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# ПРИМЕНЕНИЕ ПРЕПАРАТОВ ЖЕЛЕЗА У ПАЦИЕНТОВ С ЛЕГОЧНОЙ ГИПЕРТЕНЗИЕЙ: БЫСТРЫЙ СИСТЕМАТИЧЕСКИЙ ОБЗОР

**K.V. Balkina[1], T.V. Pavlova[1,2], D.V. Duplyakov[1,2]**

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# Iron Use in Patients with Pulmonary Hypertension: A Rapid Systematic Review

**Резюме**

Дефицит железа широко распространён у пациентов с сердечно-сосудистыми заболеваниями. В последние годы активно изучается коррекция дефицита железа у пациентов с хронической сердечной недостаточностью для улучшения прогноза и течения заболевания. В настоящее время работ, посвящённых изучению применения препаратов железа у пациентов с лёгочной гипертензией, не так много. Целью нашего обзора явилось изучение возможности использования парентеральных препаратов железа у пациентов с лёгочной артериальной гипертензией для улучшения симптоматики и прогноза. В окончательный анализ вошли 5 публикаций. По результатам представленных исследований после применения препаратов железа у всех пациентов нормализовались лабораторные данные, характеризующие дефицит железа, повысилась толерантность к физической нагрузке, улучшилось качество жизни. При этом по показателям инструментальных исследований параметры были без динамики, катетеризация правых отделов сердца также показала отсутствие влияния на гемодинамические критерии. Во всех исследованиях препараты железа хорошо переносились, серьезных побочных явлений выявлено не было, что подтверждает возможность широкого применения лекарственных средств данной группы. Своевременная диагностика и лечение анемии и скрытого железодефицита у пациентов с легочной гипертензией профилактируют прогрессирование заболевания. Однако в настоящее время в реальной клинической практике парентеральные препараты железа у пациентов со скрытым его дефицитом используются редко, вследствие чего необходима активная разъяснительная работа среди практикующих врачей с целью расширения использования данного вида лечения.

***Ключевые слова:*** *легочная артериальная гипертензия, железодефицит, анемия, карбоксиматозат железа*

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**Abstract**

Iron deficiency is widespread in patients with cardiovascular disease. In recent years, the correction of iron deficiency in patients with chronic heart failure has been actively studied to improve the prognosis and course of the disease. Currently, there are not many studies on the use of iron preparations in patients with pulmonary hypertension. The aim of our review was to explore the possibility of using parenteral iron preparations in patients with pulmonary arterial hypertension to improve symptoms and prognosis. The final analysis included 5 publications. According to the results of the presented studies, after the use of iron preparations, laboratory data characterizing iron deficiency were normalized in all patients, exercise tolerance increased, and the quality of life improved. At the same time, according to the indicators of instrumental studies, the parameters were without dynamics, catheterization of the right heart also showed no effect on hemodynamic criteria. In all studies, iron preparations were well tolerated, no serious side effects were detected, which confirms the possibility of widespread use of drugs of this group. Timely diagnosis and treatment of anemia and latent iron deficiency in patients with pulmonary hypertension prevent disease progression. However, at present, in real clinical practice, parenteral iron preparations are rarely used in patients with latent iron deficiency, as a result of which active outreach among practitioners is necessary in order to expand the use of this type of treatment.

***Key words:*** *pulmonary arterial hypertension, iron defciency, anaemia, Ferric carboxymaltose*

**Conflict of interests**

The authors declare no conflict of interests

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NT-proBNP — N-terminal pro B type natriuretic peptide, TSAT — transferrin saturation, CHD — congenital heart disorders, PWAP — pulmonary artery wedge pressure, RHC — right heart catheterization, PAH — pulmonary artery hypertension, PH — pulmonary hypertension, PVR — pulmonary vascular resistance, LV — left ventricle, MRI — magnetic resonance imaging, RV — right ventricle, PASys — pulmonary artery systolic pressure, SCTD — systemic connective tissue disorders, mPAP — mean pulmonary arterial pressure, 6MWT — 6-minute walking test, echo-CG — echocardiography, EF — ejection fraction, FC — functional class, CHF — chronic heart failure

## Introduction

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition, which is associated with an increase in the mean pulmonary arterial pressure (mPAP) to over 20 mm Hg at rest, when measured in right heart catheterization (RHC) [1, 2].

Pulmonary artery hypertension (PAH) is precapillary PH in the absence of any pulmonary conditions, chronic thromboembolism in the pulmonary artery, other rare conditions (group V) as possible causes of increased pressure in the pulmonary artery. Precapillary PH is haemodynamic PH, with mPAP of > 20 mm Hg, pulmonary artery wedge pressure (PWAP) of ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) of > 2 Wood units [3]. PAH can be idiopathic, hereditary, drug- and toxin-induced, associated with other conditions (e.g., congenital heart disorders (CHD); systemic connective tissue disorders (SCTD); portal hypertension; HIV-induced infection; snail fever), pulmonary vein occlusion/ pulmonary capillary haemangiomatosis, persistent infant PAH.

PH is a common clinical problem, which is diagnosed in approximately one percent of the global population. Its incidence grows with the age, this fact being supported by epidemiological data, according to which in the age group of 65+ years old, about 10 % have PH [4].

Recently, healthcare practitioners noted the relationship between anaemia caused by modified iron homeostasis and pathophysiology of various PH types. Studies showed that the management of iron deficiency with or without clinical anaemia in conditions, accompanied by PH, including congestive heart failure, improved patient tolerance to exercises and quality of life, and reduced the rate of hospitalisations and deaths, irrespective of presence or absence of clinical signs of anaemia [5–6, 18].

Assessment of groups of patients with PH demonstrates a high rate of iron deficiency, both with and without clinical anaemia; approximately 40–60 % of patients with this pathology have latent iron deficiency; a third of all patients with PH are diagnosed with clinical anaemia [7, 8]. Of note, both latent and clinical iron deficiency affects morbidity and mortality of this patient category [7, 9]. Available scientific data show the significant role of iron metabolism in pathogenesis and clinical outcome, both of pre and postcapillary PH [5, 9, 10, 18].

The correlation between iron deficiency and PAH is poorly studied. Currently, the main pathologic mechanisms of iron deficiency in PAH are hypoxia, inflammation, and functional changes in muscle cells of the pulmonary artery. Hypoxia can cause pulmonary vessel constriction, leading to increased pulmonary artery systolic pressure (PASys). Also, hypoxia-caused vasospasms and PH can be aggravated by iron chelation in healthy adults [11]. Pulmonary hypertensive reaction caused by altitude hypoxia can be managed with an iron infusion, where PASys is reduced by 6 mm in sea level subjects. Patients with chronic height sickness, who underwent venostomy to reduce the iron levels, demonstrated 25 % increase in their PASys [12]. It is assumed that, similar to hypoxia, iron deficiency increases PASys, which can explain PAH pathogenesis to some extent [13]. The study published in Proceedings of the National Academy of Sciences (Lakhal-Littleton S., Crosby A., Frise M.C. et al., 2019) reported a direct cause-and-effect relation between anaemia and PAH [14]. The authors demonstrated that intracellular iron deficiency in pulmonary arterial smooth muscle cells (PASMCs) results in higher concentrations of endogenous vasoconstrictor endothelin-1, which is known to be elevated in patients with PAH [15]. Besides, the authors provided evidence that impaired regulation of this cell-independent path can be a causative factor of family PAH. Pulmonary arterial smooth muscle cells in patients with mutated bone morphogenetic protein receptors (hereditary PAH) indeed reduced hepcidin expression and intracellular iron levels, and increased ferroportin and endothelin-1 levels [14]. Clinical data confirm that iron deficiency is common and correlates with reduced exercise tolerance in patients both with idiopathic and hereditary PAH [16].

It is worth mentioning that patients with pulmonary hypertension develop various forms of iron homeostasis impairments and anaemias [7]. These include hypoferric anaemia, anaemia of chronic diseases and other more complex types of anaemias, such as a combination of several forms. Management of such patients is a diagnostic and therapeutic challenge for a clinician, since precise anaemic classification can be tricky, and therapy recommendations for a combination of various anaemias are currently still unavailable.

**The objective of this review** is to study the possibility of using parenteral iron preparations in patients with PAH to improve symptoms and prognosis.

## Search for publications and selection of studies

The information search algorithm was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PubMed database was searched for publications in English for a period from 2014 to 2024 (last accessed date: June 23, 2024). Abstracts, monographs, clinical cases or their series were excluded from the analysis. Studies were searched for using keywords (MeSH) and logistic operators for the following keywords: (pulmonary arterial hypertension) AND (iron deficiency) AND (anaemia) AND (ferric carboxymaltose). Primary selection criteria were met by five publications, which were included into the final analysis [17-21].

For better visual presentation of the material from the studies, the most significant study results were visualised.

## Results

***A study by Viethen T. et al.***, published in 2014 [17], included 40 subjects. PAH was confirmed with RHC in all patients (mPAP ≥ 25 mm Hg and PVR ≤ 15 mm Hg). The first group included 20 patients with PAH, who had signs of iron deficiency. Of those, 12 patients had idiopathic PAH (iPAH); one patient — hereditary PAH; four patients — SCTD-associated PAH; three patients — CHD-associated PAH. Controls were 20 patients with PAH who did not have iron deficiency and were not taking iron preparations. The second group included: iPAH — 13 subjects; one subject had hereditary PAH; six subjects were diagnosed with SCTD-associated PAH. The groups were comparable in gender, age, PAH origin, type and duration of therapy, comorbidities and haemodynamic parameters. Patients in both groups had WHO functional class 2–3 and were treated with a stable PAH-specific regimen. During the study, PAH-specific therapy and diuretics were stable. Patients had their serum iron, ferritin and transferrin saturation (TSAT) measured; also, they underwent an assessment of their mean corpuscular volume and Hb, C-reactive protein (CRP), creatinine and N-terminal pro B type natriuretic peptide (NT-proBNP) levels. Efficacy was assessed using the 6-minute walking test (6MWT); echocardiography (echoCG) with the measurement of the right atrium area, right ventricle end-diastolic diameter, TAPSE index, tricuspid regurgitation rate; cardiopulmonary test; patients also completed the quality of life questionnaire (SF-36). Patients in group 1 had significant iron deficiency without marked inflammations (CRP < 25 mg/L). These patients did not have clinical anaemia; however, their

Hb levels were 12.0±0.6 vs. 14.6±0.4 g/dL (p = 0.001)), mean corpuscular volume was 80.0±1.8 vs. 87.3±1.0 fL (p = 0.002) for patients in groups 1 and 2, respectively.

Ferric carboxymaltose preparations were administered as a single dose of up to 1,000 mg, but no more than 15 mg/kg bw (mean dose was 925 mg). The follow-up period lasted for 8 weeks. The use of iron preparations in patients with iron deficiency resulted in significant improvement of parameters characterising iron homeostasis (serum iron: 5.7±0.4 and 11.1±1.1 μmol/L before and after the therapy, respectively (Fig. 1a); ferritin: 29.3±6.3 and 145.2±25.4 μg/L before and after the therapy, respectively (Fig. 1b); TSAT: 7.5±0.7 and 19.3±2.3 % before and after the therapy, respectively (Fig. 1c), all p ≤ 0.001). Also, patients receiving ferric carboxymaltose preparations demonstrated an increase by 37.7 m in the 6MWT distance, from 346.5±28.3 to 374.0±25.5 mm (Fig. 1d) (p = 0.007), while controls, who did not receive any iron preparations, did not show any significant differences (6MWT 389.9±25.3 and 379.6±26.2 m at baseline and after the therapy, respectively; p = N/A). Positive changes in clinical laboratory values were accompanied by improved quality of life (SF-36, from 44.3±3.7 to 50.6±3.6; p = 0.01).

Ferric carboxymaltose therapy was well-tolerated; only two patients had adverse effects without hospitalisation (flu-like syndrome and skin discolouration at the injection site).

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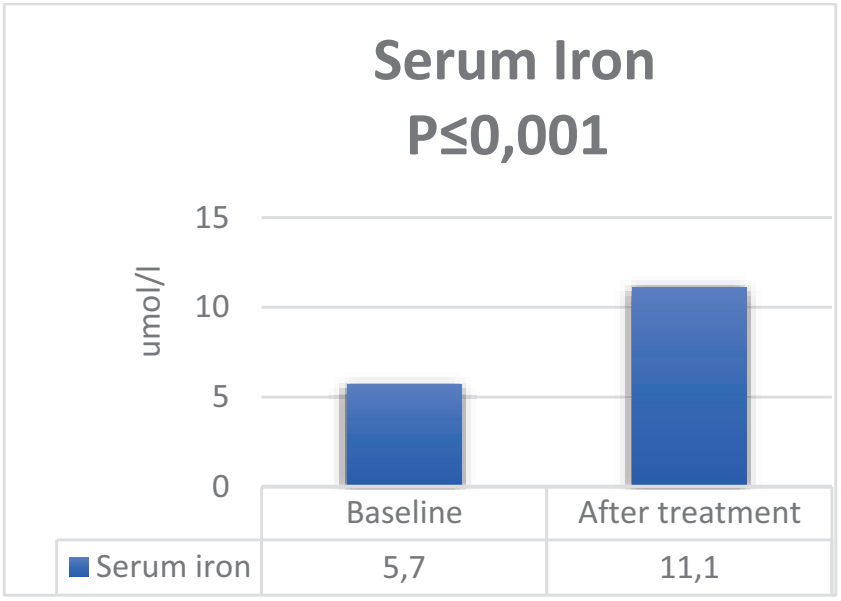


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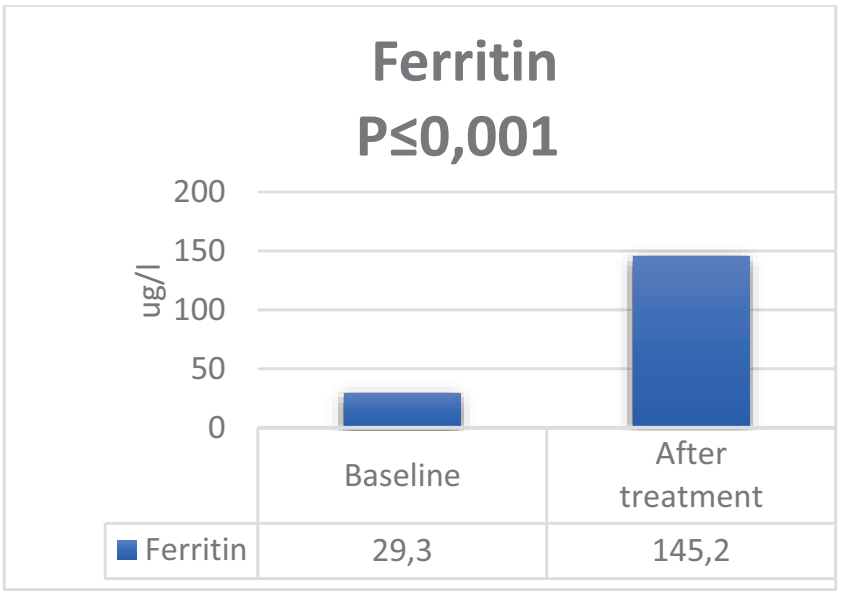


