (в, е), a high position of the dome of the diaphragm (arrowheads). The changes may be potentially reversible*

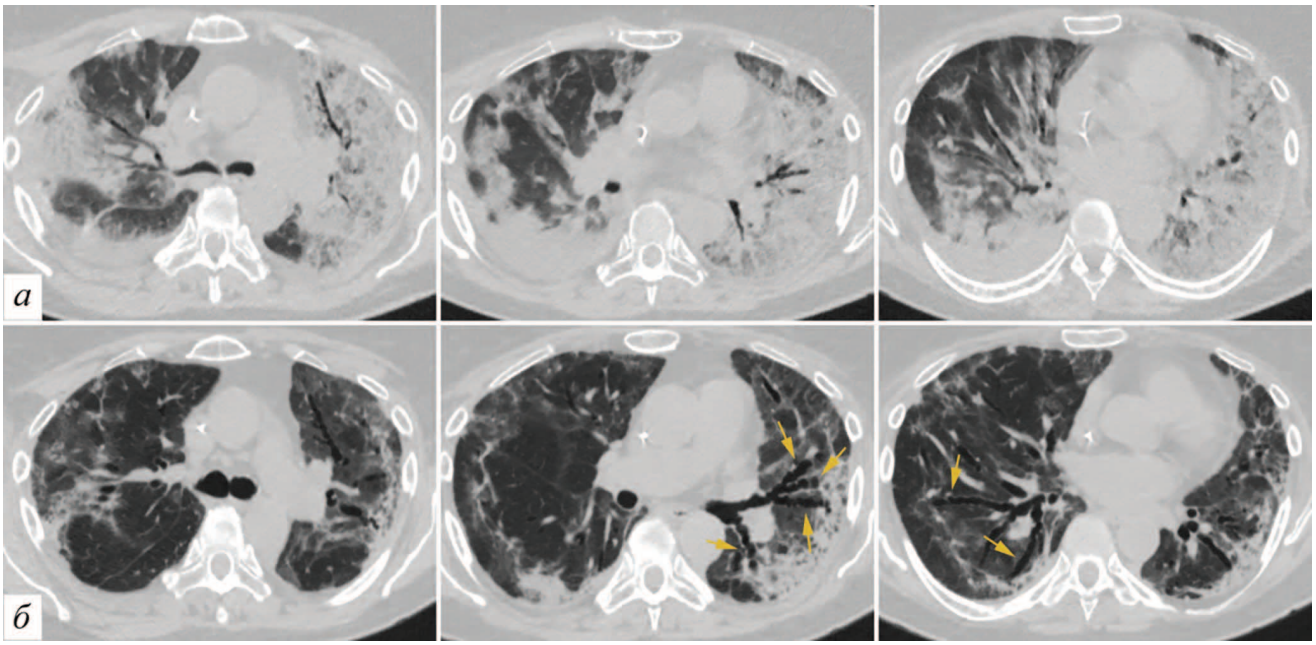


***Figure 4.*** *Patient A., 74 years old. COVID-19 (PCR+). Thoracic CT scans in the axial projection. Row a — study dated 03/25/2021 and row b — study dated 04/19/2021 at the corresponding levels, taking into account different depths of inspiration. Top (a) — CT picture of acute viral damage with a lesion volume of at least 75 %. Below (b) — dynamics at the stage of resolution, the appearance of deformation and expansion of the lumens of large bronchi, especially in the lower parts of the lungs (arrows)*

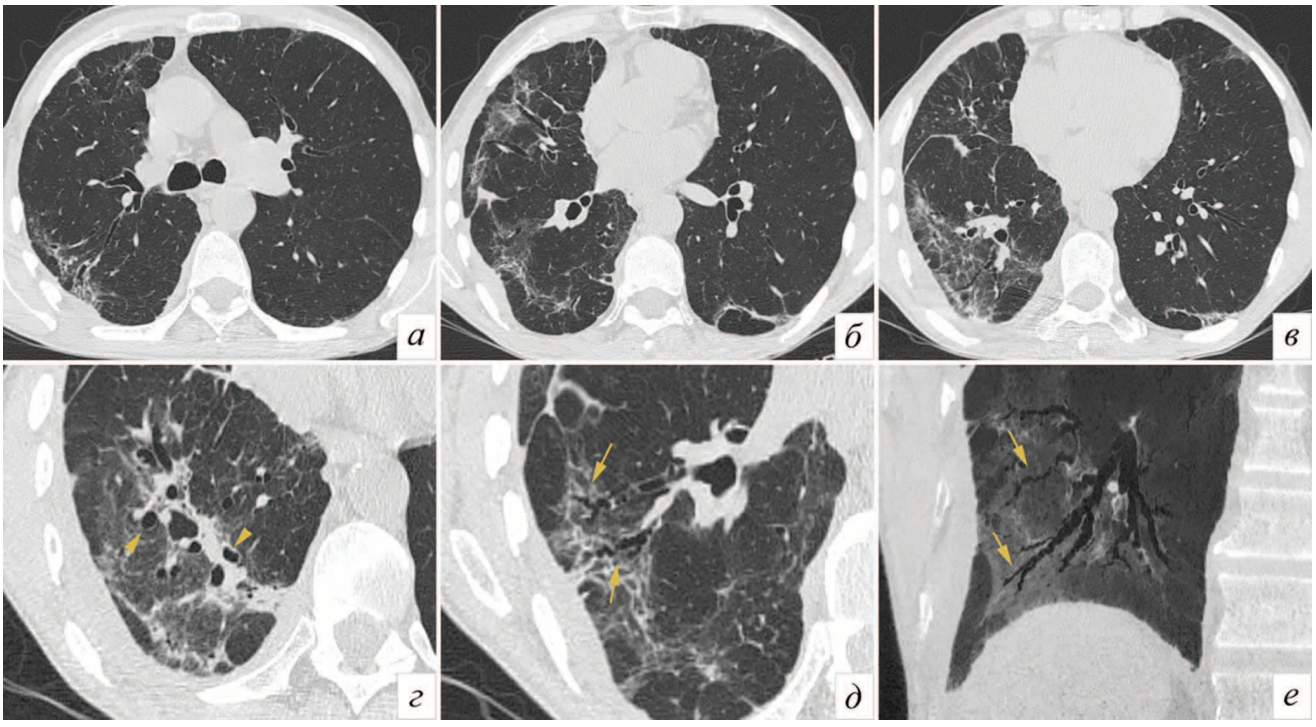


***Figure 5.*** *Patient K., 73 years old. 4 weeks after discharge for COVID-19 (PCR+). Thoracic CT scans in the axial projection (a-в), enlarged image fragments (г, д) and MinIP reformation (е). Against the background of low-intensity areas of "ground glass" (more on the right), there are stringy hardenings that deform the lung tissue and pleura. Cylindrical (arrow heads) and varicose (arrows) broncho- and bronchiolectasis are also visualized*

- The persistent areas of consolidation and ground-glass opacity with reticular changes that indicate the interstitium involvement in the pathological process [6] (inter alia, due to the decreased volume of the lobe). These areas are deaerated fragments of lung replaced by connective tissue (of varying severity). They can have homogeneous structure or include bronchiectases. Unlike reversible atelectasized tissue, these areas do not accumulate contrast agent. In the presence of one such subpleural area, one should also think about past lung infarction that can also turn into a fibrosis area.
- Thickening of pleura that is more often observed along the costal sheets. This symptom is often associated with the contracture of lung tissue (and therefore, vessels and bronchi) and subpleural strands.
- Pneumatocele is the areas of the impaired architecture of lung tissue with the development of air pseudocavities that are mainly found in the peripheral parts of lungs [17]. Alarcon-Rodrigues J. et al. (2021) give an example when pneumatoceles are partially reversible [17]. However, pneumatocele as the only sign can be hardly defined as a strict criterion of fibrosis. We recommend to consider a comprehensive assessment, for example, pneumatocele associated with ground-glass opacity, consolidations, or in the area of deformed bronchi as additional signs. We have also observed the closure of such lesions over time.
- In the most severe cases, there is a gross deformation of secondary pulmonary lobules with the development of the subpleural areas of honeycomb lung — in up to 7 % of cases [21] (Figure 6). In our practice, we mainly observed the progression of honeycomb in the place of viral damage in patients with a pre-existing presentation of PF, for example, as a common interstitial pneumonia rather, than its development in previously intact areas. At the same time, the deterioration of CT results can develop as early as in 1-2 months after the acute process.
- The long-term persistence of the abovementioned common changes in lungs can result in dilated right heart, as well as dilated and lengthened pulmonary artery trunk.
- Other possible changes, like air-trapping, are also described [21].

The areas of ground-glass opacity in the long-term follow-up period with no reticular changes call for careful interpretation in relation to PF. We observed such changes in a female patient with no current respiratory complaints one year after the acute period of the disease (Figure 7). The observations made in our clinic are compliant with the opinion of Samsonova M.V. et al. (2021) who suggest long-term persistence of ground-glass opacity in lungs on CT due to nonspecific interstitial pneumonia, or isolated intraalveolar edema, potentially in combination with hemorrhages or OP [22]. The air-trapping areas can be actually represented by a mosaic pattern associated with thrombosis of the branches of

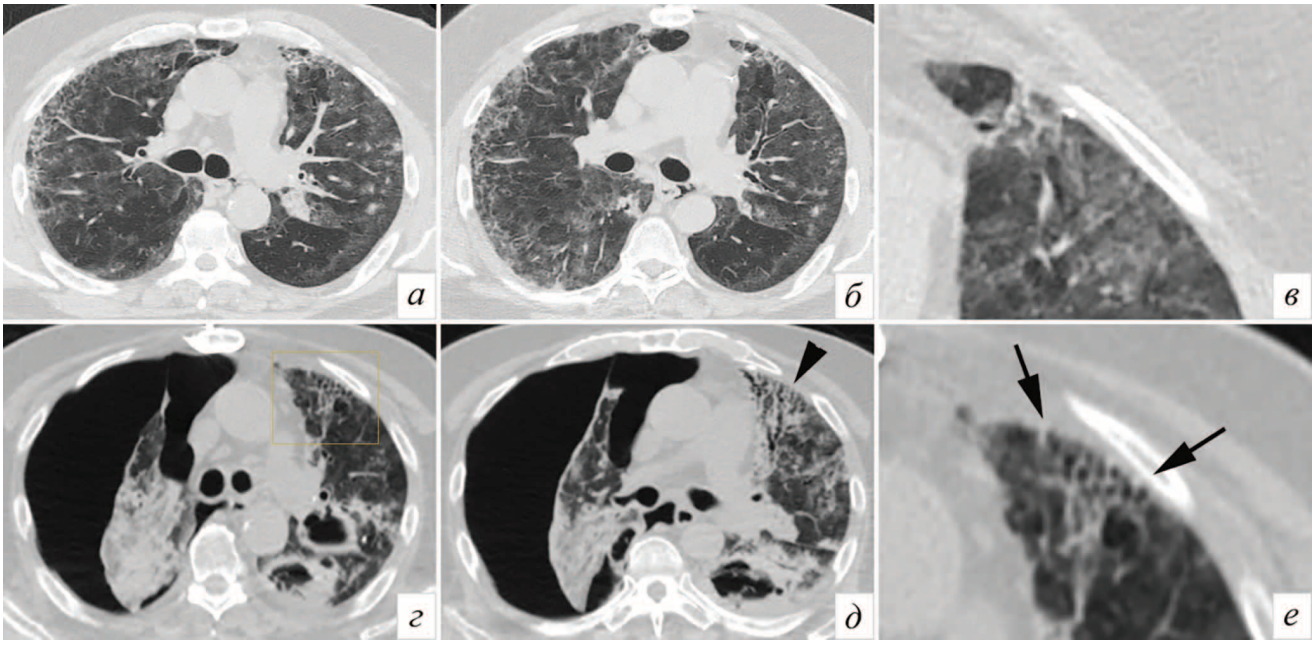


***Figure 6.*** *Patient M., 65 years old. COVID-19 (PCR+). Thoracic CT scans in the axial projection (a-e) with enlarged fragments (в, e) at the corresponding levels. The top row — the study dated 08/04/2021, the bottom row — the study dated 09/16/2021. Secondary infection (cavities) and pneumothorax on the right, in S3 on the left there is an area with varicose broncho- and bronchiolectasia (arrow head), as well as an area similar to a "honeycomb" deformation (frame, arrows)*