***Figure 1.*** *Comparison of laboratory values and 6MWD before and after therapy with ferric carboxymaltose*

**Note.** 6MWD — 6-minute-walking distance, TSAT — transferrin saturation

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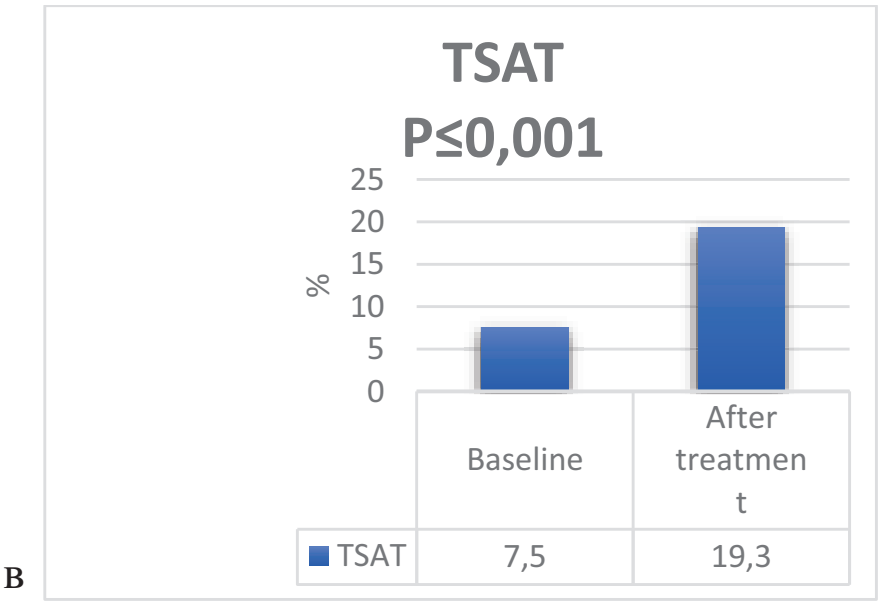


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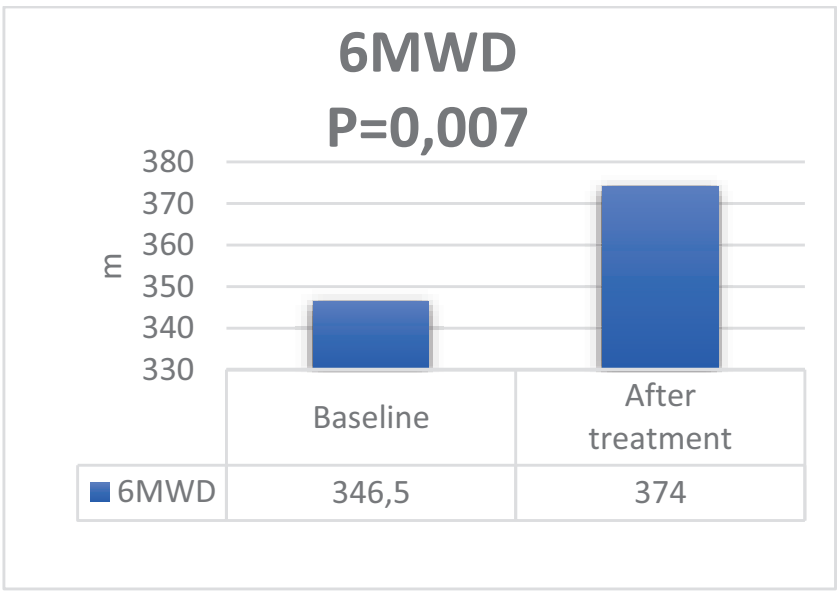


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***Figure 1.*** *(The end)*

***A study by Ruiter G. et al.*** [18] was conducted at the pulmonology ward of the University Hospital at Amsterdam; it was a non-randomised non-placebo-controlled study. The study included 18 patients with iPAH and iron deficiency. The study was conducted from January 2011 till January 2013. All patients underwent 6MWT, heart magnetic resonance imaging (MRI), cardiopulmonary testing, respiratory function assessment, and quality of life assessment. Three patients in the main group did not complete the study: one subject developed paroxysmal auricular fluttering, one subject withdrew their informed consent, and one patient required erythropoietin injection.

All enrolled patients received 1,000 mg of ferric carboxymaltose preparation. The therapy was well-tolerated; however, two patients developed headaches during infusion, and patients arrested such headaches by themselves [18]. The levels of iron, ferritin, transferrin saturation after ferric carboxymaltose injections increased: iron — 9.6±4.8 and 16.1±6.1 μmol/L before and after therapy, respectively, $p < 0.05$ (Fig. 2a); ferritin — 44±79 and 199±225 μg/L before and after therapy, respectively, $p < 0.05$ (Fig. 2b); TSAT — 13.6±6.7 % and 27.3±13.4 % before and after therapy, respectively, $p < 0.001$ (Fig. 2c).

At the same time, NT-proBNP values did not show any significant changes (1.339±2.545 vs. 1.753±4.559 pg/mL, p = N/A). Post-therapy hepcidin levels were low (4.5±4.5 vs. 6.6±4.4 ng/mL, p = N/A). 6MWT did not show any differences as well (409±110 m and 428±94 m before and after therapy, respectively; p = 0.07 (Fig. 2d));

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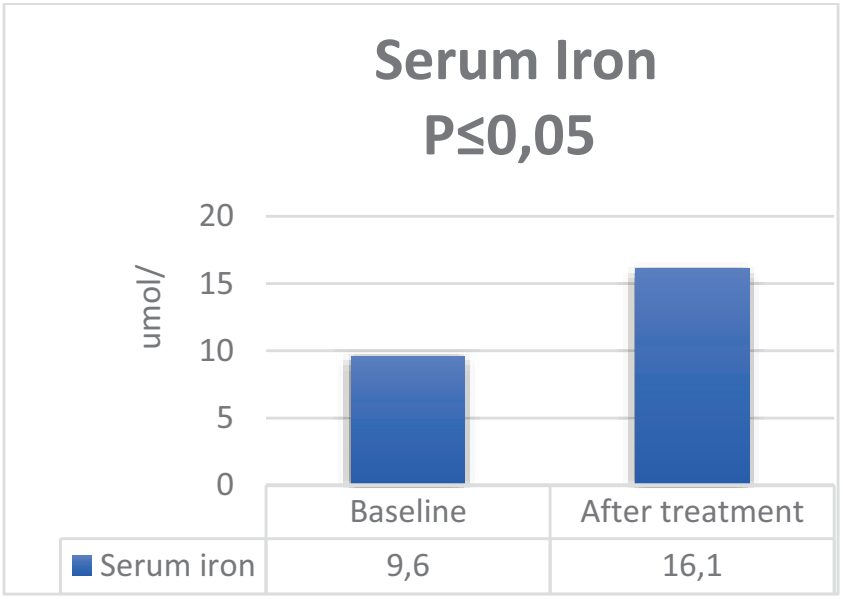


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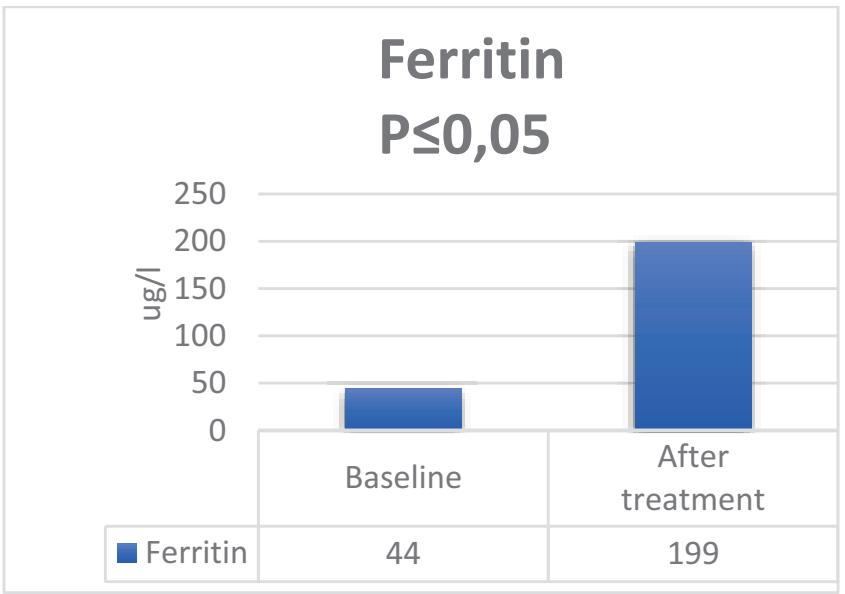


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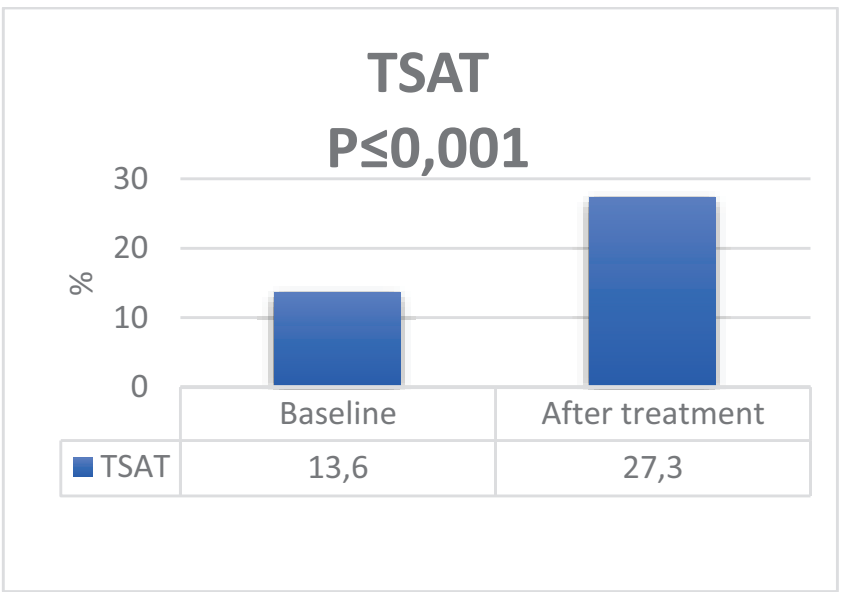


***Figure 2.*** *Comparison of laboratory values before and after therapy with ferric carboxymaltose [18]*
**Note.** 6MWD — 6-minute-walking distance, TSAT — transferrin saturation

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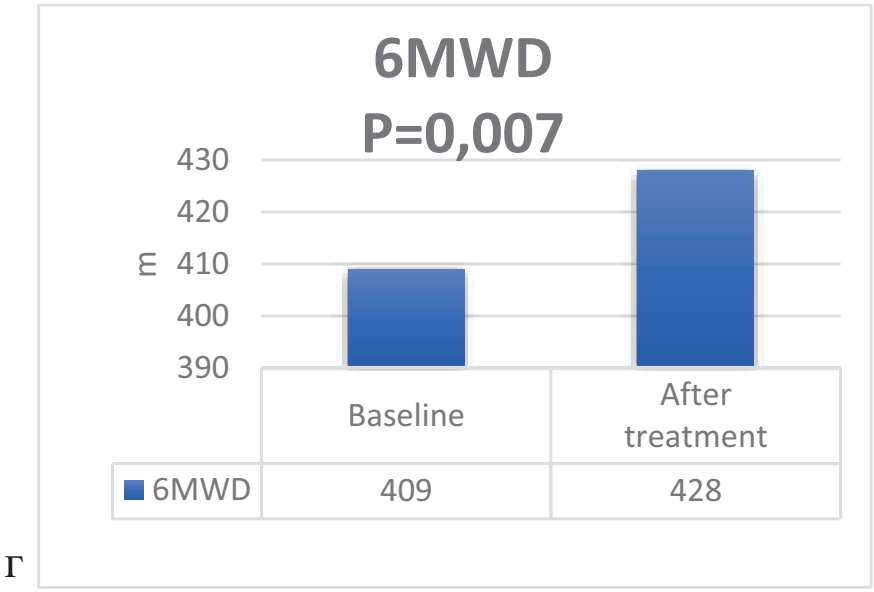


***Figure 2.*** *(The end)*

however, subjective exercise tolerance improved. Besides, cardiorespiratory testing did not demonstrate any changes: the maximum work load was 55±23 W vs. 59±27 W (p=N/A); peak oxygen consumption was 0.97±0.22 L/min vs. 0.97±0.26 L/min (p = N/A); while the time to anaerobic threshold increased (175±33 s vs. 238±43 s; p < 0.001). Exercise tolerance improved (269±89 s vs. 405±210 s; p < 0.001), and patients were able to maintain submaximal physical activity 51 % longer. Quality of life improved, as demonstrated by SF-36 (47 %±19 % vs. 56 %±19 %; p < 0.05). At the same time, RHC and echoCG results remained the same: cardiac index (2.8±0.9 L/min/m$^2$ vs. 2.5±0.8 L/min/m$^2$, p = N/A); left ventricle ejection fraction (LV EF) 62 %±12 % vs. 59 %±14 %, RV — 40 %±21 % vs. 39 %±21 % (p = N/A). The myocardial mass index for the right and left ventricles did not demonstrate any significant changes (LV: 59±15 g/m$^2$ vs. 62±17 g/m$^2$ before and after, respectively; RV: 51±29 g/m$^2$ vs. 56±31 g/m$^2$ before and after, respectively; p = N/A in both cases). Spirometry parameters ~~also~~ remained the same.

During the study, 12 patients underwent shoulder quadriceps biopsy; biopsy materials of two of them could not be analysed. An assessment of the remaining ten samples showed that myoglobin concentration was 0.34±0.17 mM and 0.44±0.11 mM before and after iron preparation injection (p < 0.05); mitochondrial oxidation capacity was 0.06±0.01 nM/mm$^3$/s and 0.09±0.02 nM/mm$^3$/s before and after therapy, respectively (p < 0.05). Capillaries/myocyte ratio in quadriceps was similar after the therapy (1.0±0.4 capillary/myocyte and 1.2±0.2 capillary/myocyte before and after therapy; p = 0.37).

***Blanche C. et al.*** [19] studied the possibilities of intravenous injections of ferric carboxymaltose in patients with CHD-associated cyanosis, both with and without pulmonary hypertension. The retrospective study included data of patients, who were followed up from August 2009 to April 2015 and received iron preparation injections. A criterion of cyanosis was peripteral oxygenation reduction of ≤ 90 % at rest or during exercises. The study included 142 patients, of whom 55 (38.7 %) were men; the mean age was 51.3±17.6 years old. Eisenmenger's syndrome was diagnosed in 41 patients (48.8 %); CHD-associated PAH was observed in 27 patients (19 %); CHD with cyanosis, but without PAH was noted in 16 patients (11.3 %); and pulmonary hypertension without PAH was recorded in 58 patients (40.8 %). The majority of patients (116 patients, 88.5 %) had at least functional class (FC) 3 (WHO); mean oxygen saturation at first examination was 86 % (80.0–90.0 %). Patients with Eisenmenger's syndrome had the lowest oxygen saturation of the blood — 82.0 % (75.0–86.0 %), but only two patients (4.9 %) were undergoing long-term oxygen therapy. The majority of patients received PAH-specific therapy (104 subjects, 73.2 %) with the first iron preparation injections. Sixty-six (66) subjects (46.8 %) were on anticoagulants. Over a half of patients with Eisenmenger's syndrome (17 patients, 58.5 %) did not take anticoagulants.

According to the study design, all patients were administered ferric carboxymaltose at a dose of 500–1,000 mg.

Given that patients with Eisenmenger's syndrome require higher Hb values, the dose and frequency of an iron preparation in this group depended on the optimal (expected) Hb concentration, calculated using the formula proposed by Broberg et al., 2011 [27]. It has been shown that the baseline Hb concentration in the study subjects was approx. 4.3±3.9 g/dL lower than the optimal value. This difference increased with an increase in the theoretical optimal concentration (0.98 g/dL (real concentration) vs. 1 g/dL (optimal concentration), 95 % confidence interval: 0.72–1.25, p < 0.0001); however, there was no correlation with the baseline ferritin level (p = 0.62) or TSAT value (p = 0.31). The first dose of 500 mg of ferric carboxymaltose was injected to 163 patients (81.1 %), while 1,000 mg was injected to 37 patients (8.4 %). In order to achieve the optimal Hb level, a repeated dose was required in 59 patients (29.4 %); 24 subjects (11.9 %) received more than two infusions during the study. Patients with Eisenmenger's syndrome required more repeated doses of iron preparations vs. other groups: 29 (41.4 %) vs. 30 (22.9 %), p = 0.01. The mean time between the first and second infusions was 11.6 (4.4–25.4) months. Currently, the formula (Broberg et al., 2011) is not common among clinicians for the assessment of the iron deficiency severity or making decisions on the dose of iron preparations. Still, it can be useful for the calculation of the required dose of iron preparations: the mean optimal actual difference in Hb value was 2.75±3.08 g/dL in the 500 mg group vs. 7.23±3.80 g/dL in the higher dose group, p = 0.0005.

During the study, there were no serious adverse reactions to the product. Two patients developed rash, which was managed with antihistamines. One patient had

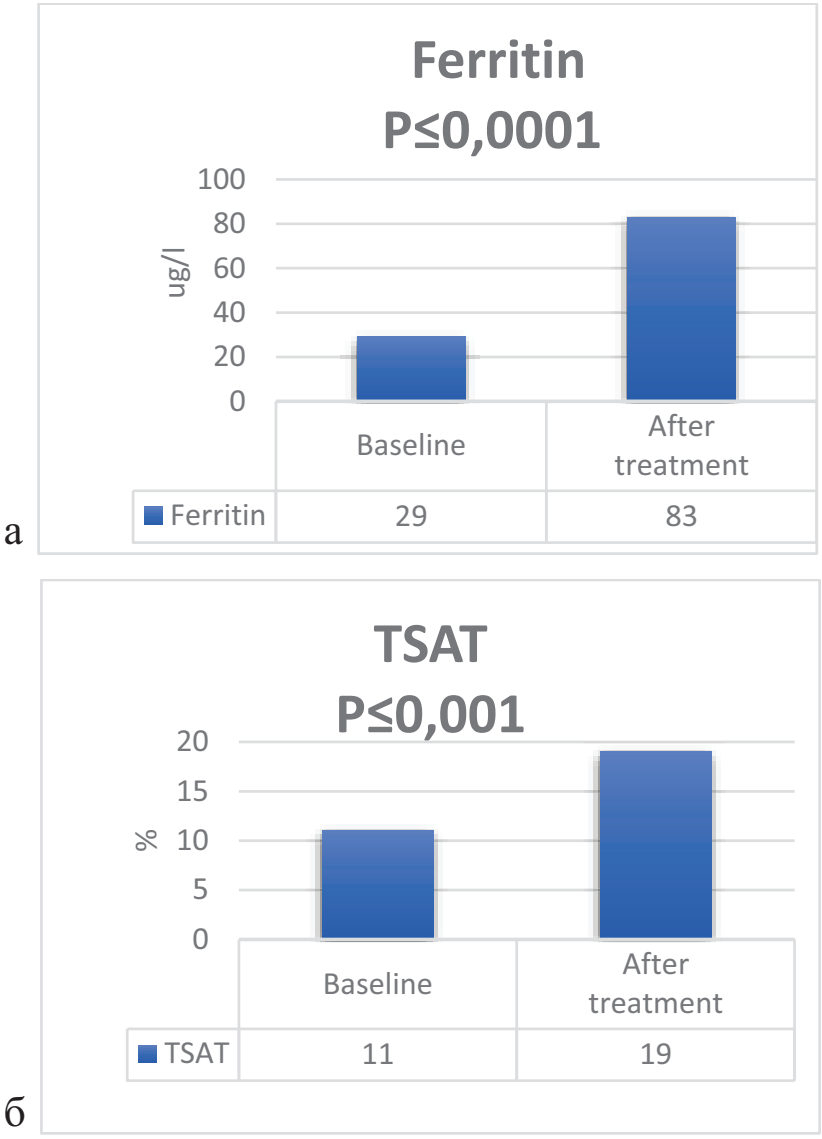


***Figure 3.*** *Comparison of laboratory values before and after therapy with ferric carboxymaltose in patients with cyanosis [19]*
**Note.** TSAT — transferrin saturation

transient neurological symptoms during iron infusion (speech disorder and arm weakness), but brain computer tomography did not show any permanent neurological deficit or signs of stroke.

In a study by C. Blanche et al., significant improvement in mean Hb saturation and higher hematocrit, ferritin and transferrin levels were observed after a median follow-up of 100.0 (70.0–161.0) days after the first infusion ($p \leq 0.0001$). Higher concentrations of ferritin (29.0 [14.0–63.0] μg/L vs. 83.0 [34.0–182.5] μg/L, $p < 0.0001$ (Fig. 3a)) and TSAT (11.0 [7.0–14.0] vs. 19.0 [13.0–26.0], $p < 0.0001$ (Fig. 3b)) were also observed; however, a majority of patients still were iron deficient by the end of the study. Forty-eight (48) patients (45.7 %) still had TSAT of < 20 %. Blood test results of 68 subjects (66.0 %) showed low ferritin levels (< 30 μg/L) or low TSAT value (< 20 %). Also, there was statistically significant reduction in platelet count (185.0 [127.0–228.0] vs. 161.0 [113.0–214.0] g/L, $p < 0.0001$) and significant correlation between oxygen saturation at rest and Hb concentration. However, the correlation between ferritin and TSAT was weak. In the group of patients with TSAT ≥ 20 %, 65 (51.6 %) subjects had ferritin concentration of < 30 μg/L, while 65 (92.9 %) patients with ferritin concentration of < 30 μg/L had TSAT ≥ 20 %. After the infusion, the difference between the optimal and actual Hb concentration was 2.6±3.3 g/dL. There were no cases of excessive erythropoiesis. Also, none of the patients developed hypercoagulation.

In 2021, pooled results of ***two double-blind placebo-controlled randomised cross-over studies*** were reported [20]; the studies included patients with iPAH or hereditary PAH and iron deficiency. The studies were simultaneously conducted in Europe and China. Over the period from March 2012 to July 2017, 39 patients were randomised 1 : 1 to receive an injection of ferric carboxymaltose or saline solution as a placebo in the European arm of the study. In China, the study included 17 patients. Once randomised, the patients received either a single 20 mg/kg dose of dextran iron hydroxide, or saline solution (placebo). The results were assessed in 12 weeks.

Initially, the primary endpoint in the European arm of the study was changes in PVR based on RHC results as a response to iron deficiency correction. Later, it was decided to modify the primary endpoint, replacing the initial parameter with cardiopulmonary testing parameters. In China, changes in the pulmonary vascular resistance were the primary endpoint, while changes in cardiopulmonary testing parameters were the secondary endpoint. Results in both studies were assessed using laboratory data and results of echoCG, 6MWT, NT-proBNP, heart MRI, and RHC. Changes in iron concentrations after iron preparation infusion were studied using log-transformed ratio of sTfR (soluble transferrin receptor) and ferritin (log sTfR/ferritin), which was proposed as an optimal measure to differentiate between anaemia caused by a chronic condition, and hypoferric anaemia. Reduced log sTfR/ferritin demonstrated better iron availability.

In the European study, patients were divided into two groups: group one received preparations from week 1 to week 12, then placebo from week 13 to week 24, while group two received placebo and then switched to iron preparations.

When discussing the results of the two cross-over studies, conducted simultaneously in Europe and China, it is worth noting that in Europe, administration of ferric carboxymaltose improved ferritin levels from 17 μg/L at baseline to 146 μg/L ($p = 0.0003$) in 12 weeks in the iron preparation group. Patients who received placebo and then iron preparations demonstrated higher ferritin concentrations, from 14 μg/L at baseline to 134.5 μg/L on week 12 to week 24. sTfR concentrations dropped in both groups in line with an increase in iron concentration. The use of iron preparations in both studies did not have significant impact on the right and left ventricle function in 12 weeks, also confirmed with repeated heart MRI.

However, a single dose of ferric carboxymaltose improved tolerance to exercises and quality of life. Twenty (20) patients who received 800–1,000 mg (mean value: 925 mg) of iron demonstrated better 6MWT results — 37.8 m in 8 weeks vs. placebo. A subgroup of eight patients underwent cardiopulmonary testing, where higher peak oxygen consumption was recorded. A study of 15 patients did not show any significant changes in 6MWT results; however, tolerance and aerobic capacity during cardiopulmonary testing improved. In the Chinese arm of the study, iron dextran increased the concentration of serum iron and ferritin, but did not impact parameters obtained during cardiopulmonary testing and RHC.

***A study by Kramer T. et al.*** [21], the results of which were published in September 2021, included 117 patients (mean age: 60.9±16.1 years old; 64.1 % were women) with confirmed iPAH and PAH-specific therapy over ≥ 3 months. All patients had their PAH confirmed in accordance with the current guidelines. A half of patients with iron deficiency (58 subjects) had intravenous ferric carboxymaltose injections; the remaining 59 patients without iron deficiency were controls.

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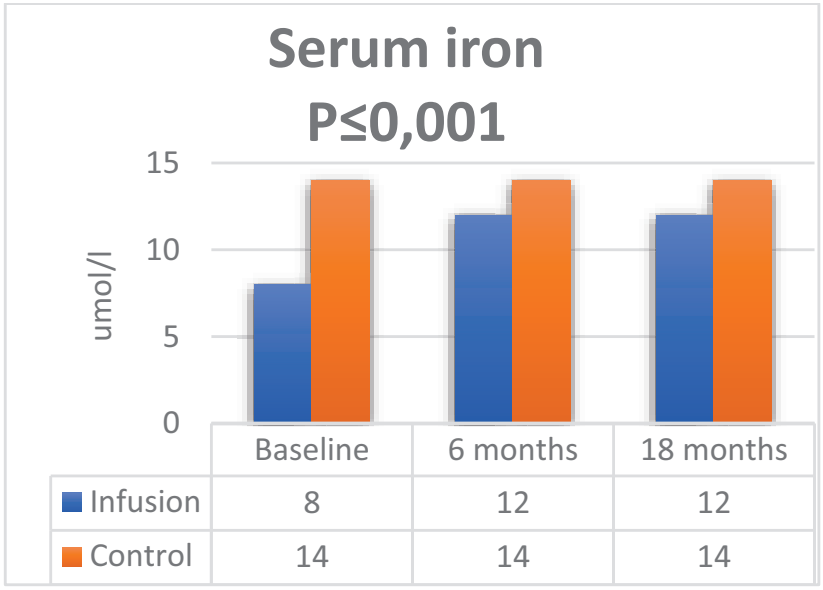


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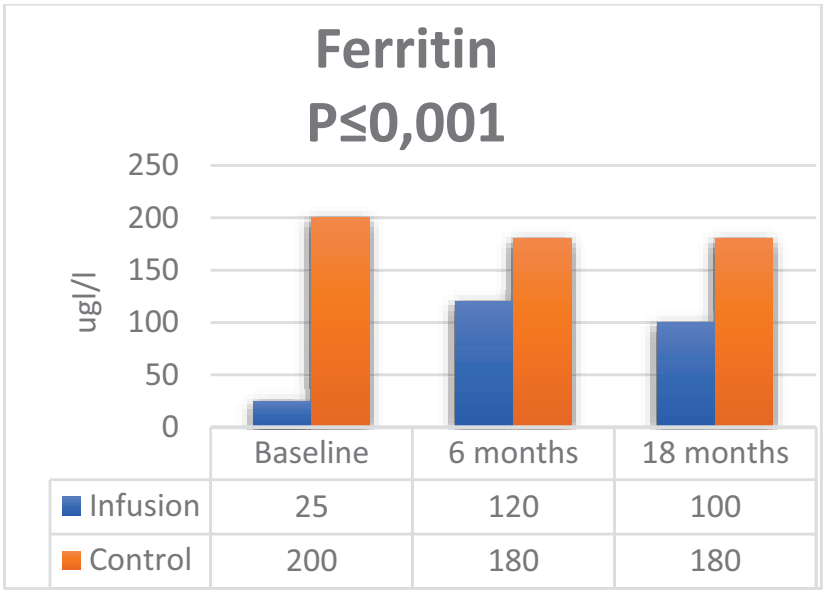


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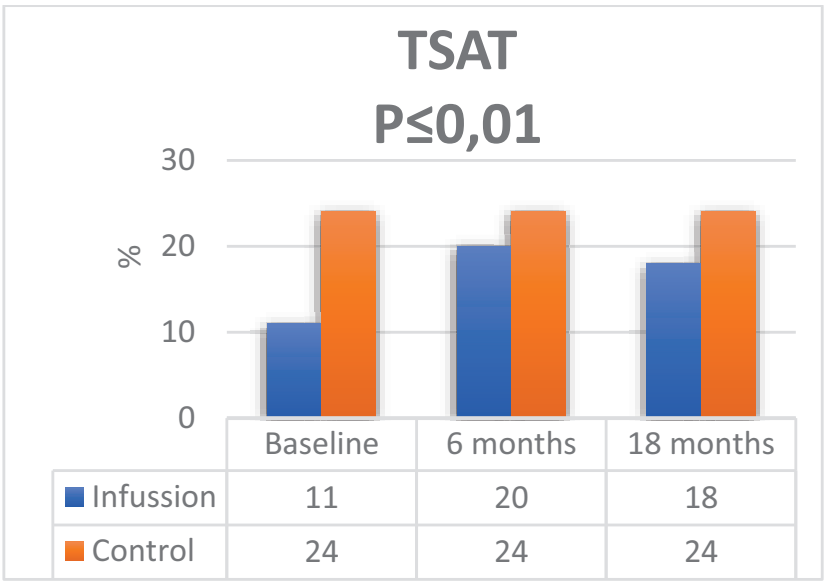


***Figure 4.*** *Comparison of laboratory values before and after therapy with ferric carboxymaltose [21]*

**Note.** 6MWD — 6 min walk distance, NT-proBNP — N-terminal–pro hormone brain natriuretic peptide, TSAT — transferrin saturation, WHO — World Health Organization functional class

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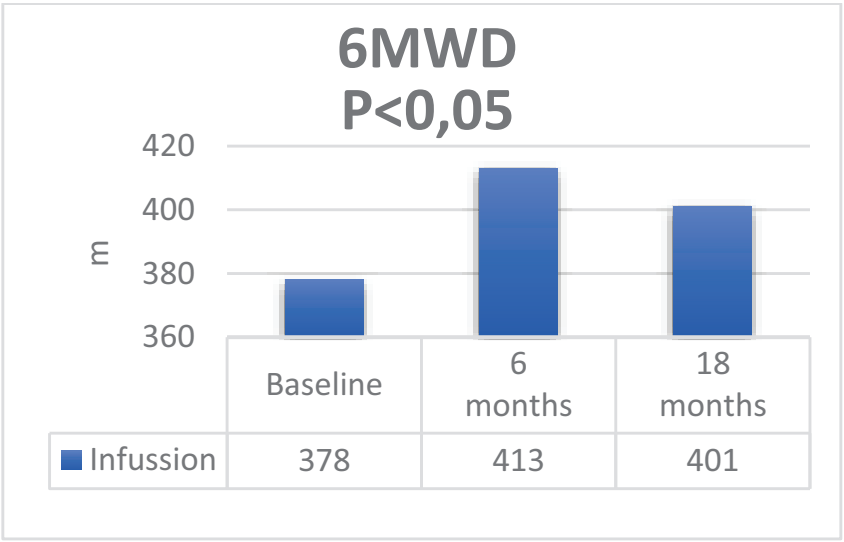