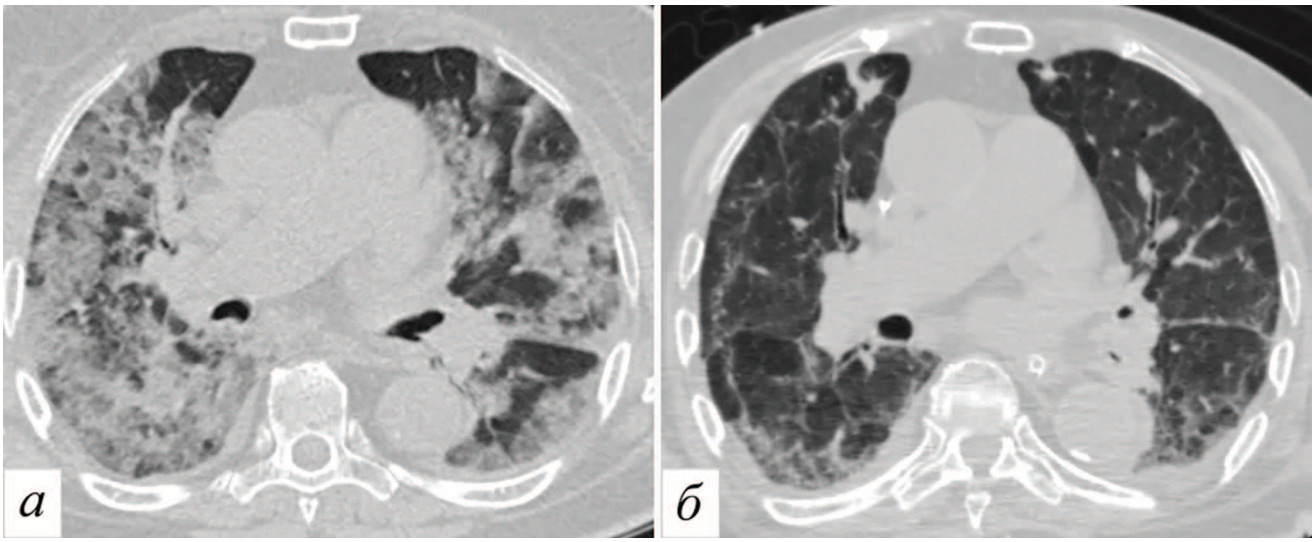


***Figure 7.*** *Patient A., 88 years old. COVID-19 (PCR+), one year after the acute phase of the disease. Thoracic CT scans in the axial projection, a — examination dated November 4, 2020, б — examination dated November 2, 2021. In place of extensive hardenings (consolidations, "ground glass"), there remain inhomogeneous areas of "ground glass" of low intensity with fuzzy contours, against which linear hardenings are presented, incl. in the form of characteristic arcs. Bronchiectasia and other areas of deformity are not clearly visible, and changes may correspond to OP or a pattern of nonspecific interstitial pneumonia*

pulmonary artery due to hypercoagulation [22] and, as a consequence, redistribution of pulmonary blood flow that creates this typical mosaic pattern. The results obtained by Jia-Ni Zou et al. (2022) indicate the incidence of fibrosis in 90 days after COVID-19 in 84.15 % of cases, mainly due to the persistent areas of ground-glass opacity (from 80.7 to 96.5 %), linear thickenings and reticular changes [23]. Such high numbers should be interpreted carefully due to too early follow-up period: some of these thickenings and linear structures could have resolved later and would no longer be regarded by the authors as PF. These conclusions are also not confirmed by morphological studies and are based only on CT results.

The most gross changes represented by true PF are observed in the patients who have been on artificial ventilation (AV) for a long time, as well as in those who underwent extracorporeal membrane oxygenation (ECMO) after extensive DAD with a lung lesion approximating 100 % and the inevitable development of a secondary bacterial infection. As a rule, when a patient stays in an intensive care unit with artificial respiratory support for 1-2 months, they develop a common deformity in the form of a honeycomb lung and bronchiectases. In most cases, lung transplantation should be considered for such patients [24].

An important task for radiologist is to determine how extensive the above-described symptoms are and to register them in the records. It should be understood that the presence of only a single area that is typical of PF is likely to have no high clinical significance due to the compensatory capabilities of lung tissue. The extensive changes on both sides, with decreased lung volume and significantly impaired architecture will be considered significant. Assumptions are made about the need to determine the volume of fibrotic lung damage similarly to the assessment in the acute COVID-19 period (CT-1, CT-2, etc.); and it will be relevant not only for this disease but for other fibrotic processes in lungs as well (for example, J.H Warrick, A.U. Wells scores, etc.) [25].

The detection of PF signs by a radiologist should not be the only cause for a pulmonologist's decision on further routing and administration of special treatment. CT data demonstrate only a pattern that naturally corresponds to irreversible changes, and their clinical significance should be determined together with clinical and instrumental examinations and functional tests. A similar situation is observed in the patients with COPD. The results of radiological examinations can help to determine emphysema, chronic bronchitis, bronchiectasis, but the diagnosis is made on the basis of functional tests of the patient. This is due to the fact that not only fibrotic changes can contribute to the development of persistent respiratory failure in the patient; it's causative factors can be the extensive microangiopathy that results in thrombosis in situ and the impaired lung perfusion; it can be detected using scintigraphy [26], or iodine maps during contrast-enhanced CT.

## Conclusion

The conclusion on irreversible changes in the lungs as the outcome of coronavirus damage is a serious prognostic marker; it should be performed jointly by a multidisciplinary commission in the presence of a pulmonologist, radiologist, functional diagnostics specialist, if possible, ~~and~~ a morphologist. Only if the patient has persistent or progressive clinical signs of respiratory failure in combination with oxygen dependence, decreased parameters or the absence of positive changes during functional tests, and a persistent radiation pattern that is typical for PF, one can conclude on the development of an irreversible process in lungs and decide on the further approach to the treatment of the patient: up to antifibrotic therapy or lung transplantation. At present, based on practical observations, it would be incorrectly to say that irreversible changes in lungs after COVID-19 are a common situation. Radiologists should be especially careful when mentioning the pulmonary fibrosis in their conclusions, since many visible changes can be potentially reversible.

### Вклад авторов

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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DOI: 10.20514/2226-6704-2022-12-5-380-388
EDN: OUJDMB
УДК 616.13-004.6-06:616.12-008.46-07

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# ОСОБЕННОСТИ ПРОГНОЗИРОВАНИЯ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ПЕРИФЕРИЧЕСКИМ АТЕРОСКЛЕРОЗОМ В ОТДАЛЕННОМ ПЕРИОДЕ

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# Features of Prediction of Heart Failure in Patients with Peripheral Atherosclerosis in the Long Period

**Резюме**

**Цель:** оценить вероятность развития сердечной недостаточности в течение трехлетнего проспективного наблюдения и разработать способ ее комплексной оценки у лиц с атеросклеротическим поражением различных сосудистых бассейнов. **Материалы и методы:** В исследование включено 519 пациентов (средний возраст 60,0±8,7лет) с атеросклеротическим поражением различных сосудистых бассейнов, из них — 360 (69,4 %) мужчин, 159 (30,6 %) — женщин. Всем пациентам выполнялись стандартные биохимические исследования с определением показателей липидного профиля. Комплекс инструментальных исследований включал выполнение эхокардиографии, ультразвукового исследования почек, брахиоцефальных артерий, при наличии клинических проявлений, вызывающих подозрение на атеросклеротическое поражение сосудистых бассейнов, были проведены коронароангиография, ангиография почечных сосудов, брахиоцефальных артерий и артерий нижних конечностей. Срок наблюдения составил — 36 месяцев, первичная конечная точка — новые случаи развития сердечной недостаточности. **Результаты:** Анализ вероятности развития сердечной недостаточности продемонстрировал, что такие факторы, как величина фракции выброса, % (p=0,04), значение основания аорты, мм (p=0,049), степень атеросклеротического поражения ствола левой коронарной артерии, % (p=0,013) и степень тяжести стеноза задней боковой ветви коронарной артерии, % (p=0,048) оказывали влияние на риск развития сердечной недостаточности в отдаленном периоде у пациентов с периферическим атеросклерозом. **Заключение:** Проведена оценка вероятности развития сосудистых событий и неблагоприятных исходов в течение трехлетнего проспективного наблюдения. Установлено, что госпитализация по поводу сердечной недостаточности в течение трехлетнего периода имела место у 3,4 % пациентов с атеросклеротическим поражением различных сосудистых бассейнов и их комбинаций. Отмечено, что такие группы факторов, как «величина фракции выброса % + значение основания аорты, мм» (p=0,025), «степень атеросклеротического поражения задней боковой ветви, % + величина фракции выброса, %» (p=0,046), оказывали влияние на риск развития сердечной недостаточности в отдаленном периоде у лиц группы обследования. С использованием уравнений логистической регрессии разработаны оригинальные таблицы прогноза, позволяющие получить информацию

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в отношении вероятности развития сердечной недостаточности, которые могут быть использованы в реальной клинической практике у пациентов с периферическим атеросклерозом.

***Ключевые слова:*** *сердечная недостаточность, периферический атеросклероз, атеросклероз почечных артерий, атеросклероз сонных артерий*

### Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

### Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 30.12.2021 г.

Принята к публикации 17.05.2022 г.

**Для цитирования:** Кобзева Н.Д., Терентьев В.П., Олейникова В.Д. ОСОБЕННОСТИ ПРОГНОЗИРОВАНИЯ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ПЕРИФЕРИЧЕСКИМ АТЕРОСКЛЕРОЗОМ В ОТДАЛЕННОМ ПЕРИОДЕ. Архивъ внутренней медицины. 2022; 12(5): 380-388. DOI: 10.20514/2226-6704-2022-12-5-380-388 EDN: OUJDMB

### Abstract

**Aim:** To assess the likelihood of developing heart failure during a three-year prospective follow-up and develop a method for its comprehensive assessment in individuals with atherosclerotic lesions of various vascular beds. **Materials and methods:** The study included 519 patients with atherosclerotic lesions of various vascular regions, of which 360 (69.4 %) were men, 159 (30.6 %) were women (mean age 60.0±8.7 years). **Results:** Analysis of the likelihood of developing heart failure clearly demonstrated that factors such as the value of the ejection fraction, % (p = 0.040), the value of the base of the aorta, mm. (p = 0.049), the degree of atherosclerotic lesions of the left coronary artery trunk,% (p = 0.013) and the severity of posterior lateral branch stenosis,% (p = 0.048) influenced the risk of developing the discussed endpoint in the long-term period in patients with peripheral atherosclerosis. **Conclusions:** The probability of developing vascular events and adverse outcomes during a three-year prospective follow-up was assessed. It was found that hospitalization for heart failure over a three-year period occurred in 3.4 % of patients with atherosclerotic lesions of various vascular beds and their combinations. It is noted that such groups of factors as "the value of the ejection fraction% + the value of the base of the aorta, mm." (p=0.025), "the degree of atherosclerotic lesions of the posterior lateral branch, % + the value of the ejection fraction, %" (p=0.046), influenced the risk of developing heart failure in the long-term period in the subjects of the survey group. Using logistic regression equations, original prognosis tables have been developed that provide information on the likelihood of developing heart failure, which can be used in real clinical practice in patients with peripheral atherosclerosis.