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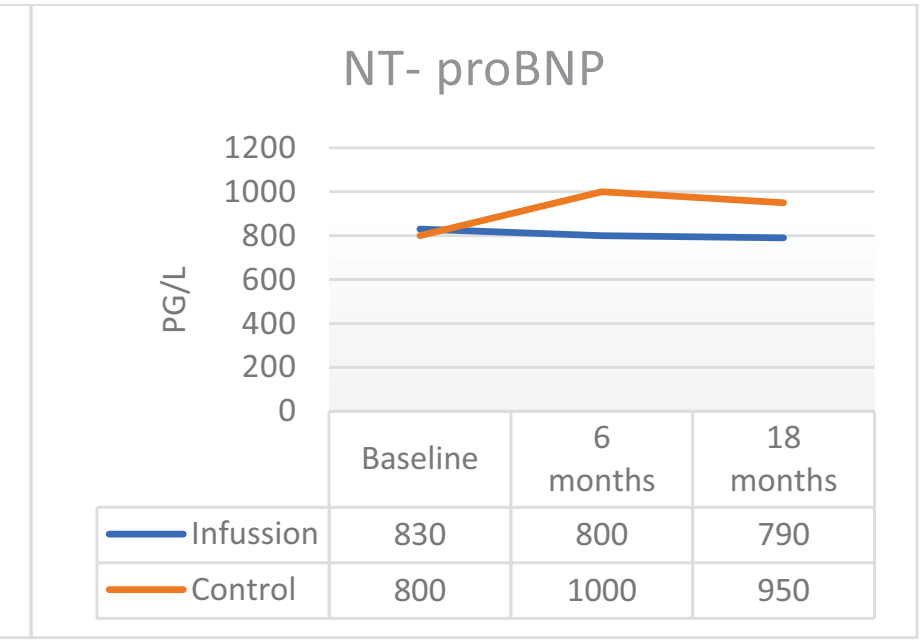


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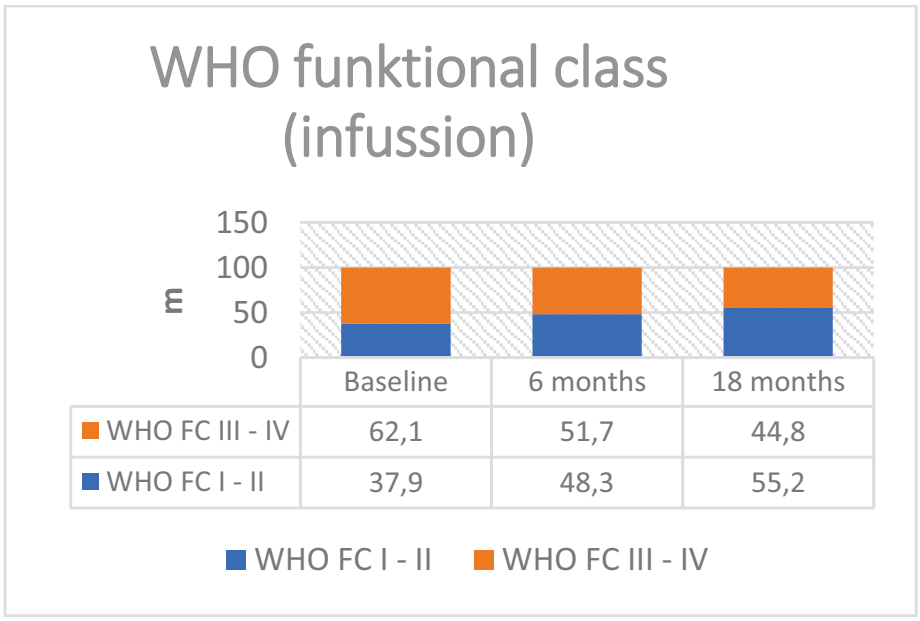


***Figure 4.*** *(The end)*

The groups were comparable in gender, age, origin of pulmonary hypertension, PAH-specific therapy, therapy duration, and haemodynamic parameters. Both groups had elevated baseline NT-pro BNP levels, and patients with iron deficiency had more pronounced clinical manifestations of cardiac failure. PASys was slightly higher in the intervention arm [14]. Clinical anaemia was not present; however, Hb concentration and mean corpuscular volume were higher in controls ($p < 0.001$). Fourteen patients (24 %) in group one received a second infusion in 9.6±4.8 months, of which four (29 %) patients needed an additional (third) infusion due to recurrent iron deficiency (mean total dose: 1,196±563 mg; range: 500–3,000 mg). In this study, patients with iron deficiency, who received iron preparations, demonstrated immediate and steady improvement in their laboratory parameters for a period of up to 18 months (serum iron, ferritin, TSAT, for all $p < 0.01$) (Fig. 4a-b), whereas the control groups did not have any noticeable changes. Peak ferritin and TSAT values were achieved within three months of the follow-up period and then dropped slightly. Iron deficiency improvement was associated with better tolerance to exercises during the follow-up period. As compared to the control group, the mean baseline 6MWT was lower in patients with baseline iron deficiency; however, at 18 months the 6MWT values in the intervention group at least reached the baseline values of controls. Six and eighteen months after the iron preparation infusion the 6MWT results improved, from 378±16 m to 413±15 m (at 6 months) and to 401±15 m (at 18 months), $p<0.05$ for both time intervals (Fig. 4d), while the 6MWT values for controls dropped ($p<0.02$). The intervention group demonstrated a slight tendency towards reduced NT-proBNP levels (Fig. 4e), while in the control group this parameter increased by 21 % by the final visit.

After the therapy, a share of patients with FC I–II in the study group increased from 38 % to 55 % at 18 months, whereas the control group demonstrated deterioration (at baseline, 52 % of patients had FC I–II vs. 43 % at 18 months) (Fig. 4f). It is important to note that the iron preparation therapy was associated with a drop in the rate of hospitalisations for decompensated PAH during 12 months vs. the pre-correction period ($p = 0.029$). There were no significant changes in controls. Of note, all above positive changes in the main group were not accompanied by significant changes in echoCG parameters, including PASys, RA EDD, EF, which remain the same in both groups. Iron preparations were well-tolerated by all patients, and no serious adverse events were reported.

## Discussion

Recently, correction of iron deficiency in patients with chronic heart failure (CHF) has been paid much attention in scientific literature. Study FAIR-HF did not show that higher iron levels significantly improved the quality of life and tolerance to exercises, reduced functional class in patients with iron deficiency and chronic left ventricular failure. Parenteral ferric carboxymaltose proved to be efficient in correction of iron deficiency in stable patients with chronic heart failure; it justifies its inclusion in the 2020 CHF management guidelines [22]. The results of Study AFFIRM-AHF [23] confirmed the feasibility of initiation iron deficiency correction right after an episode of CHF decompensation in order to reduce the risk of later hospitalisations caused by this condition. The Expert Consensus on the iron deficiency management in stable and decompensated patients with chronic heart failure [24] states that intravenous administration of ferric carboxymaltose in patients with CHF and LV EF of < 50 % and iron deficiency with decompensated CHF allows preventing further decompensations. In 2024, the results of the study conducted at V. A. Almazov National Medical Research Centre were published. The study was dedicated to iron exchange and the incidence of iron deficiency in patients with PAH and chronic thromboembolic pulmonary hypertension, as demonstrated by various laboratory criteria [25]. Generally speaking, currently there are not enough publications to confirm efficient use of iron preparations in patients with iron deficiency and pulmonary hypertension. This topic is discussed just in five reviews, which were included into this analysis [17–21].

An overview of the mentioned publications shows that iron deficiency is diagnosed in patients with various types of pulmonary hypertension. Some studies included patients with hypertension of various origin. For instance, a study by Viethen T. et al. analysed patients with the following forms: iPAH, hereditary pulmonary hypertension, pulmonary hypertension associated with connective tissue disorders, and CHD-associated PAH [17]. In a study by Blanche C. et al., a majority of patients were patients with CHD, but it also included a group of patients with cyanosis without CHD [19]. A study by Ruiter G. and Kramer T. et al. included only patients with iPAH [18,21], while two cross-over studies in Europe and China enrolled patients with iPAH and hereditary pulmonary hypertension [20]. All mentioned publications used similar iron deficiency criteria based on serum iron, ferritin, and TSAT levels. Patients with active inflammation and severe comorbidities were

excluded from all studies; it can evidence that pulmonary hypertension is the key cause of iron deficiency. It is worth noting that all studies had a small sample size, because the condition is quite rare; it also shows the need to include a larger number of subjects for a more thorough study of the use of iron preparations in patients with pulmonary hypertension to correct iron deficiency. All patients were undergoing stable PAH-specific therapy, as iron preparations can be used just as adjuvant to the primary therapy. In all publications, changes in laboratory values, tolerance to exercises and quality of life were the primary endpoint. Patients underwent laboratory tests to assess changes in iron homeostasis, echoCG or heart MRI parameters to assess the heart function, cardiopulmonary testing and 6-minute walking test to identify tolerance to exercises; some studies also included RHC to assess haemodynamic parameters. Besides, subjects completed quality of life questionnaires. The mentioned studies show that the use of iron preparations normalised laboratory parameters, which characterise iron deficiency, in all patients; tolerance to exercises and quality of life improved. Instrumental test results did not demonstrate any changes; RHC also showed no impact on haemodynamic parameters. In a study by Kramer T. et al. (2021) [21], patients receiving iron preparations had lower rate of hospitalisations for decompensated CHF. A study in patients with CHD and cyanosis [19] proved the safe use of iron preparations in patients with a high baseline RBC count, provided thromboembolic complications were prevented, and allergic reactions were controlled. Addition of iron preparations with excessive erythropoiesis did not result in hypercoagulation, even in patients with Eisenmenger's syndrome and/or very high hematocrit levels. No embolic events were reported. In all studies, iron preparations were well-tolerated with no serious adverse events, thus supporting wide applicability of these preparations. However, in current clinical settings, parenteral iron preparations are rarely used in patients with latent iron deficiency, and wide-scale outreach is needed among medical practitioners in order to advocate this therapy.

## Conclusion

Iron deficiency is common in patients with pulmonary arterial hypertension of various origin. The mechanisms of iron deficiency in this group of patients are actively studied. The use of some PAH-specific products can cause impaired iron homeostasis and can be associated with low Hb. It has been proven that iron deficiency, even it is not accompanied by clinical anaemia, worsens symptoms of the primary disease, compromises the quality of patients' life, and increases the rate of CFH decompensations and associated hospitalisations. Routine clinical practices should include regular diagnostics of this condition for timely identification of iron deficiency and assessment of indications for iron preparation administration. The latest clinical recommendations developed by the Russian Cardiology Society "Pulmonary hypertension including chronic thromboembolic pulmonary hypertension", approved in 2024, provide for iron deficiency correction and anaemia management to prevent disease progression (level C evidence, level 5 of certainty) [26]. Even in the absence of clinical anaemia, it is advisable to consider iron deficiency correction in patients with PAH (level C evidence, level 5 of certainty) [26] to improve symptoms of the primary disease, tolerance to exercises and quality of life. A study has been conducted from September 2024 at V. P. Polyakov Samara Regional Clinical Cardiology Dispensary. The objective of the study is to assess the impact of iron deficiency correction on the quality of life and prognosis in patients with pulmonary hypertension. It should be particularly emphasised that correction of anaemia and iron deficiency does not replace PAH-specific therapy, but is a ~~very~~ important addition to the combined therapy.

**Key points:**

- Iron deficiency with or without clinical anaemia is a common problem in patients with pulmonary arterial hypertension.
- Regular diagnostics of iron deficiency should be performed in this group of patients for timely correction.
- Ferric carboxymaltose improves symptoms of the primary condition, tolerance to exercises and quality of life.

**Вклад авторов:**

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

**Балькина К.В.:** сбор и обработка материала, написание рукописи

**Павлова Т.В.:** анализ и интерпретация данных, редактирование рукописи

**Дупляков Д.В.:** разработка концепции и дизайна, научное консультирование, редактирование рукописи, утверждение окончательного варианта статьи

**Author contribution:**

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

**Balkina K.V.:** collecting and processing material, manuscript writing

**Pavlova T.V:** data interpretation and analysis, editing the article

**Duplyakov D.V.:** concept and design development, scientific advice, editing the article, approval of the final version of the manuscript

***Table 1.*** *General characteristics of the studies*

| Authors | Study type, number of patients, duration of follow-up | Inclusion criteria | Initial treatment | Criteria for ID | Restrictions | End points | Study result |
|---|---|---|---|---|---|---|---|
| Kramer T., [21] | Retrospectively<br>117 patients,<br>18 months | 1. PAH was confirmed by RHC in all patients,<br>2. PAH — specific therapy for ≥ 1 months,<br>3. ID | 1. CCB — 2 ( 1 — intervention, 1 — control ),<br>2. PDE5i monotherapy — 34 (13 — intervention, 21 — control),<br>3. ERA monotherapy — 10 (5 — intervention, 5 — control),<br>4. sGC stim monotherapy — 8 (5 — intervention, 3 — control),<br>5. PDE5i + ERA — 47 (22 — intervention, 25 — control),<br>6. sGC stim + ERA — 4 (3 — intervention, 1 — control),<br>7. PDE5i + ERA + Prost — 8 (6 — intervention, 2 — control),<br>8. sGC stim + ERA + Prost — 4 (3 — intervention, 1 — control). | 1. SF<100 μg/L,<br>2. SF 100 — 300 μg/L + TSAT < 20 %. | 1. Kidney dysfunction (serum creatinine > 2.0 mg/dL),<br>2. Liver disease (serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase > 70 U/L),<br>3. Marked anaemia (haemoglobin < 8.0 mg/dL),<br>4. Inflammation (C — reactive protein > 25 mg/L). | 1. Iron status,<br>2. Exercise tolerance. | 1. Improvement in laboratory values,<br>2. Increased exercise tolerance,<br>3. WHO functional class improved,<br>4. Reduction of hospitalizations for worsening PAH,<br>5. No dynamics on echocardiography. |
| Luke S. [20] | Two randomized, double-blind, placebo-controlled,<br>Europa — 39 patients<br>China — 17 patients,<br>12 weeks | 1. PAH was confirmed by RHC in all patients,<br>2. PAH — specific therapy for ≥ 1 months,<br>3. ID. | 1.PDE5i: Europa — 33, China — 13,<br>2.ERA: Europa — 29, China — 7,<br>3.Prost: Europa — 10, China — 1,<br>4. CCB: Europa — 2 . | 1. SF <37 μg/L,<br>2. SI <10,3 μmol/L,<br>3. TSAT <16.4 %. | | 1. 6MWD,<br>2. Pulmonary vascular resistance,<br>3. Peak O2 intake in cardiopulmonary testing. | 1. SF increased,<br>2. No impact on right heart cardiopulmonary testing and catheterization data (China),<br>3. Improved exercise tolerance and QoL. |
| Viethen T. [17] | Prospective<br>20 patients +<br>20 patients (control group)<br>8 weeks | 1. PAH was confirmed by RHC in all patients,<br>2. PAH — specific therapy for ≥ 3 months,<br>3. ID. | 1. ERA monotherapy– 2 (intervention),<br>2. PDE5i monotherapy- 13 (4 — intervention, 9 — control),<br>3. sGC stim monotherapy– 5 (3 — intervention, 2 — control),<br>4. ERA + PDE 5i– 10 (7 — intervention, 3 — control),<br>5. ERA + sGC stim– 1 (intervention),<br>6. PDE5i + sGC stim — 1 (intervention),<br>7. ERA + PDE-5i + iProst — 2 (intervention),<br>8. ERA + PDE-5i + oProst — 2 (control),<br>9. PDE-5i + TK — 1 (control),<br>10. ERA + PDE-5i + TKI — 2 (control). | 1. SI <10 μmol/L,<br>2. SF <150 μg/L,<br>3. TSAT <15 %. | 1. Considerable liver disease (serum glutamic oxaloacetic transaminase / glutamic pyruvic transaminase >70 U/L),<br>2. Kidney dysfunction (serum creatinine >2.0 mg/dL),<br>3. Marked anemia (hemoglobin <7.5 mg/dL)<br>4. Marked inflammation (C-reactive protein >25 mg/L),<br>5. Left heart disease or chronic lung disease,<br>6. Chronic thromboembolic PH (ventilation/perfusion scan). | 1. Iron status,<br>2. 6MWD,<br>3. QoL. | 1. Improved iron homeostasis,<br>2. Increasing 6MWD,<br>3. Improvement in QoL. |

*Table 1. (The end)*

| Authors | Study type, number of patients, duration of follow-up | Inclusion criteria | Initial treatment | Criteria for ID | Restrictions | End points | Study result |
|---|---|---|---|---|---|---|---|
| Ruiter G, [18] | Not placebo controlled,<br>18 patients (3 did not completed the study)<br>12 weeks | 1. IPAH as defined by RHC,<br>2. Receipt of optimal PAH-specific treatment,<br>3. Clinically stable for at least 3 months,<br>4. ID. | 1. ERA monotherapy — 4,<br>2. Prost monotherapy — 4,<br>3. ERA + PDE 5i — 2,<br>4. ERA + Prost — 1,<br>5. ERA + PDE-5i + Prost — 4 | 1. SI <10 μmol/L,<br>2. TSAT <15 % [women] or <20 % [men],<br>3. SF <100 μg/L. | 1. Patients already on iron,<br>2. Participation in other studies on pulmonary hypertension and\or anemia,<br>3. Comorbidities. | 1. Primary end point — 6MWD,<br>2. Secondary end points:<br>– change in blood iron parameters,<br>– change in maximal exercise parameters and endurance capacity determined by maximal and submaximal cardiopulmonary exercise tests,<br>– change right ventricul function determined by cardiac magnetic resonance imaging,<br>– quality of life determined by the SF-36 questionnaire,<br>– skeletal muscle oxygen handling at the cellular level determined by quadriceps muscle biopsy. | 1. Did not significantly change 6MWD,<br>2. SI, SF increased slightly,<br>3. Improving submaximal exercise capacity,<br>4. No significant changes during cardiorespiratory testing,<br>5. Exercise endurance capacity was markedly improved,<br>6. Improvement in QoL,<br>7. Cardiac function was unchanged,<br>8. Skeletal muscle biopsies revealed improvements in oxygen handling capacity. |
| Blanche C, [19] | Retrospectively,<br>142 patients,<br>5,7 years | – Patients with Eisenmenger syndrome — 41 (28,8 %),<br>– PAH-CHD — 27 (19,0 %),<br>– Non -PH CHD 16 (11,3 %)<br>– Non-CHD PH 58 (40,8 %). | | 1. SF <30 μg/L,<br>2. TSAT < 20 %. | | Change in blood iron parameters | Hematocrit, SI and SF increased |

**Note.** 6MWD — 6-minute walk distance, CCB — Calcium channel blockers, CHD — congenital heart disease, ERA — endothelin receptor antagonists, ID — iron deficiency, iProst — inhaled prostanoid, oProst — oral prostanoid, PAH — pulmonary arterial hypertension, PDE-5i — phosphodiesterase type 5 inhibitor, RHC — right heart catheterization, SF — serum ferritin, sGC stim — soluble guanylyl cyclase stimulator, SI — serum iron, TKI — tyrosine kinase inhibitor, TSAT — transferrin saturation, WHO — World Health Organization, QoL — quality of life

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# КЛАПАННАЯ БОЛЕЗНЬ СЕРДЦА ПРИ АНТИФОСФОЛИПИДНОМ СИНДРОМЕ (ОБЗОР ЛИТЕРАТУРЫ)

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# Valvular Heart Disease In Antiphospholipid Syndrome (Review)

**Резюме**

Обзор посвящен особенностям клапанной болезни сердца (КБС) при антифосфолипидном синдроме (АФС). Кроме эпидемиологических данных и классификационных критериев АФС, приводятся сведения о распространенности, патогенетических механизмах, патоморфологических особенностях КБС, которая характеризуется веррукозным эндокардитом (или эндокардитом Либмана-Сакса), утолщением створок и дисфункцией клапанов. Основные патогенетические события КБС обусловлены воздействием антифосфолипидных антител, локальной агрегацией тромбоцитов, миграцией воспалительных клеток и отложением иммунных комплексов. Течение КБС при АФС нередко осложняется тромбоэмболическими осложнениями, включая эмболизацию артерий головного мозга и коронарных артерий. Диагностика КБС при АФС основывается на результатах эхокардиографии (ЭхоКГ), что позволяет выявить утолщение створок, веррукозные образования и оценить функцию клапанного аппарата. Использование чреспищеводной ЭхоКГ позволяет уточнить особенности клапанного поражения при неубедительных результатах трансторакальной ЭхоКГ. Обсуждаются вопросы ведения больных с АФС, имеющих КБС, с оценкой результатов применения антитромбоцитарной, антикоагулянтной, иммуносупрессивной терапии и хирургической коррекции выраженной клапанной патологии. Выполнение кардиохирургических вмешательств ассоциируется с повышенным риском развития послеоперационных осложнений, обусловленных кровотечениями или тромбозом, а также смертности.

***Ключевые слова:*** *антифосфолипидный синдром, клапанная болезнь сердца, эндокардит Либмана-Сакса, вальвулит, эхокардиография, лечение, тромбоэмболические осложнения*

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## Abstract

The review concerns special aspects of valvular heart disease (VHD) in antiphospholipid syndrome (APS). In addition to epidemiological data and classification criteria for APS, information is provided on the prevalence, pathogenetic mechanisms, and pathomorphological features of VHD, which is characterized by verrucous endocarditis (or Libman-Sacks endocarditis), thickening of the leaflets and valve dysfunction. The main pathogenetic events of VHD are caused by the effects of antiphospholipid antibodies, local platelet aggregation, migration of inflammatory cells and deposition of immune complexes. The course of VHD in APS is often complicated by thromboembolic complications, including embolization of the cerebral arteries and coronary arteries. Diagnosis of VHD in APS is based primary on the results of echocardiography, which allows to identify leaflet thickening, verrucous vegetations and assess the function of the valve apparatus. The use of transesophageal echocardiography makes it possible to clarify the features of valvular lesions in case of inconclusive results of transthoracic echocardiography. The issues of management of patients with and VHD are discussed, with an assessment of the results of the use of antiplatelet, anticoagulant, immunosuppressive therapy and surgical correction of severe valvular pathology. Cardiac surgery is associated with an increased risk of postoperative complications due to bleeding or thrombosis, as well as mortality.

***Key words:*** *antiphospholipid syndrome, valvular heart disease, Libman-Sacks endocarditis, valvulitis, echocardiography, treatment, thromboembolic complications*

## Conflict of interests

Co-author of the article Ignatenko G.A. is a member of the editorial council of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Ignatenko G.A. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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APS — antiphospholipid syndrome, aPLA — anti-phospholipid antibody, aCA — anti-cardiolipin antibody, anti-$\beta_2$GP1 — anti-$\beta_2$-glucoprotein 1 antibodies, LAC — lupus anticoagulant, SLE — systemic lupus erythematosus, CVD — cardiac valve disease, ACR — American College of Rheumatology, EULAR — European League Against Rheumatism, echoCG — echocardiography, MV — mitral valve, AV — aortic valve, TV — tricuspid valve, LSE — Libman-Sacks endocarditis, IE — infective endocarditis, TEC — thromboembolic complication, TTE — transthoracic echoCG, TEE — transesophageal echoCG, nBTE — non-bacterial thrombotic endocarditis, ACT — anticoagulant therapy, HCQ — hydroxychloroquine, GC — glucocorticoids

# Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease associated with venous, arterial or microvascular blood-clotting and/or complication of pregnancy, with laboratory evidence of persistent antiphospholipid antibodies (aPLA), such as anti-cardiolipin antibody (aCA), anti-$\beta_2$-glucoprotein 1 ($\beta_2$GP1) antibodies) and lupus anticoagulant (LAC) [1, 2].

APS can be primary, when the patient does not have signs of any disease, or secondary to another patholofy, e.g. an autoimmune disease (mostly systemic lupus erythematosus (SLE), neologisms and drug administration. APS can complicate the course of various infectious diseases, including coronavirus infection (COVID-19) [1, 3, 4].

According to a meta-analysis, the morbidity and incidence of APS are 1–2 cases per 100,000 and 40–50 cases per 100,000, respectively [4, 5]. APS is the leading cause of strokes in young patients, 33 % of strokes in patients below 50 years of age, and 20 % cases of recurrent miscarriages [6].

APS can be associated with involvement of almost any organ, mostly due to thrombotic and atherosclerotic processes [1, 2, 7]. A cardiac pathology in patients with APS significantly affects the clinical presentation, course, prognosis of the disease, and often results in severe complications and death. Cardiac pathologies in patients with APS are versatile and include cardiac valve disease (CVD), thrombotic and atherosclerotic coronary occlusion, ventricular dysfunction and dilatation, intracardiac thrombosis, and pulmonary hypertension [8, 9]. This review presents the data on the incidence, pathogenesis, pathomorphology, diagnosis, and current therapies of CVD in APS patients. Literature sources were searched in RSCI (Russian Science Citation Index), eLibrary, PubMed using keywords. The review includes articles

both in Russian and English, which were published over the period from 2014 to 2024. The analysis also included fundamental researches, which were conducted earlier, but which are highly valuable for this topic. Keywords for the literature search: antiphospholipid syndrome, cardiac valve disease, Libman-Sacks endocarditis, valvulitis, echocardiography, treatment, thromboembolic complications, events. The focus was on the articles published in scientific journals and peer reviewed.

## Antiphospholipid syndrome diagnosis

There are currently no proper diagnostic criteria for APS; however, classification criteria developed mostly for clinical and interdisciplinary studies to identify homogenous groups are widely used [10, 11]. APS classification criteria usually include its most specific manifestations: arterial, venous thrombosis, microvascular thrombosis, miscarriage in patients with aPLA. In additional to laboratory findings, in each case APS is diagnosed based on a set of all clinical parameters, taking into account also non-specific manifestations of the disease[12]. Therefore, in clinical settings, APS classification criteria are used mostly for justification and confirmation of the diagnosis [12, 13].

The first classification criteria were proposed after the VIII International APS Congress, which was held in Sapporo (Japan) in 1998. During their discussion, the working group experts noted that although some clinical manifestations of APS (particularly low platelet count, haemolytic anaemia, *livedo reticularis*, CVD) are sometimes associated with APS, they do not demonstrate strong associations as signs included into the proposed classification criteria. During a separate workshop to discuss APS criteria held in November 2004 as part of the International APS Congress in Sydney (Australia), new criteria were proposed, which differed from the previous Sapporo wording of the laboratory criteria [14]. Moreover, experts proposed the wording for clinical manifestations, including CVD, which were not included into the classification criteria, but were useful for the diagnostics in some patients as possible, non-critical signs of APS or APS-associated characteristics [15].

The classification criteria developed by the American College of Rheumatology (ACR) together with the European League Against Rheumatism (EULAR) were published in 2023. They were based on the current idea of APS, which allowed weighing individual criteria, with exceptional performance characteristics and possible specificity of criteria [2] (Table 1).

It is worth mentioning that the 5th clinical domain is represented by CVD variants: thickened valve leaflets and/or valve vegetation, having relatively high weight — 2 and 4 points, respectively.

As compared to the 2006 Sydney criteria, 2023 ACR/EULAR criteria had a modified CVD definition [2, 14] (Table 2). The latest criteria describe age-related leaflet thickness; vegetation description is revised: vegetation can be villous, lobulated or round; and the most common size (< 1 cm) is mentioned. It is also noted that vegetations can be found not only on the mitral valve (MV) and aortal valve (AV), but also on any side of any valve leaflet.

## Characteristics of cardiac valve disease in patients with antiphospholipid syndrome

CVD is the most common cardiac pathology in patients with APS, which affects approximately one third of patients. In patients with primary or secondary APS, changes in the endocardium are mostly thickened valve leaflets and vegetations. MV is the most common location (33.3–88.8 % of cases), followed by AV (13.1–51.3 %), tricuspid valve (TV) (3–12 %) and pulmonic valve (1 %) [15-22]. The causes of a higher incidence of left-side valve involvement include higher susceptibility of the endothelium to microdamage due to shear stress and higher loads at systolic blood expulsion from the left ventricle [23].

Generally, valve insufficiency prevails over stenosis and is usually not associated with significant haemodynamic disorders. The incidence of haemodynamic valve disorders in APS is approximately 1 to 4 % [22]. Valve involvement can manifest through global valve thickening, local thickening, usually involving the proximal or middle part of the leaflet, uneven nodes or verrucous vegetations on leaflets (known as Libman-Sacks endocarditis (LSE); mild to moderate valve dysfunction [9, 15, 17, 20, 24, 25].

A prospective study by N. Nagy et al. [26] compared the incidence of CVD variants in patients with SLE with aPLA (n = 258, 69.9 %) and without aPLA the (n = 111, 30.1 %). All cardiac manifestations were more common in the aPLA group; however, a significant difference was found in tricuspid (31.4 % vs. 18.0 %, p = 0.008) and mitral insufficiency (33.7 % vs. 21.6 %, p = 0.02). Besides, patients with aPLA have statistically significantly more such clinical manifestations of SLE, as disorders of the CNS (n = 73, 28.3 % vs n = 14, 12.6 %, p=0.001), peripheral nervous system (n = 32, 12.4 % vs n = 6, 5.4 %, p = 0.043) and mental disorders (n = 60, 23.3 % vs n = 14, 12.6 %, p = 0.019), which can be partially attributable to CVD and its complications.

***Table 1.*** *Classification criteria for antiphospholipid syndrome (ACR/EULAR, 2023)*

| Clinical criteria | Weight, scores |
|---|---|
| **Domain 1 — Macrovascular (venous thromboembolism, VTE)** | |
| • VTE with a high-risk VTE profile | **1** |
| • VTE without a high-risk VTE profile | **3** |
| **Domain 2 — Macrovascular (arterial thrombosis, AT)** | |
| • AT with a high-risk CVD profile | **2** |
| • AT without a high-risk CVD profile | **4** |
| **Domain 3 — Microvascular** | |
| **Suspected (one or more of the following):** | |
| • livedo racemosa (by physical examination) | **2** |
| • livedoid vasculopathy lesions (by physical examination) | |
| • Acute/chronic aPl nephropathy (by physical examination or laboratory tests) | |
| • Pulmonary hemorrhage (by clinical symptoms and imaging) | |
| **Established (one or more of the following):** | |
| • livedoid vasculopathy (by pathology) | **5** |
| • Acute/chronic aPl nephropathy (by pathology) | |
| • Pulmonary hemorrhage (by BAL or pathology) | |
| • Myocardial disease (by imaging or pathology) | |
| • Adrenal hemorrhage or microthrombosis (by imaging or pathology) | |
| **Domain 4 — Obstetric** | |
| • ≥3 consecutive pregnancy loss before 10 weeks and/or early fetal loss (10 weeks 0 days and 15 weeks 6 days) | **1** |
| • Fetal death (16 weeks 0 days — 34 weeks 0 days) without preeclampsia with severe features or placental insufficiency with severe features | **1** |
| • Preeclampsia with severe features (<34 weeks 0 days) **or** placental insufficiency with severe features (<34 weeks 0 days) with/without fetal death | **3** |
| • Preeclampsia with severe features (<34 weeks 0 days) **and** placental insufficiency with severe features (<34 weeks 0 days) with/without fetal death | **4** |
| **Domain 5 — Cardiac valve** | |
| • Valve thickening | **2** |
| • Valve vegetation | **4** |
| **Domain 6 — haematology** | |
| • Thrombocytopenia (20-130×$10^9$/liter) | **2** |
| **Laboratory Criteria** | |
| **Domain 7 — aPl test by coagulation-based functional assay** | |
| • Positive LAT (single-one time) | **1** |
| • Positive LAT (persistent) | **5** |
| **Domain 8 — aPL testing by solid-phase assays: aCL and/or anti-β2GPI antibody enzyme-linked immunosorbent assay** | |
| • Moderate or high positive (IgM alone) (aCL and/or anti-$\beta_2$GPI) | **1** |
| • Moderate positive (IgG) (aCL and/or anti- ß$_2$GPI) | **4** |
| • High positive (IgG) (aCL **or** anti-$\beta_2$GPI) | **5** |
| • High positive (IgG) (aCL **and** anti-$\beta_2$GPI) | **7** |

**Note.** APS is classified for research purposes if there are at least 3 points from clinical domains **and** at least 3 points from laboratory domains
**Abbreviations:** AT — arterial thrombosis, VTE — venous thromboembolism, aPL — Antiphospholipid antibody, BAL — bronchoalveolar lavage, BP — blood pressure, CVD — cardiovascular disease, LAT — lupus anticoagulant, aCL — anticardiolipin antibody, anti-$\beta_2$GPI — anti-$\beta_2$-glycoprotein I antibody. Adapted from M. Barbhaiya et al. [2].