***Key words:*** *heart failure, peripheral atherosclerosis, renal atherosclerosis, carotid atherosclerosis*

### Conflict of interests

The authors declare no conflict of interests

### Sources of funding

The authors declare no funding for this study

Article received on 30.12.2021

Accepted for publication on 17.05.2022

**For citation:** Kobzeva N.D., Terentev V.P., Oleinikova V.D. Features of Prediction of Heart Failure in Patients with Peripheral Atherosclerosis in the Long Period. The Russian Archives of Internal Medicine. 2022; 12(5): 380-388. DOI: 10.20514/2226-6704-2022-12-5-380-388 EDN: OUJDMB

AH — arterial hypertension, BCA — brachiocephalic arteries, CHF — chronic heart failure, CKD — chronic kidney disease, ECG — electrocardiography, EF — ejection fraction, FC — functional class, GFR — glomerular filtration rate, HF — heart failure, LCA — left coronary artery, LLA — lower limb arteries, LV — left ventricle, MI — myocardial infarction, PLB — posterolateral branch, TIA — transient ischemic attack

## Introduction

Despite the continuous improvement of diagnostic methods, optimal drug treatment in accordance with accepted standards and implementation of new preventive programs, patients with cardiovascular pathologies still demonstrate a high incidence of adverse long-term events and outcomes [1].

Atherosclerotic lesions of peripheral vessels are, no doubt, associated with high risk of heart failure development. In general, this association is characterized by increased left ventricular (LV) afterload due to the increased stiffness of aortic walls and, as a result, deterioration of coronary blood flow that results in hypertension, LV hypertrophy, diastolic dysfunction, and the development of heart failure [2,3].

High mortality due to heart failure is undoubtedly caused by cardiac issues and rapid progression of the underlying disease. According to OPTIMIZE-HF register data, about 30 % of individuals with reduced LV ejection fraction (EF) and 29.2 % with EF >40 % are rehospitalized within 90 days after discharge from the hospital [4].

A long-term task related to cardiovascular diseases is the development of a personalized approach to patients with atherosclerosis of any vascular territory.

Despite the fact that the prevalence of peripheral atherosclerosis is high, and the patients with this pathology

belong to one of the most difficult to cure groups, today we have no reliable scores for qualitative assessment of long-term prognosis [5].

The issue of treating patients with atherosclerotic pathology of peripheral arteries requires multidisciplinary solutions due to the high risk of adverse vascular events.

## Study objective

To assess the probability of heart failure development during a three-year prospective follow-up and to develop a method for its comprehensive assessment in individuals with atherosclerotic lesions of various vascular territories.

## Materials and methods

This prospective study included 519 patients (average age 60.0 ± 8.7 years) with atherosclerotic lesions of different vascular territories and their combinations (380 men and 139 women) who received treatment in specialized departments of State Budgetary Institution of Rostov Region Rostov Regional Clinical Hospital (GBU RO ROKB). The study protocol was approved by the local independent Ethics Committee of Federal State Budgetary Institution of Higher Education Rostov State Medical University of the Ministry of Health of the Russian Federation.

Inclusion criteria were as follows: peripheral arterial diseases in patients that meet the criteria of the recommendations of European Society of Cardiology (ESC) and the European Society of Vascular Surgeons (EOVS) for the diagnosis and management of peripheral arterial diseases (2017) [6]; informed consent form signed by the patient. Exclusion criteria were as follows: comorbidity with severe dysfunction of organs and systems; oncological and mental diseases; acute infectious processes.

Arterial hypertension (AH) was diagnosed according to the Guidelines for the Management of Arterial Hypertension developed by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (2013). [7]. Chronic heart failure was diagnosed according to the Guidelines "Chronic Heart Failure (CHF)" developed by the Society of Heart Failure Specialists of the Russian Cardiological Society (2016) [8].

Standard laboratory test with lipid panel was performed for all patients. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (2011). The set of instrumental studies included electrocardiography (ECG), echocardiographic examination, ultrasound examination of kidneys, brachiocephalic arteries (BCA); if there were clinical signs with suspected atherosclerotic lesions of vascular territories, coronary angiography, angiography of renal vessels, BCA and lower limb arteries (LLA) were performed.

Design of this clinical study is provided in Figure 1.

AH was observed in 500 (96.3 %) patients. Hereditary diseases were registered in 239 (46.0 %) patients, smoking — in 209 (40.2 %) patients (Table 1).

Based on the results of angiographic examination, the patients were divided into groups depending on the number and combinations of the affected vessels.

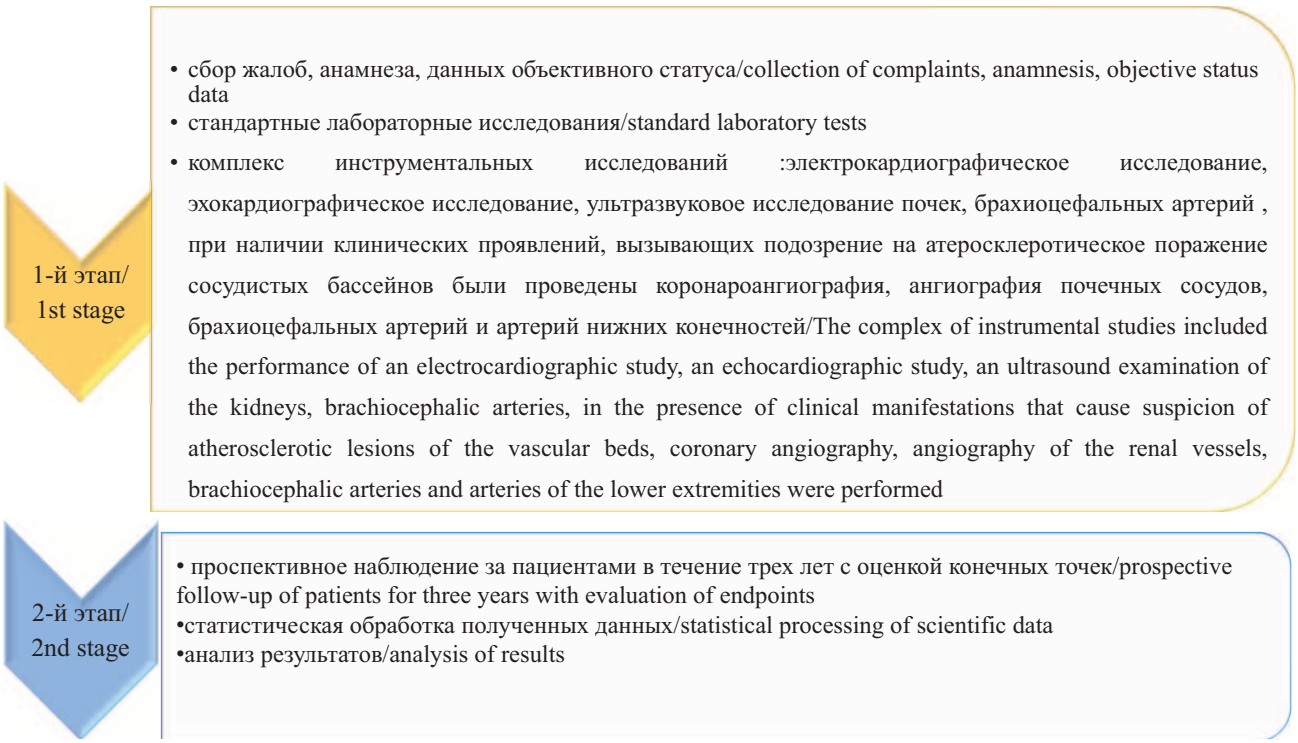



***Figure 1.*** *Study Design*

Atherosclerotic lesion of one vascular territory was confirmed in 258 (49.7 %) patients, of two territories — in 171 (2.9 %) patients; of three territories — in 84 (16.2 %); of four vascular territories — in 6 (1.2 %) patients.

BCA lesion was diagnosed in 199 (38.3 %) patients, while BCA mono-lesion was confirmed in 4.6 % of cases. Atherosclerotic lesions of renal arteries were observed in 103 (19.8 %) patients, of LLA — in 105 (20.2 %) examined individuals (Table 2).

The second stage of this study included a prospective three-year follow-up. The patients or their relatives were contacted by telephone survey.

***Table 1.*** *Clinical characteristics patients*

| Parameter | n (%) |
|---|---|
| men/women (n, %) | 380/139 (73,2/26,8) |
| smoking (n, %) | 209 (40,2) |
| burdened heredity (n, %) | 239 (46,0) |
| presence of hypertension (n, %) | 500 (96,3) |
| acute cerebrovascular accident in history (n, %) | 98 (18,8) |
| myocardial infarction in history (n, %) | 205 (39,4) |
| history of lower limb amputation (n, %) | 3 (0,57) |
| chronic cerebrovascular insufficiency (n, %) | 173 (33,3) |
| the presence of chronic ischemia of the lower extremities (n, %) | 90 (17,3) |
| history of angina pectoris (n, %) | 362 (69,7) |
| chronic heart failure (n, %) | 333 (64,2) |
| functional class of chronic heart failure<br>1 FC | 135 (40,5) |
| 2 FC | 166 (49,8) |
| 3 FC | 32 (9,7) |
| CHF with low EF (less than 40 %) (n, %) | 15 (4,5) |
| CHF with intermediate EF (from 40 % to 49 %) (n, %) | 113 (33,9) |
| CHF with preserved EF (50 % or more) (n, %) | 205 (61,6) |
| glomerular filtration rate less than 60ml/min/1.73m$^2$ | 130 (25,1) |
| presence of diabetes (n, %) | 112 (21,5) |

**Note:** FC/functional class of chronic heart failure / CHF/chronic heart failure / EF/ejection fraction

***Table 2.*** *Features of atherosclerotic lesions of various vascular beds in patients*

| Parameter | n (%) |
|---|---|
| damage to one vascular bed | 258 (49,7) |
| damage to two vascular beds | 171 (32,9) |
| damage to three vascular beds | 84 (16,2) |
| damage to four vascular beds | 6 (1,2) |
| monolesion (coronary arteries) | 225 (43,4) |
| monolesion (brachiocephalic arteries) | 24 (4,6) |
| monolesion (renal arteries) | 3 (0,6) |
| monolesion (arteries of the lower extremities) | 4 (0,8) |
| coronary arteries + renal arteries | 83 (15,9) |
| coronary arteries + brachiocephalic arteries | 70 (13,4) |
| coronary arteries + arteries of the lower extremities | 5 (0,9) |
| lower extremity arteries + brachiocephalic arteries | 12 (2,3) |
| brachiocephalic arteries + renal arteries | 2 (0,4) |
| coronary arteries + brachiocephalic arteries + lower extremity arteries | 76 (14,8) |
| brachiocephalic arteries + lower extremity arteries + renal arteries | 2 (0,4) |
| coronary arteries + brachiocephalic arteries + renal arteries | 7 (1,3) |
| coronary arteries + brachiocephalic arteries + lower extremity arteries + renal arteries | 6 (1,2) |

During the period specified, the following events and outcomes were analyzed: development of transient ischemic attack, stroke (nonfatal/ fatal stroke), myocardial infarction (MI) (nonfatal/fatal MI), development of heart failure (HF) (nonfatal/fatal HF), chronic kidney disease (CKD) (nonfatal/fatal CKD) , hospitalization for cardiovascular reasons, amputation of lower limb.