***Table 2.*** *Comparison of formulations of valvular heart disease in APS based on the materials of the APS Congresses 2006 and 2023*

| **The 2006 APS classification criteria**<br>**Definition of aPL-associated valvular heart disease** | **The 2023 APS classification criteria**<br>**Domain 5 — Cardiac valve** |
|---|---|
| Coexistence of aPL (Laboratory Criteria for APS) along with:<br>- Echocardiographic detection of lesions and/or Regurgitation and/or stenosis of mitral and/or aortic valve or any combination of the above.<br>- Defining valve lesions include:<br>- Valve thickness >3 mm,<br>- Localized thickening involving the leaflet's proximal or middle portion,<br>- Irregular nodules on the atrial face of the edge of the mitral valve, and/or the vascular face of the aortic valve. | Criteria for inclusion and:<br>- Valve thickening<br>- MV thickening is defined as >4 mm between ages 20–39 years; >5 mm for those older than age 40 years, and>3 mm for other valves for any age (valve thickening can be associated with valvular dysfunction (regurgitation or stenosis)).<br>- Valve vegetation is defined as shaggy, lobulated, or rounded masses typically located on the atrial side of atrioventricular valves (MV and tricuspid valve) or ventricular side of the AV, but can be located on any side of any valve (size is highly variable but usually <1 cm). |

**Notes:** APS — antiphospholipid syndrome; AV — aortic valve; MV — mitral valve; aPL — antiphospholipid antibodies. Adapted from S. Miyakis et al. [14] и M. Barbhaiya et al. [2]

A large systemic review and meta-analysis conducted by S. Zuily et al. [27] reported that aPLA in patients with SLE is associated with 3-fold increase in the risk of CVD, including LSE. The available data are the most conclusive evidence of the correlation between aPLA and damages to the heart valves.

A meta-analysis of 25 studies with the total number of 8,089 patients with SLE showed that the presence of aPLA significantly increased the risk of CVD (HR = 2.24, 95 % CI: 1.58–3.18, p < 0.001) [22]. It is worth mentioning that among the laboratory findings, the highest risk of CVD is typical for LAC (HR = 4.90, 95 % CI: 2.26-10.60, p < 0.001). Positive aCA test doubled the risk (HR = 2.69, 95 % CI: 1.47–4.93, p = 0.001), while positive anti-$\beta_2$GP1 test increased the risk by 70 % (HR = 1.70, 95 % CI: 1.17–2.45, p = 0.005).

## Pathogenesis

The pathogenetic mechanisms of CVD in APS have not been studied sufficiently; however, aPLA is assumed to have the leading role in endocardium damage [9, 17, 28, 29]. Both inflammatory and thrombolytic mechanisms associated with aPLA have been discussed [25, 30]. In APS patients, endothelial damage results from the action of autoantibodies targeting negatively charged phospholipids in endothelial membranes, endothelial microdamages caused by shear stress or blood flow turbulence, as well as antibody production due to molecular mimicry associated with infectious agents [9, 19, 25, 31]. Valve endothelium damage leads to local platelet aggregation, inflammatory mononuclear cell migration and deposits of immune complexes forming a blood clot intertangled with fibrin [32]. A number of studies demonstrated positive correlation between aCA titer and CVD severity [15-17, 25, 33, 34]. Initial inflammatory changes cause subsequent subendocardial inflammation, vascular proliferation, fibrosis, calcification, leading to leaflet thickening, rigidity and in some cases commissure fusion [35, 36].

L. Ziporen et al. [36] found aPLA deposits and complement components in tissues of deformed cardiac valves in patients with primary SLE-associated APS. The data confirm the pathogenetic value of aPLA in the development of valve damage in APS. Moreover, affected valves of patients with APS showed anti-$b_2$GP1 antibodies, among which at least anti-$b_2$GP1-associated peptides were target epitopes of these antibodies [37]. The peptides had a similar amino acid sequence with various bacterial and viral antibodies. Based on the data, the authors assumed that non-bacterial LSE can be indirectly caused by an infection due to molecular mimicry and production of antibodies initially targeting infectious agents.

It is assumed that aPLA and especially LAC associated with pronounced hypercoagulation [38] are critical for the pathogenesis of heart valve destruction in SLE patients [25, 30]. LSE is secondary to deposits of fibrinous platelet plugs on the affected valve. It is likely that aPLA facilitate blood clotting on valves, which are already damaged by inflammation [17, 25].

A study by Yu. S. Bakhareva et al. of the role of polymorphism of 18 candidate genes in the development of non-infectious endocarditis in patients with APS showed that polymorphism of some genes is reliably associated with valve damages, suggesting genetic susceptibility in these patients [20].

## Morbid anatomy

The histologic pattern of aPLA-associated valvulopathy is non-specific and includes fibrosis, calcification, vascular proliferation, verrucous deposits on the valve endocardium, and thrombotic capillaries in the valve. Typical verrucous vegetations are represented by low, flat warted formations with a fibrous plaque and focal calcification. Vegetation formation is associated with marked scarring, fibrous tissue proliferation, often resulting in leaflet thickening and valve deformity with later valve dysfunction [9, 31]. Usually vegetations in APS patients are small (up to 10 mm), but sometimes they can be large (≥ 10 mm) and are located in any place on the endocardial surface, in some cases resulting in valve insufficiency. Vegetations typical for LSE in SLE patients are reported approximately in 10 % of patients and correlate with the disease duration and severity as well as aCA [9, 24].

## Clinical presentation

APS patients are often asymptomatic or have unclear clinical manifestations, which make timely diagnosis of the syndrome and CHD challenging. Clinical manifestations and instrumental findings can resemble presentations of infectious endocarditis (IE) or rheumatic heart disease. It is not uncommon that LSE vegetations mimic cardiac myxomas [35, 40]. In valve insufficiency or stenosis, clinical manifestations are influenced by the respective valve pathology. The majority of patients remain asymptomatic for a long period of time and just some of them develop cardiac failure and need heart surgery [31, 41]. Absence or unclear symptoms of CVD are the cause of unawareness on the part of clinicians as to the possible endocardium involvement in APS patients [15].

CVD in APS patients requires special attention not only because of valve dysfunction development, but also due to the risk of arterial thromboembolic complications (TEC), including strokes [20, 25, 42]. Unlike IE, LSE vegetations are sterile, more loose and prone to embolization [19, 43]. In case of APS with MV involvement, the rate of arterial embolization is as high as 77 % [23].

A prospective study by J. Pardos-Géa et al. demonstrated that CVD in patients with APS is associated with 8.4-fild risk of arterial thrombosis within the 12-month period [44]. Similar results were obtained in a prospective study by S. Morelli et al. [45], who noted that left-sided CVD is a powerful risk factor of cerebrovascular conditions in patients with SLE. The authors found out that the presence of CVD is associated with a 10.8-fold increase in the risk of stroke and/or transient ischemic attack.

In 2005, S.A. Roldan et al. [46] suggested that CVD in patients with SLE causes ischemic brain damage and cardiovascular pathology. An examination of 37 patients with SLE showed that LAC, moderately thickened MV leaflets or mitral valve insufficiency were associated with a 10-fold increase in the risk of cerebral infarction. Besides, in patients with SLE, CVD diagnosed with the help of transthoracic echoCG (TTE) is an independent predictor of a brain damage shown on magnetic resonance imaging (cerebral infarction, white matter damages or small pinpoint abnormalities), neurological disorders (strokes, transient ischemic attacks, cognitive dysfunction) and mental disorders (acute confusional state consciousness, fits or psychosis) [47].

In a large study of 284 patients with APS, I. Krause et al. [48] established that CVD is associated with higher rates of impaired cerebral circulation, epilepsy and migraines. A sub-analysis showed significant correlation between CVD (vegetations and/or thickened valve leaflets) and CNS abnormalities in patients with primary APS; however, there was no such correlation in patients with secondary SLE-associated APS.

R. Cevera et al. [49] demonstrated that, in patients with APS, the rate of TECs during the first five years and subsequent five years of follow-up was 16.6 % and 14.4 %, respectively. According to a number of studies, the most common TEC in APS is strokes (19.8–35.2 %), myocardial infarction (7.4–8.64 %), transient ischemic attacks (4.7 %), deep venous thrombosis (4.3 %) and pulmonary artery thromboembolia (3.5 %) [20, 48, 49].

The data of a prospective 12-year follow-up of 53 patients with APS demonstrate that CVD is often associated with TEC [44]. For instance, patients with baseline echoCG signs of valvulopathy vs. controls without signs of CVD more often had arterial thrombosis (69 % vs. 20 %, $p < 0.001$), risk factors of atherosclerosis (62 % vs. 29 %, $p = 0.01$), *livedo reticularis* (48 % vs. 16 %, $p = 0.01$), and migrain (41 % vs. 12 %, $p = 0.02$). CVD (thickened leaflets and verrucous vegetations) can be a risk factor of CNS damage, early onset of atherosclerosis and severe underlying disease [44].

Results of a recent study by S. Niznik et al. [42] to analyse the clinical characteristics and outcomes of primary APS with CVD show that patients with APS and CVD more often have cerebrovascular events (56.3 % vs 25 %, $p = 0.005$) and *livedo reticularis* (24.2 % vs. 7.8 %, $p = 0.013$), as compared to patients with intact valves. Besides, unlike patients with APS without valve pathologies, patients with APS and CVD more often had catastrophic APS (12.1 % vs. 2.4 %, $p = 0.034$), recurrent

thrombosis (33.3 % vs. 4.7 %, p < 0.001) and needed effective therapy (IV immunoglobulin, plasma exchange or rituximab). Given the more severe course of APS in patients with CVD, the authors think that the valve pathology is a high risk APS category [42].

**Diagnosis of cardiac valve disease in patients with antiphospholipid syndrome** is based mostly on the TTE results, the sensitivity and specificity of which are 35–45 % and 75 %, respectively. The most common echoCG sign is locally thickened proximal and middle part of leaflets, diffuse increase in leaflet thickness (> 3 mm), uneven nodes on any side of any valve (usually MV and/or AV), endocardium vegetation [9]. Not uncommon are the so-called kissing foci, located on the opposite sides of the closing line on both MV and AV [25, 50].

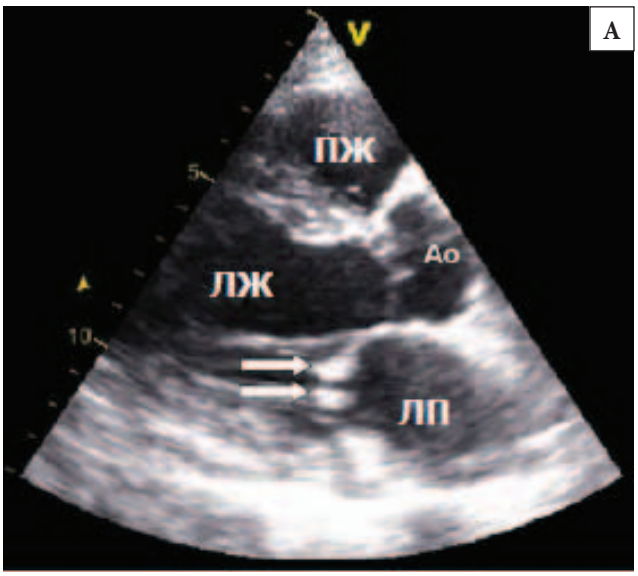
According to prospective echoCG studies, CVD in APS patients persists or progresses, irrespective of the use of anticoagulants or antiplatelet therapy [24, 50].

TTE should be considered as primary screening of CVD in APS patients; it should be used to monitor the efficiency of anticoagulant therapy (ACT), which in some cases allows minimising or removing vegetations [9].

When transesophageal echoCG (TEE) is used, sensitivity is higher (73–97 %); however, its specificity drops (37 %). The use of TEE is justified to explore the characteristics of CVD and to find any changes, which cannot be identified with TTE [18, 41, 51, 52]. Better findings of verrucous endocarditis visualisation in TEE result from the use of high-frequency sensors, which ensure better quality of images and make it possible to see even tiniest changes. According to the results of a meta-analysis of 11 studies, the rate of CVD in patients with SLE, as shown by TTE, and aPLA is statistically higher than in patients with negative aPLA: 131/300 (44 %) vs. 120/488 (25 %), p < 0.0005 [41]. At the same time, there is a comparable rate of CVD signs seen at TEE in patients with SLE with and without aPLA: 30/50 (60 %) vs. 26/41 (63 %), p = 0.9. Thus, TEE demonstrates higher sensitivity in identification of valve pathologies in patients with SLE depending on aPLA status: 44 % seen at TTE vs. 60 % seen at TEE in patients with SLE and aPLA (p < 0.04) and 25 % seen at TTE vs. 63 % seen at TEE in patients with SLE without aPLA (p < 0.0005).

When TTE is used, valve pathologies in patients with APS are diagnosed more often than in healthy population: 55 out of 137 (40 %) and three out of 125 (2 %), p < 0.0001, respectively. Patients with primary APS have more cases of CVD when TEE is used as compared to TTE: 132 out of 180 (73 %) and 61 out of 157 (39 %), p < 0.0005, respectively [41].