Statistical data analysis was performed using a set of applied statistical programs Microsoft Office Excel 2010 (Microsoft Corp., USA) and STATISTICA 10.0 (StatSoft Inc., USA). Kolmogorov–Smirnov test was used to assess the type of data distribution; for $p > 0.05$, distribution was considered to be normal. The data were presented as M±SD (M — arithmetic mean, SD — standard deviation) for normal distribution, and as Me [Q1; Q3] (Me — median, Q1 and Q3 — first and third quartiles) for abnormal distribution. Student's test was used for a normal distribution of sample, and Mann-Whitney test and $\chi 2$ test or Leuven test with F — for those different from the normal distribution. Besides, the authors used logistic regression analysis with the calculation of relative risks (RR) and the determination of $\chi^2$; the relationship was considered statistically significant at $p < 0.05$.

## Results

The development of vascular events and adverse outcomes was registered in 126 (24.2 %) patients, while hospitalization for new cases of heart failure was confirmed in 14 (3.4 %) patients.

During the analysis of the heart failure development probability, such factors as EF, % ($p = 0.04$), aortic base, mm ($p = 0.049$), degree of atherosclerotic lesion of left coronary artery (LCA), % ($p = 0.013$), and the severity of posterior lateral branch (PLB) stenosis, % ($p = 0.048$), affected the risk of developing the discussed endpoint in patients with peripheral atherosclerosis (Table 3).

Based on the data obtained, a nomogram was constructed to assess the possibility of heart failure development depending on risk factors. Thus, at EF 40 %, the risk of heart failure development during three year follow-up was 10 %, at EF 50 % — 7 %. In cases of LCA trunk stenosis 40 %, the risk of heart failure development during three years was 10 %; if the diagnosis of LCA stenosis 60 % was confirmed, the risk was 40 % (Table 4).

Two-factor logistic regression analysis allowed defining a combination of features that had a pathological

***Table 3.*** *Probability of developing heart failure*

| *Parameter | B0 | Estimate | OR (ratio) | $\chi^2$ | p |
|---|---|---|---|---|---|
| ejection fraction, % | 0,21 | -0,006 | 0,03 | 4,21 | 0,040 |
| base of the aorta, mm | -8,35 | 0,13 | 593 | 3,97 | 0,049 |
| lesion of the trunk of the left coronary artery, % | 0,63 | -0,19 | 0,0001 | 6,17 | 0,013 |
| damage to the posterior lateral branch, % | -13,2 | 0,11 | 1163 | 3,88 | 0,048 |

* p <0,05

***Table 4.*** *Nomogram for assessing the risk of developing heart failure within three years, depending on risk factors*

| | | | | | | |
|---|---|---|---|---|---|---|
| ejection fraction, % | 20 | 30 | 40 | 50 | 60 | 70 |
| risk of developing heart failure, % | 24 | 17 | 10 | 7 | 3 | 1 |
| base of the aorta, mm | 25 | 30 | 35 | 40 | 50 | 55 |
| risk of developing heart failure, % | 1 | 3 | 5 | 7 | 17 | 26 |
| lesion of the trunk of the left coronary artery, % | 10 | 20 | 30 | 40 | 50 | 60 |
| risk of developing heart failure, % | 1 | 4 | 8 | 10 | 25 | 40 |
| damage to the posterior lateral branch, % | 50 | 60 | 70 | 80 | 90 | 100 |
| risk of developing heart failure, % | 1 | 2 | 3 | 4 | 9 | 20 |

***Table 5.*** *The likelihood of developing heart failure, depending on a combination of factors*

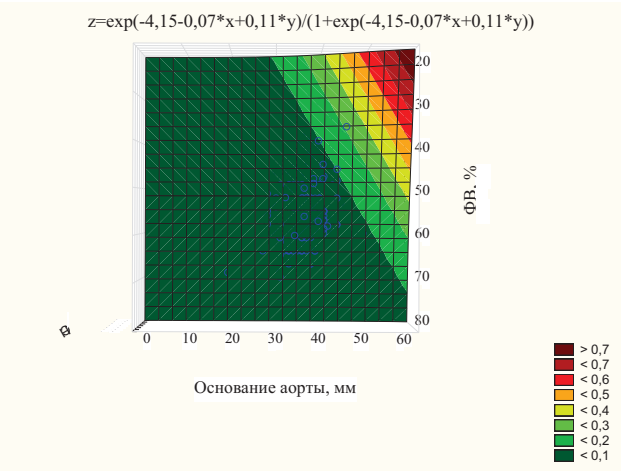
| *Parameter | B0 | Estimate | OR (ratio) | $\chi^2$ | p |
|---|---|---|---|---|---|
| ejection fraction, % + aortic base, mm | -4,15 | -0,07 /0,11 | 0,04 /234 | 7,4 | 0,025 |
| damage to the posterior lateral branch, % + ejection fraction, % | -9,24 | -0,09 /0,12 | 0,05 /1732 | 4,9 | 0,046 |

* p <0,05

effect on long-term prognosis, namely, “EF, % + aortic base, mm” (p = 0.025), “PLV, % + EF, %” (p = 0.046) (Table 5, Figure 2).

Nomograms based on logistic regression equations demonstrated that, if a patient has an aortic base equal to, for example, 30 mm and EF 60 %, the risk of heart failure during three years will be 13 %; in the case of EF v40 % with the same value of aortic base, the risk is 28 % (Table 6).

Confirmed EF 50 % and an atherosclerotic plaque 60 % in PLB area lead to the risk of developing heart failure during three years of 24 %, while vessel occlusion lead to 41 %. PLB stenosis 50 % and EF 40 % lead to the possibility of heart failure development 20 % (Table 7).

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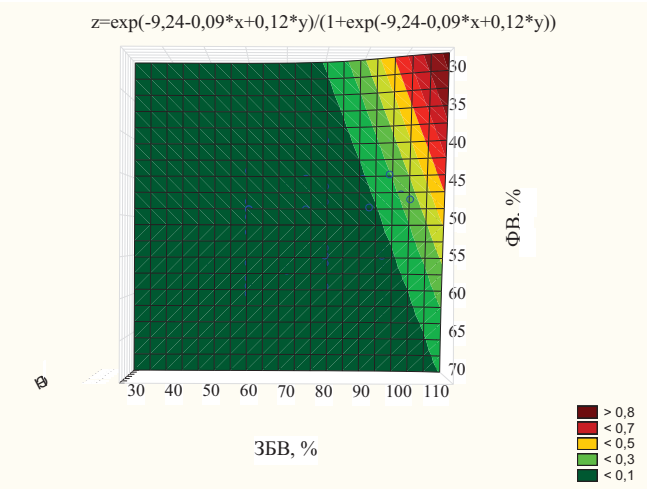


(б) / (b)

***Figure 2.*** *Assessment of the risk of developing heart failure depending on the size of the ejection fraction and the base of the aorta (a), the magnitude of the ejection fraction and the severity of the lesion of the posterior juic branch (b)*
**Note:** PBV — posterior lateral branch, EF — ejection fraction

***Table 6.*** *Nomogram for assessing the risk of developing heart failure depending on the size of the ejection fraction and the base of the aorta*

| | | Ejection Fraction, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | 20 | 30 | 40 | 50 | 60 | 70 |
| aortic base, mm | 5 | 9 | 8 | 7 | 5 | 4 | 3 |
| | 10 | 20 | 10 | 8 | 6 | 5 | 4 |
| | 20 | 45 | 29 | 16 | 10 | 8 | 6 |
| | 30 | 56 | 40 | 28 | 17 | 13 | 7 |
| | 40 | 68 | 52 | 39 | 24 | 17 | 8 |
| | 50 | 82 | 76 | 54 | 32 | 20 | 9 |

***Table 7.*** *Nomogram for assessing the risk of developing heart failure depending on the value of the ejection fraction and the severity of the lesion of the posterior lateral branch of the*

| | | Ejection Fraction, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | 20 | 30 | 40 | 50 | 60 | 70 |
| damage to the posterior lateral branch, % | 30 | 8 | 7 | 6 | 5 | 4 | 2 |
| | 40 | 25 | 20 | 17 | 14 | 10 | 8 |
| | 50 | 44 | 33 | 20 | 18 | 16 | 13 |
| | 60 | 57 | 48 | 29 | 24 | 20 | 17 |
| | 80 | 69 | 51 | 34 | 28 | 24 | 20 |
| | 100 | 85 | 68 | 50 | 41 | 33 | 22 |

## Discussion

In atherosclerotic lesions of a certain vascular territory, not only this area of blood supply is at risk. Atherosclerosis quite often becomes generalized, and if a patient has a monofocal lesion, the risk of adverse cardiovascular events nevertheless remains high.

According to a review of 17 studies involving more than 10,000 patients with asymptomatic carotid stenosis (>50 %), about 60 % of deaths were directly related to the existing cardiac pathology [9]. The following cardiovascular events were registered in patients with peripheral arterial disease during the first year of follow-up: 1.8 % — death due to cardiovascular causes, 1.4 % — noncardiovascular death, 1.9 % — acute myocardial infarction, 1 % — hospitalization for unstable angina, 0.9 % — ischemic stroke, 1.3 % — acute limb ischemia, 1.2 % — amputation [10].

Results of many studies clearly demonstrated that patients with peripheral atherosclerosis, even with adjusted risk factors, remain at high risk of fatal and non-fatal vascular events (myocardial infarction, stroke, HF) [11].

Analysis of literature sources demonstrated that existing models for predicting heart failure have been actively created and modified over the past decades, while most of them have been created and validated for patients with low EF and are used to assess one-year survival. The most common models are SHFMHFSS, MAGGIC, MECKI, 3C-HF, MUSIC. Thus, SHFM (Seattle Heart Failure Model) is the most common for assessing the life expectancy of patients with CHF at the outpatient stage. It was developed on the basis of the PRAISE1 trial and tested in USA and Italy. [12].

MAGGIC risk score can be applied to patients with reduced or preserved ejection fraction. The only biomarker considered by this score is serum creatinine; thus, on the one hand, it is easily available for common use, however, on the other hand, its informative value is reduced. [13].

At the same time, none of the presented models is aimed at assessing the risk of heart failure development in patients with peripheral atherosclerosis during three-year period.

It is known that the survival rate of patients with the new onset of heart failure that requires hospitalization is about 40 % during the first year [14]. According to a meta-analysis of 60 trials in the period from 1950 to 2016 that included 1.5 million patients with heart failure with reduced EF in the "stable" phase of the disease, the total one-year survival rate is 86.5 % [15].

Certain established risk factors that determine the prognosis of patients with regard to the nature and severity of heart failure include LV EF, functional class of CHF (NYHA), and appropriate treatment strategy [16]. In addition, one of the main indicators of the severity of pathological process in patients with heart failure is LV EF. Meanwhile, heart failure can also develop along with preserved LV EF [17].

Analysis of literature sources revealed that more than half of the total number of patients with CHF have preserved LV EF, and their number continues growing rapidly [18]. Results of the Rochester Epidemiological Project clearly demonstrated that more than 40 % of patients with heart failure are diagnosed with LV EF >50 % [19]. According to the EPOCH-CHF study, preserved or intermediate LV EF in the range of 40–60 % was diagnosed in more than 50 % of patients [20]. The analysis of a Canadian study results revealed that above 40 % of the examined patients had preserved EF [21]. The complex of such endpoints as total mortality + rehospitalizations in the groups with reduced and preserved EF had no statistical differences, while the mortality rate during the first year in patients with preserved EF was 29 %. [22]. It was found that patients with reduced EF and ejection fraction >35–40 % had a more favorable prognosis [23].

Based on the results of our study, EF <40 % was registered in 4.5 % of patients, intermediate EF was observed in 33.9 %, and preserved EF was observed in 61.6 % of patients. It should be mentioned that EF value had an effect on the long-term prognosis of patients what is consistent with the literature data. At the same time, in the course of our study, combinations of factors were presented that have an effect on the long-term prognosis of the presented group of patients.

## Conclusion

Thus, in the course of a prospective study, it was found that hospitalization for heart failure occurred in 14 (3.4 %) patients with atherosclerotic lesions of various vascular territories and their combinations.

It was mentioned that such factors as EF, aortic base, size of atherosclerotic lesions of LCA trunk, and severity of PLB stenosis had an effect on the risk of long-term heart failure development in patients with peripheral atherosclerosis.

It was revealed that the risk of heart failure was influenced by such groups of factors as EF + aortic base, severity of PLB atherosclerotic lesions + EF.

Based on logistic regression equations prognosis, original tables were developed allowing to obtain information on the possibility of heart failure development that can be used in real clinical practice in individuals with peripheral atherosclerosis.

**Вклад авторов:**

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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DOI: 10.20514/2226-6704-2022-12-5-389-393
EDN: VVORKA
УДК 616.125.2-006.325-036.1-07

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# КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ БЕССИМПТОМНОЙ МИКСОМЫ ЛЕВОГО ПРЕДСЕРДИЯ

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# Clinical Observation of Asymptomatic Left Atrial Myxoma

**Резюме**

Миксомы являются наиболее распространенным типом первичных доброкачественных опухолей сердца у взрослых, частота которых в популяции по данным аутопсий составляет около 0,2 %. Миксомы развиваются из мультипотентной мезенхимы и обычно представляют собой недифференцированное предсердное образование, имеющее ножку и прикрепленное к овальной ямке на левой стороне межпредсердной перегородки. Частое бессимптомное течение заболевания затрудняет своевременную диагностику и лечение. Представленное клиническое наблюдение демонстрирует случайное выявление миксомы левого предсердия у пациентки 68 лет с последующим успешным оперативным вмешательством.

***Ключевые слова:*** *миксома сердца, диагностика, клиническое наблюдение, бессимптомное течение*

**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 27.04.2022 г.
Принята к публикации 08.06.2022 г.

**Для цитирования:** Сергеева В.А., Толстов С.Н., Сычкова Е.Д. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ БЕССИМПТОМНОЙ МИКСОМЫ ЛЕВОГО ПРЕДСЕРДИЯ. Архивъ внутренней медицины. 2022; 12(5): 389-393. DOI: 10.20514/2226-6704-2022-12-5-389-393 EDN: VVORKA

**Abstract**

Myxomas are the most common type of primary benign cardiac tumor in adults, with an incidence of about 0.2 % in the population at autopsy. Myxomas develop from multipotent mesenchyme and are usually an undifferentiated, pedunculated atrial mass attached to a fossa ovale on the left side of the atrial septum. Frequent asymptomatic course of the disease complicates timely diagnosis and treatment. The presented clinical observation demonstrates the accidental detection of left atrial myxoma in a 68-year-old patient with subsequent successful surgical intervention.

***Key words:*** *cardiac myxoma, diagnosis, clinical observation, asymptomatic course*

**Conflict of interests**

The authors declare no conflict of interests

**Sources of funding**

The authors declare no funding for this study

Article received on 27.04.2022
Accepted for publication on 08.06.2022

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**For citation:** Sergeeva V.A., Tolstov S.N., Sychkova E.D. Clinical Observation of Asymptomatic Left Atrial Myxoma. The Russian Archives of Internal Medicine. 2022; 12(5): 389-393. DOI: 10.20514/2226-6704-2022-12-5-389-393 EDN: VVORKA

BP — blood pressure, CT — computed tomography, ECHO-CG — echocardiography, LA — left atrium, MRI — magnetic resonance imaging

## Introduction

Until the middle of the 20th century, intravital diagnosis of space-occupying lesions in heart was scarcely performed due to the lack of the required instrumental examination methods. With the implementation of angiocardiography in 1951, the ability to detect cardiac tumors in patients has increased significantly. However, surgical treatment of space-occupying intracardiac lesions consistently failed [1]. A breakthrough event was the development of heart-lung machine and the successful surgical removal of cardiac myxoma in 1954 performed by a Swedish cardiac surgeon Clarence Crafoord [2]. A new milestone in the diagnosis of cardiac tumors was the implementation of echocardiography into clinical practice in 1959 [3]. It is still the basic method in the diagnosis of any cardiac pathology. Comprehensive information about the size, position and the suspected nature of an intracardiac mass can be obtained using computed tomography (CT) and magnetic resonance imaging (MRI) of heart with contrast enhancement.

Myxomas are the most prevalent primary benign cardiac tumors that account for up to 80 % of all diagnosed intracardiac neoplasms [4]. Myxomas are most often located in left atrium (LA) (up to 75 %); about 2-3 times as frequently in women, in the age group of 30 to 60 years [5]. In most cases, this disease is detected during occasional examination, however, with no timely treatment, intracardiac hemodynamics may be disturbed with the development of progressive heart failure and embolic complications that can result in disability and death of the patient.

Etiology of this disease is not completely understood. It is assumed that herpes simplex virus type I is a trigger; it can cause chronic endocarditis and neoplastic transformation, since antigens and DNA of herpes simplex virus type I are detected in 70 % of patients with myxoma [6]. Cardiac myxomas are also found in patients with a mutation in PRKAR1A gene that is located on the long arm of chromosome 17 (17q23-q24) as part of a rare hereditary neoplastic syndrome with an autosomal dominant mode of inheritance, the so-called Carney complex [7]. The clinical signs of this genetic pathology also include spotty skin pigmentation and myxomas, active tumors of endocrine system (nodular hyperplasia of adrenal cortex, breast fibroadenoma, testicular tumors, pituitary tumors with gigantism or acromegaly) and the sheaths of nerve trunks. About 10 % of all heart myxomas are a sign of Carney complex and are considered to be the main clinical criteria of this disease; they are found in 30-40 % of cases of this pathology. However, to diagnose Carney complex, two or more major clinical criteria, or one major and one additional (hereditary) factor are required [7].

The size, shape and weight of a myxoma can vary over a wide range. In various clinical observations report on tumors from a few millimeters to 16 centimeters in diameter and from 2 to 250 grams in weight [5]. World Health Organization defines a cardiac myxoma as a neoplasm consisting of stellate or plump, cytologically soft mesenchymal cells located in the myxoid stroma. Cardiac myxoma cells often form rings, nests, and linear syncytia that originate from vascular structures. Fibrosis, calcification and organized thrombosis are common; however, mitoses are scarcely found. A myxoma usually has a pedicle and is attached to the oval fossa on the left side of interatrial septum [8].

Regardless of the presence or absence of clinical signs of cardiac myxoma, the only method of treatment is the surgical removal of this tumor. Surgery should be performed by a skilled cardiac surgeon, since incomplete removal of a myxoma may result in its relapse [5]. Following the surgical treatment, regular echocardiography is recommended to monitor the patient's condition. According to the literature, sporadic myxoma relapse develops in about 3 % of tumors [5]. It may occur months or years after the first surgery. Ricardo Oliveira et al. [9] presented a study where 19 patients underwent surgery for cardiac myxoma; on average, 2 relapses were diagnosed over a period of 5.2 ± 3.7 years (relapse rate was 10.5 %).

We present our own clinical experience of follow-up a patient with asymptomatic cardiac myxoma; the neoplasm was found during computed tomography of thoracic organs as part of examination for COVID-19.

## Case report

In June 2021, patient M., female, 68, a resident of the Saratov region (Ershov) had malaise, weakness, fever, sore throat, palpitations. She visited a therapist at a local clinic to exclude novel coronavirus infection. To diagnose SARS-CoV-2, nasopharyngeal swabs were taken. Positive PCR result confirmed COVID-19. Outpatient treatment was provided. The patient underwent chest CT to exclude lung damage. No pulmonary parenchyma infiltration was found, however, the change in the size of mediastinum was observed. The mediastinum was expanded due to the dilatation of heart chambers, mainly of LA to 5 cm with decreased density of X-ray radiation

and small linear high-density inclusions. A routine additional examination in the Regional Cardiac Surgery Center was recommended after the recovery from COVID-19. The patient had no apparent cardiovascular clinical signs. For about two years, she has high blood pressure (BP) up to 150 and 100 mm Hg maximum; she regularly receives antihypertensive therapy (indapamide + bisoprolol), and complies with the therapy. Therapy-associated BP is 120 and 80 mm Hg. Besides, she regularly receives acetylsalicylic acid (ASA) and atorvastatin. After the novel coronavirus infection, she had dyspnea at moderate exercise and asthenia. The patient was hospitalized to the Regional Cardiac Surgery Center in August 2021 for further examination. At admission, the patient had almost no complaints. From past medical history: the patient grew and developed according to her age. Comorbidities: chronic non-obstructive bronchitis, chronic erosive gastritis (not tested for Helicobacter pylori), varicose veins disease. Past surgeries — cholecystectomy in 2005, epidemiological and allergic anamnesis within normal, bad habits — denies. Upon admission, negative PCR for SARS-CoV-2.

## Physical examination

Satisfactory condition. Active position. Clear consciousness. Height 165 cm, weight 85 kg. Body mass index 31.22 kg/m$^2$ — class 1 obesity. Respiratory organs: respiratory rate 18 per minute, vesicular respiration is heard in all lung fields. No adventitious breath sounds. Circulatory organs: apex beat is felt in 5 intercostal space along the midclavicular line. On percussion, borders of relative cardiac dullness are expanded along the upper border to the 2nd rib (enlarged LA). On auscultation, muffled rhythmic heart sounds. Heart rate coincides with the pulse and is 67 bpm. BP in both brachial arteries is 110 and 70 mm Hg.

## Results of laboratory tests and instrumental examinations

Results of laboratory tests revealed no significant deviations. Acute phase indicators were within normal. Due to the constant intake of 20 mg of atorvastatin per day, total cholesterol was 3.2 mmol/L, and low-density lipoprotein cholesterol — to 1.6 mmol/L.

Results of electrocardiography is presented in **Fig. 1.** Conclusion: PQ 0.2 s, QRS 0.08 s, QT 0.4 s, sinus rhythm with heart rate of 92 per minute. Vertical QRS axis. Slowing of atrioventricular conduction. Enlarged atria. Left ventricular hypertrophy.

During inpatient examination, transthoracic echocardiography (ECHO-CG) was performed; it revealed increased LA (ESD 57 mm; normal range 27-38 mm). Mass lesion in LA, large (59 x 48 x 30 mm), almost filling its entire cavity. Mass lesion of homogeneous, hypoechoic structure, with single calcifications, sharp smooth contours, poorly mobile with blood flow, however, with no signs of mitral intracardiac obstruction. This mass is supposed to be attached to the interatrial septum with a broad pedicle. No significant cardiac valve dysfunction was found. The size of LV cavity and its contractility were within normal. Left ventricular myocardial mass index 81 g/m$^2$ (normal range 44 — 88 g/m$^2$). Inferior vena cava is of normal size and with normal respiratory variation. No effusion in pericardial cavity.

To detect the degree of atherosclerotic lesions of vascular bed and to exclude thrombotic lesions of the deep veins of lower limbs, coronary angiography and duplex scanning of brachiocephalic arteries and of the vessels of lower limbs were performed. There were no indications for coronary revascularization. Early signs of atherosclerosis were found in brachiocephalic arteries. Varicose veins of lower limbs were observed. Deep veins were patent. There were no signs of valvular insufficiency or deep vein thrombosis of lower limbs.