Diagnosis of non-bacterial thrombotic endocarditis (NBTE), which includes LSE, can be more challenging because of smaller size of vegetations after embolization,



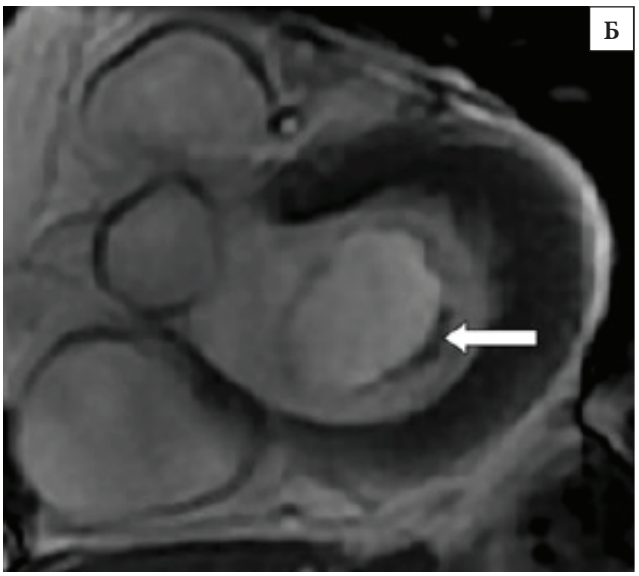




**Figure. 1** *66-year-old male patient with APS:*
***A.*** *Echocardiography, parasternal long axis view. The "kissing" vegetation is clearly visualized (marked with white arrows), located near the free margins of both mitral leaflets come into contact during systole.*
***B.*** *Cardiac magnetic resonance imaging parasternal short axis view. The arrow indicates a localized thickening (dark color) of the distal part of the MV leaf. Adapted from S. Zuily et al. [25].*
**Notes:** RV — right ventricle; LV — left ventricle; LA — left atrium; Ao — Aorta

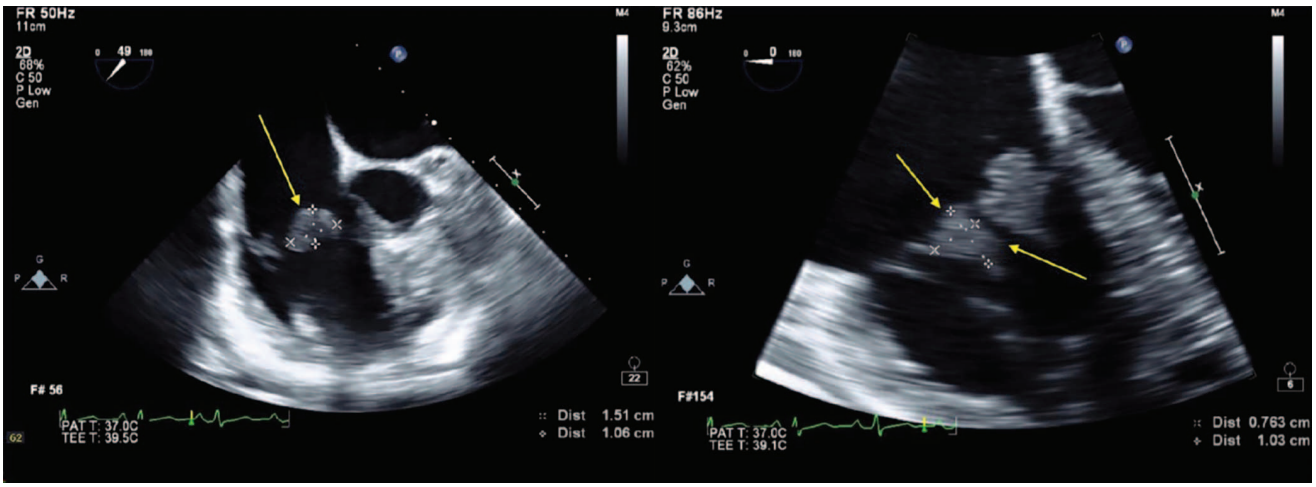



***Figure 2.*** *A 44-year-old female patient, secondary antiphospholipid syndrome associated with systemic lupus erythematosus. Transesophageal echocardiogram. On the left: non-bacterial vegetation (marked with an arrow) on the anterior leaflet of the tricuspid valve measuring 1.51×1.06 cm. On the right: vegetation is also visualized on the posterior leaflet of the tricuspid valve measuring 0.76×1.03 cm. Adapted from T. Nagi et al. [43]*

which a common cause of false negative results of initial echoCG. M. A. Zmaili et al. [18] followed up a 47-year-old patient with SLE and significant mitral insufficiency, as shown by TTE and TEE, and with no evident signs of endocarditis. However, a histopathological examination after MV prosthesis revealed NBTE. Thus, diagnosis of CVD in patients with APS requires high clinical suspicion [18, 53].

There are publications on the use of 3D real-time TEE as an additional imaging method in patients with suspected CVD and APS [24, 25, 54]. As for other imaging methods, heart CT and MRI are alternative methods to diagnose cardiovascular conditions, including detection of endocavitary clots; they are also useful for differential diagnosis of the nature of endocardium involvement (Fig. 1–3) [24, 25, 40].

## Management

Patients with APS are at a higher risk of primary and recurrent TEC, irrespective of their CVD status, that is why management of such patients requires discussion of preventive measures [55]. Given that estimated risks in studies vary a lot, several models for APS prediction were proposed in order to identify patients who will benefit from antithrombotic preventive measures [56, 57].

In 2003, the International Expert Committee published recommendations for the treatment of cardiac pathologies, including CVD, in patients with APS [58]. For instance, symptomatic patients with signs of valvulopathy are recommended ACT. Antiplatelet drugs can be used in asymptomatic patients for prevention.

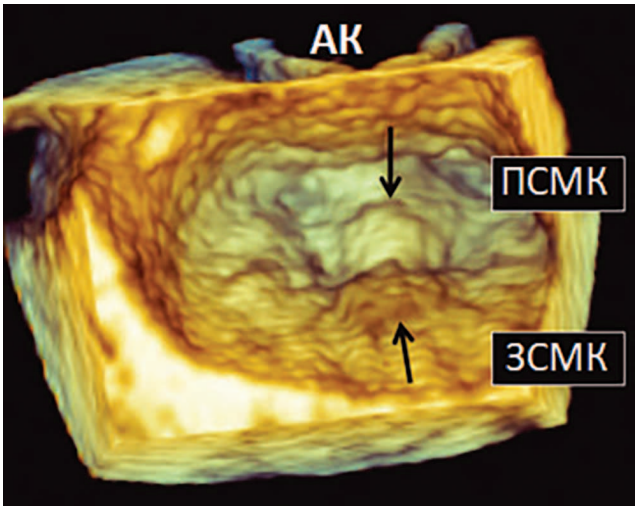



***Figure 3.*** *Libman–Sacks endocarditis in the performance real time 3D transesophageal echocardiography. Face view of the mitral valve seen from the left atrial perspective. Mitral valve Libman–Sacks endocarditis appears as mound-like protuberances (arrows) on the tips of the A2 scallop of the anterior leaflet and the P2 scallop of the posterior leaflet. AV — aortic valve; AML — anterior mitral leaflet; PML — posterior mitral leaflet*

For patients with APS and CVD, immunosupressive, antiplatelet, anticoagulant therapy and surgical correction of valve defects are indicated [17, 40, 43, 51, 59].

The results on the efficacy of ACT to reduce the size of vegetations and the risk of TEC, are controversial [15, 18, 60]. According to the data on case studies and series of cases, the use of anticoagulants, hydroxychloroquine (HCQ) and glucocorticoids (GC) can reduce the size of

vegetations or eliminate them within a period from one week to one year, including regression of relatively large masses (with the baseline size of 2 to 4 cm) (Table 3). At the same time, there are some reports on the absence of any effects of antiplatelet and anticoagulant therapy [40, 52, 79, 80]. It is worth mentioning that, in a number of LSE cases refractory to traditional therapy, vegetation was found on TV, despite the fact that the right-sided valves are rarely involved, as compared to MV and AV [40, 79, 80].

NBTE is also treated with immunosuppressants: HCQ and GC. By targeting platelets, endothelial and immune cells, HCQ reduces inflammation and the risk of blood clotting. A number of studies demonstrated favourable effects of HCQ in the reduction of the risk of blood clotting in patients with APS and asymptomatic aPLA carriers [72, 76, 81, 82]. A very low risk of haemorrhagic complications with the use of HCQ should be mentioned [81, 82].

It is assumed that GCs are justified in patients with CVD in secondary APS caused by an autoimmune condition, despite the current discussions of their benefits [73]. Some papers mention the ability of GC to significantly reduce the overall disease severity, leading to clinical improvements as regards valve structure and functions [83, 84]. Despite the mentioned favourable effects, it is still uncertain whether CGs should be prescribed, given their cardiovascular side effects (arterial hypertension, increased post- and preload, intensification of atherosclerosis processes, etc.). There is also little evidence in favour of GCs in CVD and primary APS [15, 73]. During the study of outcomes in patients who underwent heart valve surgery, T. Eviatar et al. [85] noted a higher rate of complications in the group of patients who were treated with CGs perioperatively vs. patients who did not take any steroids. It is assumed that GCs are prescribed to patients with a more severe course of disease, where visceral organs are involved, which also impacts the rate of complications of cardiovascular interventions. Besides, GCs predispose patients to infections and haemorrhagic complications [85].

Indications for cardiac surgery in patients with LSE remain unclear, while valve replacement results are limited to case studies or series of cases. According to Y. Le Ho et al. [31], the clear indications for surgery in patients with APS are severe valve dysfunction, large vegetations and recurrent embolism, despite ACT. Besides, unlike IE, NBTE is associated with a higher surgical risk of embolism with whole vegetations or their fragments due to higher susceptibility of APS patients to TEC [86]. As opposed to IE, where the valve needs to be dissected completely in order to remove infected tissue, in LSE patients, valve replacement and reconstruction can be sufficient, and there is no need for life-long ACT [31].

Patients with APS, who underwent heart surgery, demonstrate a higher risk of post-surgery complications and mortality caused by bleeding or blood clots [15, 51, 85, 87]. In addition to bleeding and blood clots, common post-surgery complications include sepsis, heparin-induced thrombocytopenia, as well and rhythm disturbance and impaired conductivity [88, 89]. According to T. Eviatar et al. [85], out of 26 patients, who underwent surgery for CVD in AOS, severe complications were reported in 14 patients (53.8 %), including four deaths (15.4 %). N. B. Chalvon et al. [89] followed up 23 patients with SLE and/or APS, who underwent heart surgery. Nine (39 %) patients had early post-surgery complications, including three cases of dramatic APS and death.

S. Masoumi et al. [91] describes a 32-year-old female patient with primary APS, who was diagnoses with MV LSE in addition to significant mitral insufficient (TEE procedure). Two vegetations were found: one 30×5 mm, attached to the base of the anteromedial side of MV leaflet; and a larger one measuring 26×12 mm at the anterior MV leaflet. The patient underwent heart surgery to dissect vegetations and partially reconstruct the MV using autologous pericardium and a pair of artificial chords. Four months later, the patient developed signs of pulmonary hypertension and right ventricular failure. TEE showed severe TV and MV failure, as well as perforated pericardial flap on the reconstructed MV, requiring another heart surgery to impact an artificial MV and repair TV.

In a retrospective analysis of 32 patients with APS, who underwent valve replacement, early mortality was 7 %, long-term mortality — 12.5 % [92]. Only 42 % of patients who underwent heart valve surgery recovered without complications. Higher mortality rates (up to 20 %) were recorded in other studies [87, 93]. Assessment of thrombotic and haemorrhagic risks, as well as close monitoring of the patient's condition and valve function evaluation in the post-surgery period are essential for reduction of the rate of complications [51, 85, 87]. Since there are no results of long-term follow-ups, the opinion on prosthetic valve selection remains unclear: whether it should be mechanic or biological one. In patients with primary or secondary APS, antibacterial therapy to prevent IE is considered unjustified [15, 88].

***Table 3.*** *Results of drug therapy in the treatment of vegetations in antiphospholipid syndrome*

| № | First author | Year | Age, gender | Presentation | Autoimmune disease | Affected valve | Vegetation size (cm) | Treatment | Time to dissolution |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Skyrme-Jones R [61] | 1995 | 16, F | Strokes | PAPS | MV | 0,8×0,5 | VKA | 9 months |
| 2. | O'Neill D. [62] | 1995 | 40, F | Strokes | PAPS | MV | NA | VKA | 7 weeks |
| 3. | O'Neill D. [62] | 1995 | 47, F | Splinter hemorrhages | PAPS | MV | NA | heparin, VKA | 6 weeks |
| 4. | Agirbasli M.A. [63] | 1997 | 56, F | STEMI | PAPS | MV | 0,3 и 0,8 | VKA | 4 months |
| 5. | Ebato M. [64] | 2002 | 62, F | PE | PAPS | TV | 1,7×1,8 | heparin, VKA | 7 days |
| 6. | Tomcsanyi J. [65] | 2004 | 58, F | Splenic infarct | PAPS | MV, TV | NA | Anticoagulants | 6 weeks |
| 7. | Brito F.A. [66] | 2004 | 34, F | Murmur | SLE, APS | MV | NA | VKA | 6 months |
| 8. | Ruan Y. [67] | 2008 | 43, F | TIA | Seroneg. APS | MV | 1,0 | Aspirin, heparin, warfarin | 42 days |
| 9. | Salzberg S.P. [68] | 2009 | 30, м<br>30, F | Strokes | PAPS | AV | 4×2,0 | heparin | 4 months |
| 10 | Prashanth P. [69] | 2011 | 27, F | Incidental TTE | Seroneg. RA, SLE, APS | MV, PAV | 2,0 | heparin, with subsequent reception VKA (INR 2-3) | 4 weeks |
| 11 | Stevanovic D. [70] | 2014 | 33, F | Erythematous rash | PAPS | MV | NA | LMWH, CS, cytostatics | 1 year |
| 12 | Rachwan R.J. [71] | 2017 | 38, F | TIA, murmur | PAPS | AV | 3,7×2,1 | LMWH | 4 months |
| 13 | Yuriditsky E. [59] | 2018 | 36, м<br>F | Strokes | PAPS | AV | 2,7 | LMWH | 21 days |
| 14 | Yuriditsky E. [59] | 2018 | 29, м<br>29, F | Strokes | SLE, APS | AV | 2,8 | Heparin | 9 days |
| 15 | Sirinvara-vong N. [72] | 2018 | 65, F | Incidental TTE | PAPS | MV | 1,4×0,7 | LMWH, HCQ, CS | 6 months |
| 16 | Granowicz E. [73] | 2018 | 43, F | Chest pain, dyspnoea | SLE, APS | AV | 2,0 | 1. Rivaroxaban<br>2. HCQ, CS | 1. 0 effect<br>2. 24 weeks |
| 17 | Kitano T. [74] | 2019 | 51, F | Dizziness, right-sided ataxia | SLE, APS | AV | NA | 1. Apixaban<br>2. Heparin | 1. 0 effect<br>2. 7 days |
| 18 | Shipman J. [75] | 2020 | 64, F | Incidental TTE | PAPS | Mitral | 1) 1,4×0,9<br>2) 1,3×0,8 | VKA | 8 weeks<br>1. full resolution<br>2. reduced to 1,2×0,3 |
| 19 | Haertel F. [76] | 2021 | 27, F | Night sweats, weight loss, reduction in performance, dizziness | PAPS | MV | 1,6×0,9 | VKA (INR 2-3), HCQ, CS | 3 months |
| 20 | Bahar AR. [77] | 2024 | 47, F | Chronic weakness, weight loss | PAPS | AV | 0,61×1,2 | VKA, rivaroxaban, dabigatran | 2 months |
| 21 | Bowden A [78] | 2024 | 60, F | Strokes | SLE, APS | MV | 0,4 × 0,4 | LMWH, VKA | 25 days |

**Abbreviations:** TIA — transient ischemic attack, TTE — transthoracic echocardiogram, PE — pulmonary embolism, APS — antiphospholipid syndrome, PAPS — primary APS, Seroneg. — seronegative, SLE — systemic lupus erythematosus, RA — rheumatoid arthritis, AV — aortic valve, MV — mitral valve, PAV — pulmonary artery valve, TV — tricuspid valve, NA — not available, INR — international normalized ratio, VKA — vitamin K antagonist, LMWH — Low-molecular-weight heparin, CS — corticosteroids, HCQ — hydroxychloroquine, 0 effect — no effect.

## Conclusion

CVDs are the most common cardiac pathology in patients with APS, which is diagnosed approximately in one third of patients; it is associated with local, diffuse thickening of leaflets, development of verrucous endocarditis, valve failure and (in rare cases) stenosis. Diagnosis of CVD is based mostly on echoCG findings, including TEE. CVD is often associated with various TECs, such as cerebrovascular disorders, arterial or venous thrombosis, myocardial infarction, migraines, and mental disorders. Management of patients with CVD and APS is challenging, given the lack of any conclusive evidence in favour of the use of immunosuppressive, antiplatelet and anticoagulation therapy. In case of significant valve dysfunction, patients with APS should be consulted by a heart surgeon in order to decide whether surgery is required or not, because the risk of post-surgery complications is high.