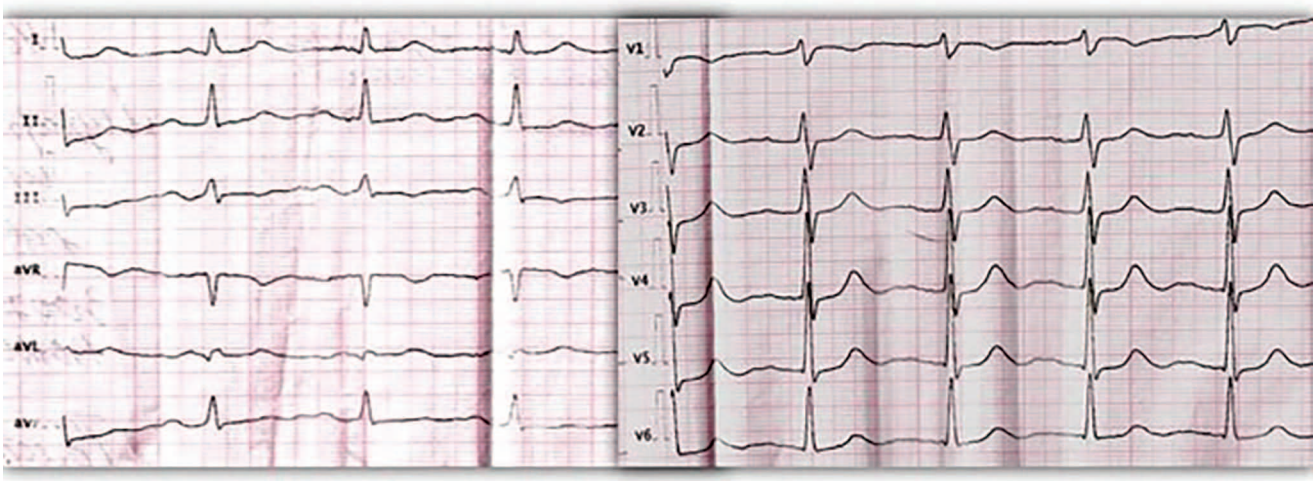


***Figure 1.*** *ECG of patient M., 68 y.o.*

Minor atherosclerotic changes in the arteries of lower limbs were found. Results of the ultrasound examination of abdominal organs revealed steatohepatosis and non-uniformity of the contours of pancreas.

In order to visualize a mass lesion in LA, CT with IV bolus contrast enhancement (Ultravist) was performed (**Fig. 2**). According to CT data, a contrasting defect was visualized in LA; it was caused by a soft-tissue mass lesion with uneven tuberous contours, of inhomogeneous structure (due to inclusions of small calcifications). The size of this mass lesion was up to 60 x 55 x 61 mm (mediolateral, sagittal, vertical), volume — 117 mL, it occupied almost the entire LA cavity. The mass lesion described is broadly adjacent to the middle third of interatrial septum; it spreads in the mouth of right superior pulmonary vein with no significant stenosis of lumen; it does not accumulate contrast agent. LA volume with auricula was 225 mL. Conclusion: LA myxoma.

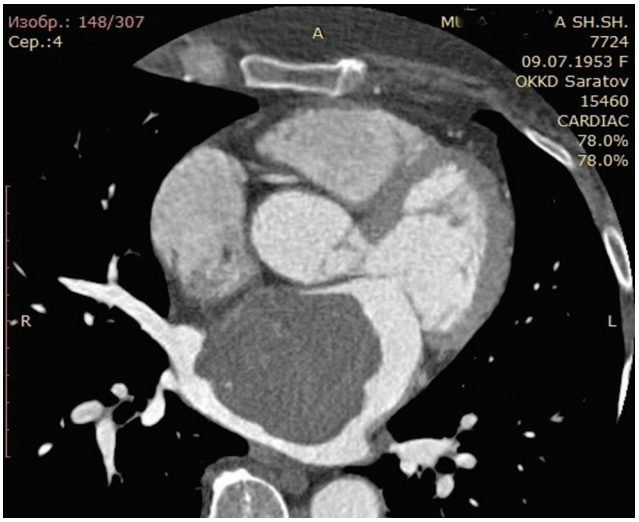


***Figure 2.*** *Cardiac computed tomography with contrast of patient M., 68 y.o.*

## Treatment

On September 3, 2021, the patient underwent routine surgical treatment: removal of LA mass, atrial septal defect closure with xenopericardium patch in conditions of artificial circulation and pharmaco-cold cardioplegic protection. The mass removed — myxoma (no histological signs of malignancy found) is presented on **Fig. 3**. In the early postoperative period, the patient had a rhythm disorder — paroxysm of atrial fibrillation with a rate of 65–170 bpm. Successful pharmacological cardioversion with amodarone was performed. Control CT and ECHO-CG revealed no intracardiac hemodynamic disorders. The patient was discharged for further rehabilitation at the outpatient stage with sinus rhythm, stable hemodynamics, in a satisfactory condition on September 15, 2021. 6 months after the surgery the patient confirmed stable and satisfactory condition during a telephone call. She has a usual lifestyle. She had no irregular heart function. She adhered to all recommendations.

## Discussion

In about 20 % of cases, cardiac myxomas are characterized by an asymptomatic course and slow progression what complicates the early diagnosis of this disease [8].

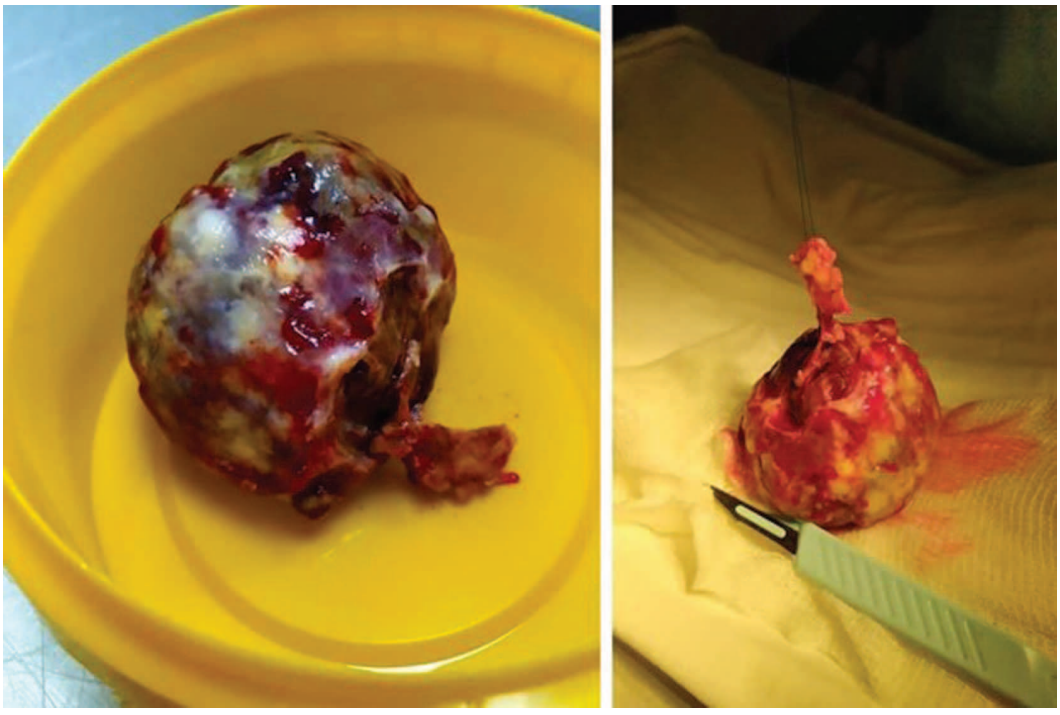

***Figure 3.*** *Intracardiac tumor removed during surgery — myxoma*

In the above case report, a mass lesion was found incidentally, during the examination of lungs as part of examination for COVID-19. Despite the large size of the intracardiac mass, there were no clinical signs. According to many literature sources, the asymptomatic course of this process depends not so much on the size of mass lesion, but to a greater extent, on the presence of intracardiac hemodynamic disorders. In regard to LA myxomas, on the presence of mitral obstruction [5, 10]. Clinical signs include hemodynamic signs (signs of heart failure, arrhythmias, sudden cardiac death), signs of systemic embolism (peripheral vascular embolism, transient ischemic attacks or strokes) and constitutional signs (fever, weight loss, arthralgia, asthenia) [10]. The onset of these symptoms, of course, leads to active diagnostic search and diagnosis.

Cardiac myxoma does not belong to diseases that are hard to diagnose. To find a mass lesion, one should have any available imaging method for examination of the heart (ECHO-CG, CT, MRI).

Despite the asymptomatic course, surgical treatment is the "gold standard" for the management of myxoma, since complications associated with further tumor growth can be fatal for a patient.

## Conclusion

Chest CT for the novel coronavirus infection contributed to the timely diagnosis of asymptomatic LA myxoma, and the successful surgery made it possible to avoid severe cardiovascular complications. Despite the outpatient follow-up for arterial hypertension, no ECHO-CG was performed over several years. Timely performed, this routine instrumental examination could contribute to the earlier detection and surgical management of cardiac myxoma.

**Вклад авторов:**

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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DOI: 10.20514/2226-6704-2022-12-5-394-400
EDN: WGQVKA
УДК 616.155.35-06:616.1/.8-005

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# ИДИОПАТИЧЕСКИЙ ГИПЕРЭОЗИНОФИЛЬНЫЙ СИНДРОМ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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# Idiopathic Hypereosinophilic Syndrome. A Clinical Case

**Резюме**

Идиопатический гиперэозинофильный синдром является редким феноменом во врачебной практике. Основным критерием диагностики является стойкое повышение уровня эозинофилов выше 1,5*10$^9$/л в сыворотке крови и отсутствие клинических и лабораторно-инструментальных данных, объясняющих возможную природу данного состояния.

Представлен клинический случай идиопатического гиперэозинофильного синдрома, протекающий под маской острого коронарного синдрома. Детальный разбор данного случая проведен с целью освещения возможного варианта течения данного заболевания, а также для повышения настороженности в области «больших» эозинофилий.

***Ключевые слова:*** *гиперэозинофилия, полиорганная недостаточность, острое нарушение мозгового кровообращения, тромбоэмболия легочной артерии*

**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 15.03.2022 г.
Принята к публикации 14.07.2022 г.

**Для цитирования:** Лопина Е.А., Душина А.Г., Либис Р.А. ИДИОПАТИЧЕСКИЙ ГИПЕРЭОЗИНОФИЛЬНЫЙ СИНДРОМ. КЛИНИЧЕСКИЙ СЛУЧАЙ. Архивъ внутренней медицины. 2022; 12(5): 394-400. DOI: 10.20514/2226-6704-2022-12-5-394-400 EDN: WGQVKA

**Abstract**

Idiopathic hypereosinophilic syndrome is a rare phenomenon in medical practice. The main criterion for diagnosis is a persistent increase in the level of eosinophils above 1.5 * 10$^9$/ l in the blood serum and the absence of clinical and laboratory and instrumental data explaining the possible nature of this condition.

A clinical case of idiopathic hypereosinophilic syndrome, which occurs under the guise of acute coronary syndrome, is presented. A detailed analysis of this case was carried out in order to highlight a possible variant of the course of this disease, as well as to increase alertness in the area of "large" eosinophilia.

***Key words:*** *hypereosinophilia, multiple organ failure, acute cerebrovascular accident, pulmonary embolism*

**Conflict of interests**

The authors declare no conflict of interests

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**Sources of funding**
The authors declare no funding for this study

Article received on 15.03.2022
Accepted for publication on 14.07.2022

**For citation:** Lopina E.A., Dushina A.G., Libis R.A. Idiopathic Hypereosinophilic Syndrome. A Clinical Case. The Russian Archives of Internal Medicine. 2022; 12(5): 394-400. DOI: 10.20514/2226-6704-2022-12-5-394-400 EDN: WGQVKA

BP — blood pressure, CBC — complete blood count, HR — heart rate, IHES — idiopathic hypereosinophilic syndrome, LV — left ventricle, RR — respiratory rate

The outcome of any disease is largely determined by its timely and correct diagnosis. The difficulties in diagnosing idiopathic hypereosinophilic syndrome (IHES) are caused by the variety of the clinical signs of this disease, however, as well as by the absence of an obvious etiological factor with a clear mechanism for the development of complications. Hematological changes detected during the examination of patient suggest the possible causes of development of the disease and contribute to preventing such development by adjusting the treatment [1].

Eosinophilia in blood serum is not an independent disease, but only its laboratory sign, therefore, it is impossible to predict the specific features of disease course based only on blood test results. However, it is the increase in the number of eosinophils that will narrow the diagnostic search for the causes of disease development [2].

The increased eosinophils in blood serum are primarily associated with the development of an immediate allergic reaction or with persistent helminthiasis. Eosinophil count within $0.6\times10^9$/L is considered as eosinophilia, and an increase over $1.5\times10^9$/L — as hypereosinophilia, or "major" eosinophilia [1]. The exclusion of these diseases from the possible eosinophilia causes allows ~~us~~ suspecting other pathologies, including systemic connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis), diseases of gastrointestinal tract (eosinophilic gastritis and colitis), blood diseases (lymphoma, lymphogranulomatosis, Kostmann syndrome), etc. [3].

Hypereosinophilic syndrome is an extremely rare disease. This syndrome is more common in men than in women (9:1). The age of onset is 20-50 years. The clinical presentation is characterized by polymorphism of symptoms and desadaptative changes of body functions [1].

IHES is the diagnosis of exclusion. It is established by a detailed diagnostic search aimed at exclusion of all possible causes of the reactive process and the presence of clonal hypereosinophilia markers.

## Case report

Patient N., male, 41; on July 26, 2017 he was delivered by an ambulance team to the admission department of the city clinical hospital with complaints of pressing pain in the region of heart, palpitations, sweating, pronounced weakness.

It is known from the case history that for the first time the patient felt pressing pain in the region of heart a week before the previous hospitalization, due to emotional stress, he relieved the pain by Corvalol drops. He did not seek medical help. The intensity of pain syndrome increased on July 26, 2017; it was accompanied by tachycardia, sweating and weakness in limbs. Self-administration of Corvalol resulted in no effect. He called an ambulance team that transported him to the admission department of the city hospital.

Past medical history: no abnormalities. According to the patient, he had no chronic diseases.

At the time of examination, patient's condition was satisfactory. Clear consciousness. Body mass index 31 kg/m$^2$. Skin: no rash, moderately pale, wet. Visible mucous membranes: without rash. Palpable lymph nodes are not enlarged, painless, not matted to the skin, underlying tissues and each other. Examination of musculoskeletal, respiratory, cardiovascular and urinary systems revealed no abnormalities. Blood pressure (BP) 130/80 mm Hg on both arms, heart rate (HR) 100 bpm, respiratory rate (RR) 18 per minute. No edemas.

Troponin I blood test of July 26, 2017 — negative.

After the initial therapeutic examination, the patient was admitted to the Cardiology Department with the diagnosis of acute coronary syndrome.

Complete blood count (CBC) results leukocytosis ($18\times10^9$/L), relative lymphopenia (14 %) and eosinophilia (53 %), granulocytes 61.8 %. Blood biochemistry revealed increased concentration of creatinine up to 162 μmol/L (GFR 45 mL/min/1.73 m$^2$), urea: up to 18.3 mmol/L, glucose: up to 8.4 mmol/L. Common urinanalysis revealed proteinuria (protein 0.52 g/L) and yeast fungi in large quantities.

ECG demonstrated sinus tachycardia with HR of 98 bpm. Left axis deviation. Right bundle branch conduction disorder — widened S wave in I, rSR pattern in V1. Left ventricular (LV) hypertrophy — Sokolow-Lyon index 38 mm. Focal changes on the lower wall cannot be excluded: pathologic Q wave in leads III and AVF, ST segment on flatline, flattened T wave. Repolarisation abnormality along LV lateral wall.

The patient received drug treatment according to the standards of management of patients with non-ST segment elevation acute coronary syndrome: acetylsalicylic acid, clopidogrel, nitroglycerin, heparin, bisoprolol, enalapril, atorvastatin.

Despite the ongoing treatment, on July 31, 2017, the patient's condition deteriorated sharply: there appeared severe headaches with no definite localization, dizziness, increased dyspnea and general weakness. The patient was not ambulant, however, he sat in bed without support. Speech became indistinct. General condition was assessed as severe. Skin was pale, covered with cold sweat. Abdomen was not distended, painless on palpation. In lungs — vesicular breathing, diffusely weakened throughout all lung fields. Heart sounds were muffled, rhythm was regular, no heart murmur heard, BP 110/70 mm Hg on both arms, HR 110 bpm.

The patient was urgently transferred to the intensive care unit.

CBC over time: leukocytosis $23.4\times10^9$/L; lymphopenia 8.5 %; granulocytes 81.0 %; increased erythrocyte sedimentation rate up to 48 mm/h; eosinophilia persisted at 50 %, with varying degree of maturity: eosinophilic myelocytes — 1 %, immature eosinophils — 2 %, stab eosinophils — 23 %, segmented eosinophils — 24 %. Serum concentrations of urea and creatinine increased to 29.1 mmol/L and 215 μmol/L, respectively, of glucose — up to 13.6 mmol/L. C-reactive protein value was 53.6 mg/L.

Due to build-up of dyspnea, thromboembolism of the small branches of pulmonary artery was suspected. D-dimer serum concentration was 1.0 mg/L at normal range of 0-0.5 mg/L. Coagulation parameters (activated partial thromboplastin time, prothrombin time, Quick prothrombin index, international normalized ratio) were within normal range.

Chest X-ray suggests the embolism of the small branches of pulmonary artery enhanced vascular pulmonary pattern; dilated, poorly structured roots; right hemidiaphragm at the level of the fourth rib; moderately enlarged heart, flattened cardiac arches; venous congestion.

On day 6th after hospitalization, ECG demonstrated persistent sinus tachycardia up to 100 bpm. There were signs of subendocardial ischaemia in the antero-apical-lateral LV region — high T wave in lead I, AVL, V1-V6.

On the same day, due to the onset of the symptoms of motor aphasia and dysarthria, an urgent brain MRI was performed that revealed multiple lacunar infarcts in cerebellum and cerebral hemispheres. During contrast enhanced brain MRI, none of the described foci and meninges accumulated the contrast agent.

The patient was seen by a neurologist and diagnosed with "multiple lacunar infarcts in both hemispheres of brain and cerebellum, probably of atherosclerotic subtype, associated with arterial hypertension, cerebral atherosclerosis."

From July 31 (day 6th after hospitalization), ethylmethylhydroxypidine succinate with antioxidant, antihypoxant and membrane-protective purposes, as well as succinic acid in combination with inosine, nicotinamide and riboflavin as an energy-synthesing agent were added to the ongoing drug therapy. Due to increasing signs of manifest inflammatory process in blood (leukocytosis, leftward shift), ceftriaxone and metronidazole were added to the treatment regimen for antibacterial and anti-inflammatory purposes. In view of the suspected embolism of the small branches of pulmonary artery, aminophylline was prescribed to reduce pressure in the pulmonary artery and facilitate the patient's breathing. Unfractionated heparin followed by enoxaparin sodium were added for antithrombotic purposes.

On August 1, 2017 (day 7th of hospitalization), the patient's condition was assessed as extremely severe. There were negative changes in the form of increased signs of cerebral insufficiency: consciousness was lost, verbal contact was absent. Skin was moderately pale. Spontaneous breathing: vesicular breathing in lungs, weakened in the lower parts, RR 22 per minute. BP 110/70 mm Hg on both arms, HR 120 bpm. No reaction to painful stimulus. There was edema of left lower limb.

Ultrasound examination of the vessels of lower limbs revealed phlebothrombosis of left femoral vein. Thrombectomy of the floating part of the thrombus with phleboplication was immediately performed.

In view of anticoagulants administration, esophagogastroduodenoscopy was performed to exclude erosive and ulcerative lesions of gastrointestinal tract, it identified a duodenal ulcer and Forrest 2B bleeding risk.

Aminocaproic acid and esomeprazole for parenteral administration were added to the treatment. Aminocaproic acid was prescribed to achieve injection hemostasis and to prevent relapse that may occur due to Forrest 2B.

CBC demonstrated persisting significant eosinophilia, leukocytosis, and increased erythrocyte sedimentation rate.

Considering the objective status and the results of laboratory tests and instrumental examinations, the patient's condition on day 7th of hospitalization was regarded as progressive multiple organ failure due to a systemic inflammatory response of an unspecified nature with organic damage of brain (multiple lacunar ischaemic foci), kidneys (necrotizing glomerulonephritis with increasing renal failure), lungs (thromboembolism of the small branches of pulmonary artery with the development of infarction pneumonia); left-sided acute phlebothrombosis. The patient was diagnosed with disseminated intravascular coagulation syndrome, acute

course; duodenal peptic ulcer complicated by gastrointestinal bleeding that was stopped with non-surgical methods.

After a multidisciplinary team meeting, meropenem and dexamethasone i/v were added to the treatment at a dose of 12 mg 2 times a day due to the persisting febrile fever and suspicion of a bacterial nature of the inflammatory process.

On day 8th, the patient's condition continued to deteriorate. Spontaneous Babinski reflex was observed on both sides. There were no meningeal signs. Body temperature increased to 38-39°C. Saturation 92 %. RR 34 per minute, breathing rhythm was regular. Moist rales in large number were heard in lungs. Tachycardia up to 120 bpm. The patient was given artificial lung ventilation.

Sternal puncture was performed for diagnostic purposes. Bone marrow cell differential count: the composition of punctate is polymorphic with a predominance of eosinophilic cells. Granulocytic lineage is preserved. Neutrophil maturation is not impaired. Eosinophilic lineage is significantly expanded from promyelocytes to mature forms. Maturation index of eosinophils was 0.44 (normal value 0.7). Lymphoid, monocytic and plasmacytic lineages are preserved. Erythrocyte lineage is preserved: normoblastic type of erythropoiesis. Megakaryocytic lineage functions with the release of platelets.

In order to exclude parasitic invasion, feces were tested for helminth eggs — the result was negative. Negative IgM and IgG titers to the causative agents of giardiasis, echinococcosis, opisthorchiasis, toxacorosis trichinosis were also obtained. The values of the components of the complement of circulating immune complexes C1g and C3d, antibodies (AT) to double-stranded DNA (anti-dsDNA; 1.06 IU/mL) and AT to single-stranded DNA (anti-ssDNA; 15.6 IU/mL), anti-nuclear AT (8-AT, ANA-Screen; 0.42 points), antineutrophilic antibodies (ANCA screen: antigens PR3, MPO; 0.2 points) were within the acceptable range.

Lumbar puncture performed on day 9th of hospitalization (August 3, 2017) revealed an insignificant erythrocyte sediment; protein 0.30 g/L; glucose 5.5 mmol/L; Pandy's test is negative.

Echocardiography (doppler Echo CG) revealed ultrasound signs of LV hypertrophy. Hepatosplenomegaly was diagnosed based on the results of the ultrasound of abdominal organs.

Ultrasound of the vessels of lower limbs over time (August 4, 2017) revealed thrombosis of great saphenous vein, deep veins of lower leg, popliteal vein. The patient continued receiving the infusion of enoxaparin sodium at a dose of 0.4 ml 2 times a day.

Leukocytosis with significant eosinophilia persisted until August 5 (day 11th in the hospital). Lymphocyte count normalized. Anemia and thrombocytopenia gradually increased, and on August 9, hemoglobin value was 84 g/L, RBC $2.70\times10^{12}$/L and platelet count $80\times10^{9}$/L. The concentration of urea and creatinine over time (day 15) was 36.4 mmol/L and 459 μmol/L, respectively. The patient was diagnosed with acute kidney injury of prerenal type.

On ECG, sinus tachycardia and ischaemia in the inferior and antero-apical- posterior regions of the LV persisted.

The patient's condition continued to deteriorate, on August 8th, 2017 (day 14th) was regarded as extremely severe: the patient didn't open his eyes, did not fix his gaze. There were no active movements in limbs. The skin was pale, moist to the touch. Body temperature was 38.3°C. Breathing through the endotracheal tube. Breathing in lungs was heard from both sides. During the irrigation of tracheobronchial tree, purulent sputum with streaks of blood was observed. Regular heart rhythm on auscultation, muffled heart tones. BP 130/70 mm Hg, RR 120 bpm. Abdomen was not distended and did not respond to palpation. No edema of lower limbs.

Considering the available data, on August 9th, 2017 (day 15), based on the results of clinical examinations and laboratory tests, as well as on the exclusion of probable etiological factors, the patient was diagnosed with "idiopathic hypereosinophilic syndrome with multiple organ damage."

Doppler Echo CG on day 15 revealed a small amount of fluid in pericardium. Ultrasound of abdominal organs demonstrated hepatosplenomegaly, diffuse focal changes in spleen and liver, and signs of intestinal paresis.

On August 9, at 02:30 p.m. the patient had cardiac arrest. 30 minutes of resuscitation measures with no effect. Biological death was confirmed at 03:00 p.m.

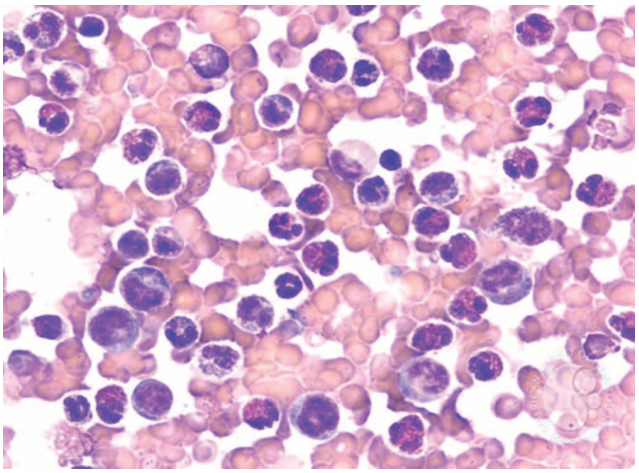

***Figure 1.*** *Microscopic preparation for idiopathic hypereosinophilic syndrome*

**Note:** for illustration of clinical case, source: URL: https://ru.techsymptom.com/50355-hypereosinophilic-syndrome-92 (date of the application: 14.07.2022)

Extract from the autopsy protocol (August 09, 2017). IHES. Disseminated intravascular coagulation involving heart, brain, spleen and kidneys. Multiple cerebral infarcts, non-coronary foci of myocardial necrosis. Vein thrombosis of left lower limb. Embolism of the small branches of pulmonary arteries. Hemorrhagic infarction in the middle lobe of right lung. Ulcer of duodenal bulb. Left-sided phleboplication (Figure 1).

## Discussion

Eosinophilia develops in connection with many diseases; however, the number of eosinophils should not exceed 5-10 % of the total number of WBC [1].

"Major" eosinophilia is extremely rare, its etiological factor is often unknown, and its pathogenesis is unclear. The most illustrative examples of pronounced hypereosinophilia include: Churg-Strausssyndrome that includes severe bronchial asthma with hypereosinophilia, eosinophilic infiltrates, necrotizing eosinophilic vasculitis and granulomas in different organs [2] and IHES.

In the presented clinical case, the patient had no bronchial asthma or maxillary sinus pathology, there was no data on the history of neuropathy what made it possible not to stop on the diagnosis of Churg-Strauss syndrome, but to suspect IHES.

IHES was first described in 1968 by W. Hardy et al. [3], and in 1975 M. Chusid et al. identified three typical features of this syndrome [4]:

1) peripheral blood hypereosinophilia that persists for at least 6 months (more than 1,500 cells/μL or more than 37 % of the total number of all WBC);
2) no other causes for eosinophilia;
3) changes in organs or their functions associated with eosinophilia.

Literature sources describe sporadic clinical cases of IHES that manifested as endocardial fibroelastosis, encephalopathy, peripheral neuropathy, transient ischemic attacks, eosinophilic infiltrates in lungs, hepatitis [1].

In IHES, hematological syndrome occurs in 100 % of patients, cardiac damage — in 58 %, skin manifestations — in 56 %, pulmonary syndrome — in 49 %, hepatic damage — in 30 %, gastrointestinal symptoms — in 23 % [5–7].

In the presented clinical case, the patient had severe eosinophilia (more than 50 % of the total number of

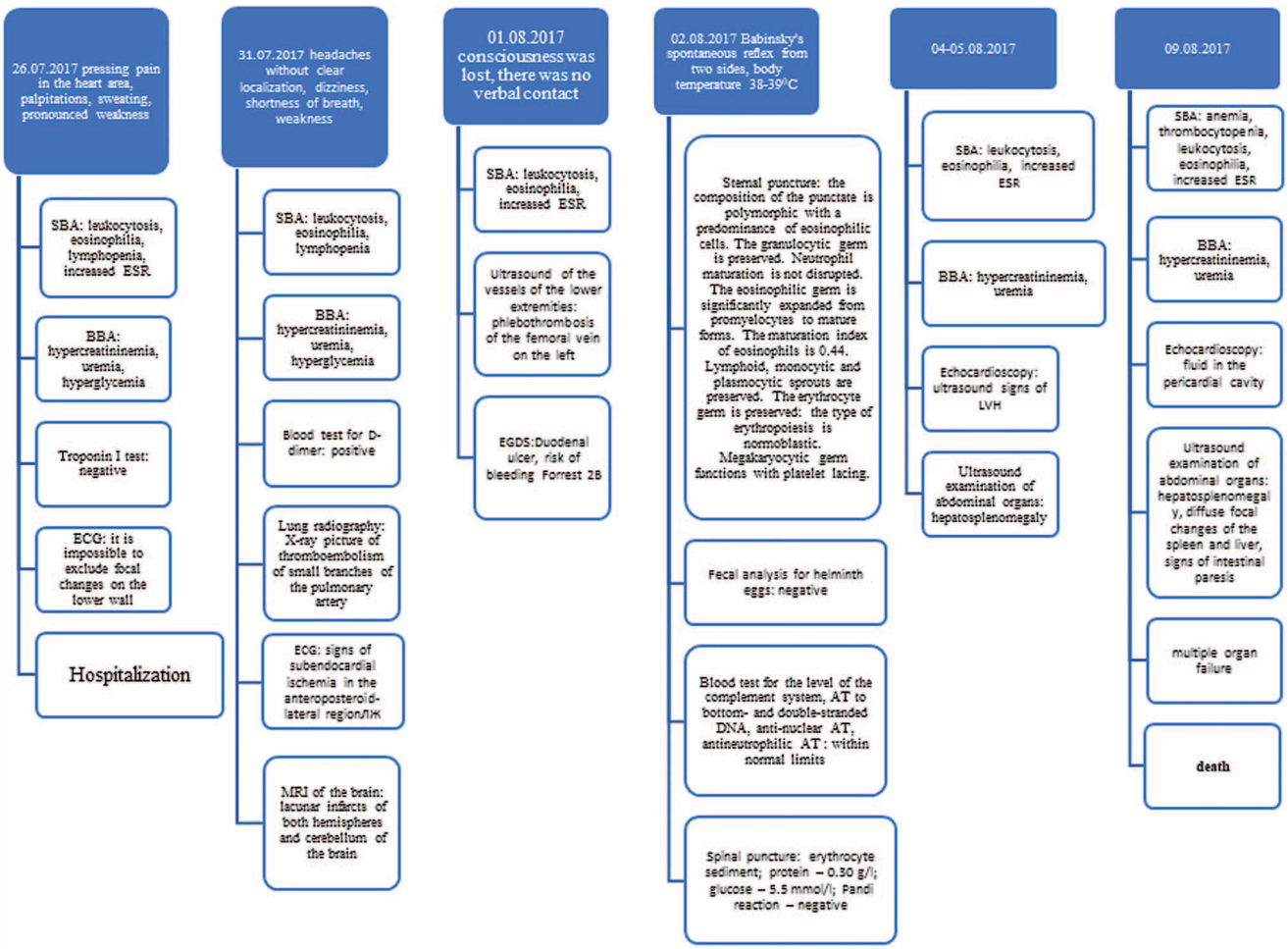


***Figure 2.*** *Chronology of the course of the disease*

WBC) what corresponds to the IHES criteria. The patient's clinical presentation started with the development of eosinophilic myocarditis that was considered as an acute coronary syndrome. During the next three days, the following also developed: acute impairment of cerebral circulation — damage to central nervous system, thromboembolism of the small branches of pulmonary artery and atelectasis of the right lung — pulmonary syndrome, duodenal ulcer complicated by bleeding — gastrointestinal syndrome. Later, there were floating thrombi in the vessels of lower limbs, signs of acute renal failure caused, with underlying IHES, by necrotizing glomerulonephritis, i.e. renal syndrome. By day 7 of hospitalization, the patient developed disseminated intravascular coagulation syndrome.

According to the results of CBC and sternal punction, no convincing data were found for a blood disease what allowed excluding hematological diseases from the possible etiological factors in the development of hypereosinophilia. Since all obvious causes of hypereosinophilia were excluded during the diagnostic search, the final clinical diagnosis was IHES.

Despite intensive drug therapy, the patient developed fatal multiple organ failure that led to death.

Thanatogenesis in this pathology is based on the imbibition of the tissues of heart, brain, spleen, kidneys and blood vessels by eosinophils. Upon death, eosinophils secrete cationic proteins and eosinophilic neurotoxins with bactericidal activity; they stimulate histamine release by mast cells that causes desquamation of healthy epithelial and endothelial cells [5]. The processes described were observed in the patient in the presented clinical case.

In this case, the disease was characterized by a rapidly progressive course with no positive changes in response to the treatment. The clinical presentation of IHES is always complex and unpredictable. However, we would like to pay special attention to the initial clinical symptoms of the disease: its primary sign was the ACS. Although cardiac damage in IHES develops in 58 % of cases [5], it most often occurs under the "mask" of inflammatory myocardial damage. Disease onset in most cases is manifested by skin and articular syndromes. A specific feature of this case that requires the attention of practitioners is the ACS-type heart disease that further complicated differential diagnosis and, possibly, affected the outcome of the disease.

## Conclusion

The presented clinical case draws the clinicians' attention to the existence of "major eosinophilia" and the need for its differential diagnosis and management. Alertness and awareness of the idiopathic hypereosinophilic syndrome in clinical practice will help to timely identify this disease and prevent the development of life-threatening complications.

**Вклад авторов:**

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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