**Вклад авторов:**

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# СРАВНИТЕЛЬНАЯ КЛИНИКО-ЛАБОРАТОРНАЯ ОЦЕНКА ЭФФЕКТИВНОСТИ ВОССТАНОВИТЕЛЬНОЙ ТЕРАПИИ У БОЛЬНЫХ ОСТЕОАРТРИТОМ КОЛЕННЫХ СУСТАВОВ

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# Comparative Clinical and Laboratory Assessment of the Effectiveness of Rehabilitation Therapy in Patients with Osteoarthritis of the Knee Joints

**Резюме**

**Цель**. Оценить эффективность курсового введения озоно-кислородной смеси в периартикулярные ткани коленного сустава у пациентов с остеоартритом, перенесших тотальное эндопротезирование одного из суставов и изучить влияние этой методики на состояние перекисного окисления липидов и антиоксидантной системы защиты организма относительно традиционных методов восстановительного лечения. **Материалы и методы.** В исследование включено 120 больных, с двусторонним гонартрозом, после эндопротезирования одного из коленных суставов. Средний возраст пациентов составил 60 [46; 76] лет. В зависимости от способа реабилитационного лечения пациенты были разделены на 3 равные группы (n=40): 1-й группе была назначена периартикулярная подкожная озонотерапия в сочетании с лечебной физкультурой, 2-й группе — магнитотерапия и электрофорез на область коленного сустава в комбинации с лечебной физкультурой, и 3-й группе — только комплекс лечебной физкультуры. У всех больных перед реабилитационным лечением и после него (через 14 дней и через 3 месяца) была произведена оценка клинико-функционального состояния с помощью шкалы Western Ontario and McMaster Universities Osteoarthritis Index и исследованы показатели интенсивности течения процессов свободнорадикального окисления и активности антиоксидантной защиты. **Результаты.** При детальном анализе клинико-функционального состояния среди больных 1-й группы относительно 2-й и 3-й был выявлен наилучший «отдаленный» результат: выраженное снижение уровня боли ($p < 0,05$, $p < 0,0001$), скованности ($p < 0,05$, $p < 0,0001$), ограничения физической активности ($p < 0,01$, $p < 0,0001$) — за счет улучшения на фоне проводимой терапии основных показателей антиоксидантной системы защиты: каталазы ($p < 0,01$) и супероксиддисмутазы ($p < 0,01$). **Заключение.** Применение периартикулярной озонотерапии позволяет добиться более стойкого положительного эффекта у больных после тотального эндопротезирования коленного сустава относительно традиционных методов восстановительного лечения, за счет выраженного антиоксидантного действия, направленного на стабилизацию процессов перекисного окисления липидов.

***Ключевые слова:*** *остеоартрит; реабилитационное лечение; периартикулярная озонотерапия*

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

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## Abstract

**Purpose.** To evaluate the effectiveness of the course administration of an ozone-oxygen mixture into the periarticular tissues of the knee joint in patients with osteoarthritis who underwent total arthroplasty of one of the joints and to study the effect of this technique on the state of lipid peroxidation and the antioxidant defense system of the body relative to traditional methods of restorative treatment. **Materials and methods.** The study included 120 patients with bilateral gonarthrosis after endoprosthetics of one of the knee joints. The average age of the patients was 60 [46; 76] years. Depending on the method of rehabilitation treatment, the patients were divided into 3 equal groups (n=40): the 1st group was prescribed periarticular subcutaneous ozone therapy in combination with therapeutic exercise, the 2nd group — magnetotherapy and electrophoresis on the knee joint area in combination with therapeutic exercise, and 3rd group — only the complex of therapeutic exercise. In all patients, before and after rehabilitation treatment (after 14 days and 3 months), the clinico-functional status was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index scale and the indicators of the intensity of the free radical oxidation processes and the activity of antioxidant protection were studied. **Results.** A detailed analysis of the clinico-functional state among patients of group 1 relative to group 2 and 3 revealed the best "long-term" result: a marked decrease in pain ($p < 0.05$, $p < 0.0001$), stiffness ($p < 0.05$, $p < 0.0001$), limitations physical activity ($p < 0.01$, $p < 0.0001$) due to the improvement of the main indicators of the antioxidant protection system against the background of ongoing therapy: catalase ($p < 0.01$) and superoxide dismutase ($p < 0.01$). **Conclusion.** The use of periarticular ozone therapy makes it possible to achieve a more stable positive effect in patients after total knee arthroplasty relative to traditional methods of restorative treatment due to its pronounced antioxidant effect aimed at stabilizing the processes of lipid peroxidation.

***Key words:*** *osteoarthritis; rehabilitation treatment; periarticular ozone therapy*

## Conflict of interests

The authors declare no conflict of interests

## Sources of funding

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## Conformity with the principles of ethics

The study was approved by the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education Orenburg State Medical University of the Ministry of Health of the Russian Federation (protocol No. 235 dated September 27, 2019).

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APS — antioxidative protection system, ROI — reactive oxygen intermediate, VAS– visual analogue scale, DC — diene conjugates, BMI — body mass index, CAT — catalase, KJ — knee joint, ET — exercise therapy, MDA — malonyldialdehyde, OA — osteoarthritis, LPO — lipid peroxidation, RF — rheumatoid factor, SOD — superoxide dismutase, CRP — C-reactive protein, SRO — free-radical oxidation, TEP — total endoprosthetics, NO — nitrogen oxide, WOMAC — Western Ontario and McMaster Universities Osteoarthritis Index

# Introduction

Patients, whose osteoarthritis (OA) is resistant to the standard therapy, need total endoprosthetics (TEP) of the joint. This method can resolve the pain syndrome and improve physical functioning. However, the positive result of surgery in a majority of patients can be completely negated without sufficient rehabilitation measures in the post-surgery period [1].

As of today, periarticular ozone therapy is gaining popularity; this method is based on the use of the curative properties of ozone/oxygen mix (OOM) in the projection of operated joints. Biological effects of ozone are associated with a jump in the levels of reactive oxygen intermediate (ROI) in the injection site, which triggers a cascade of consecutive reactions to induce expressing genes, encoding antioxidative protection system (APS) enzymes [2-3].

A drawback of this method is the lack of a clearly approved algorithm to use the calculated OOM doses in para-articular administration in order to achieve therapeutic effects, which is why this study is so relevant.

**The objective** of the study is to assess the efficiency of a course of OOM administration to periarticular tissue of the knee joint (KJ) in patients with OA, who underwent TEP of one of the joints, and to study the effects of this method for lipid peroxidation (LPO) status and body APS in comparison to the standard rehabilitation treatments.

## Patients and methods

The medical rehabilitation ward No. 1 of the Regional Centre for Medical Rehabilitation was used as the site for the study of 120 patients (74 females and 46 males) aged 45 to 80 years with bilateral KJ OA (based on the OA ACR classification criteria (Altman et al., 1991) [4], after endoprosthesis replacement of one KJ, who were referred to the third stage of rehabilitation. The mean age of patients was 60 [46; 76] years; body mass index (BMI) [5] — 30.60 [27.00; 32.40] kg/m$^2$. The average clinical duration of KJ OA was 16 [2; 30] years; first complaints were recorded approx. at the age of 29 [25; 32] years of age. The median post-surgery period was 4 [3; 5] months.

Inclusion criteria for rehabilitation therapy were: 45 to 80 years old; post-surgery period of 3 to 6 months.

Exclusion criteria were: other rheumatoid conditions with articular syndrome; acute conditions or exacerbation of chronic diseases during the study; malignancies; recurrent thromboembolic complications.

The study was approved by the Local Ethics Committee at the Orenburg State Medical University of the Ministry of Health of Russia (Minutes No. 235 dated September 27, 2019).

According to the rehabilitation treatment strategy, patients were randomised to three equal groups (n = 40) using the stratified randomisation for preliminary definition of the parameters, which could affect the varied efficacy of rehabilitation (age, gender, BMI, disease duration and onset, X-rate stage and clinical functional presentation (pain, extra-articular and infra-articular oedema, limitation of active and passive movements in the operated KJ), caused by surgery). Thus, we have taken into account those parameters, which could affect the rehabilitation therapy efficiency. All patients were recommended a set of rehabilitation exercises for post-TEP patients (10 days). Patients in group 1 had periarticular subcutaneous ozone therapy combined with rehabilitation exercises; group 2 — physical therapy (magnet therapy and electrophoresis with 3 % potassium iodide and 2 % Novocaine on their KJ) combined with rehabilitation exercises; and group 3 — only a set of rehabilitation exercises.

Magnet therapy was administered using Polyus-2m (Russia) for 20 minutes prior to electrophoresis. Electrophoresis with 3 % potassium iodide and 2 % Novocaine (Potok-1, Russia) lasted for 20 minutes. A cycle of physical therapy comprised 10 daily sessions before rehabilitation exercises.

The ozone/oxygen mix produced by Medozon VM-03 (Russia), where ozone concentration was 5,000 μg/L, administered every other day after rehabilitation exercises in a volume of 20 mL. The total cycle included seven sessions.

Clinical functional status of patients with gonarthrosis after KJ TEP was determined with the help of WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) (N. Bellamy et al., 1998) [6].

Laboratory tests were performed to measure serum C-reactive protein (CRP) and rheumatoid factor (RF).

The interdepartmental biochemistry laboratory of the Orenburg State Medical University of the Ministry of Health of Russia was engaged in assessing APS enzymes in all patients before and after rehabilitation therapy (14 days and three months later): superoxide dismutase (SOD) and catalase (CAT) in RBC hemolysate (spectrophotometer GENESYS 5); and LPO product levels: diene conjugates (DC) and malonyldialdehyde (MDA) in dark blood (spectrophotometer BeckmanCoulter DU 800 (Germany)).

For pain management, patients used non-steroidal anti-inflammatory drugs (NSAIDs) symptomatically.

Statistica 10.0 software was used for statistical data processing. Results were presented as a median value (Me) or interquartile range (25th; 75th centile). Qualitative variables were presented as absolute and relative values. In order to compare three independent groups in terms of quantitative attributes, the level of significance of p was determined using Kruskal-Wallis test; if there were significant differences ($p \le 0.05$) or trends, a further pairwise analysis was performed for the study groups using non-parametric Mann–Whitney U test. A correlation analysis was conducted, where Spearman's rank correlation was calculated. Differences were statistically significant at $p < 0.05$.

## Results

The WOMAC scale (Table 1) was used to assess changes in the clinical functional status before and after rehabilitation therapy (14 days and three months later) in patients with gonarthrosis after KJ TEP.

As shown in Table 1, when clinical functional parameters were compared, patients after KJ TEP were comparable in all subscales of the WOMAC questionnaire to values before rehabilitation therapy. In the pairwise comparison of WOMAC values, the closest rehabilitation therapy result (14 days later) was recorded in patients on complex therapy, comprising physical therapy and rehabilitation exercises ($p < 0.001$). However, the best long-term outcome (three months later) vs. baseline data was observed in group 1: marked abatement ($p < 0.001$),

*Table 1. Distribution of the WOMAC index values before and after rehabilitation treatment in both groups*

| | The period of therapy | 1st group (n=40) | 2nd group (n=40) | 3rd group (n=40) | p |
|---|---|---|---|---|---|
| Tenderness | Before treatment | 13,00 [8,50; 14,00] | 12,50 [9,50; 14,00] | 12,70 [8,50; 13,50] | н.д./ n.r. |
| | After 14 days | 6,50 [3,50; 9,50]* | 5,50 [4,50; 7,00]** | 7,50 [5,50; 10,00]** | <0,05# <0,001## <0,0001### |
| | After 3 months | 3,80 [2,50; 4,00]*** | 4,50 [3,00; 4,70]** | 8,00 [5,50; 8,50] | <0,05# <0,01## <0,0001### |
| Swelling | Before treatment | 6,00 [4,00; 6,00] | 6,00 [4,50; 8,00] | 6,00 [4,00; 6,00] | н.д./ n.r. |
| | After 14 days | 4,50 [4,00; 5,00] | 4,00 [2,00; 5,00]** | 5,00 [3,00; 5,00] | н.д./ n.r. |
| | After 3 months | 2,50 [2,00; 3,50]** | 3,50 [2,00; 4,00]** | 5,00 [3,05; 5,50] | <0,05## <0,01### |
| Physical function | Before treatment | 47,20 [45,00; 48,00] | 48,00 [42,00; 50,00] | 48,00 [42,00; 50,00] | н.д./ n.r. |
| | After 14 days | 34,00 [30,00; 37,00] | 30,00 [19,00; 33,50]** | 38,00 [33,50; 43,50] | <0,05## |
| | After 3 months | 23,50 [18,50; 28,00]*** | 27,00 [18,50; 34,00]** | 38,50 [33,00; 42,00] | <0,05# <0,001## <0,0001### |
| Final score | Before treatment | 64,50 [57,50; 71,50] | 63,00 [53,00; 69,50] | 64,50 [57,50; 71,00] | н.д./ n.r. |
| | After 14 days | 45,00 [34,00; 53,50] | 37,50 [24,50; 46,50]** | 52,50 [45,00; 59,50] | <0,001## |
| | After 3 months | 29,00 [26,50; 35,00]*** | 34,00 [24,50; 37,50]** | 53,00 [46,50; 59,50] | <0,01# <0,001## <0,0001### |

**Note.** n.r. — not reliable; reliability in relation to the initial data (before treatment): ** — p <0,01, *** — p <0,001; # — comparison of patients of 1st and 2nd groups, ## — comparison of patients of 2nd and 3rd groups, ### — comparison of patients of 1st and 3rd groups

*Table 2. Dynamics of the main parameters of the APS and POL products before and after rehabilitation therapy*

| Group | The period of therapy | CD, nmol/ml | MDA, mcmol/l | CAT, mcmol $H_2O_2 r^{-1}c^{-1}$ | SOD, U/ml |
|---|---|---|---|---|---|
| 1st group (n=40) | Before treatment | 1,30 [0,80; 1,40] | 5,60 [4,50; 8,80] | 48,80 [34,20; 60,80] | 98,10 [57,50; 126,90] |
| | After 14 days | 1,20 [0,90; 1,50] | 5,40 [4,10; 8,30] | 52,30 [33,90; 59,10] | 104,00 [78,90; 144,90] |
| | After 3 months | 0,70 [0,30; 0,90]** | 3,60 [2,80; 8,20]** | 66,50 [60,80; 71,70]**/II | 149,60 [126,10; 237,02]**/II |
| 2nd group (n=40) | Before treatment | 1,20 [0,75;1,40] | 5,60 [4,10; 6,10] | 49,50 [31,70; 56,90] | 98,90 [77,60;139,70] |
| | After 14 days | 0,90 [0,80; 1,40]* | 4,70 [3,50; 9,70] * | 58,30 [33,90; 59,10] ** | 123,60 [83,40; 112,20]** |
| | After 3 months | 0,80 [0,70; 1,20]* | 4,40 [3,30; 9,10] * | 61,20 [44,50; 63,40] ** | 126,00 [78,90; 144,90]** |
| 3rd group (n=40) | Before treatment | 1,20 [0,70; 1,50] | 5,50 [3,80; 7,00] | 47,80 [39,30; 57,80] | 97,70 [49,20; 84,90] |
| | After 14 days | 1,00 [0,60; 1,10] | 4,70 [3,01;7,60] * | 53,70 [36,40; 82,80] | 110,60 [126,10; 237,02]* |
| | After 3 months | 1,10 [0,80; 1,40] | 5,00 [3,30; 9,10] | 52,20 [33,90; 59,10] | 105,30 [83,40; 112,20] |

**Note.** Reliability in relation to the initial data (before treatment): * — p <0.05, ** — p <0.01; reliability in relation to data obtained 14 days after treatment: II — p <0.01

*Table 4. Correlation coefficients between the clinical and functional indicators of the WOMAC scale and laboratory parameters after 3 months of treatment*

| WOMAC | CD, nmol/ml | MDA, mcmol/l | CAT, mcmol $H_2O_2 r^{-1} c^{-1}$ | SOD, U/ml |
|---|---|---|---|---|
| **Tenderness** | 0,38* | 0,53* | 0,38 | 0,54** |
| **Swelling** | 0,22 | 0,27 | 0,34 | 0,41* |
| **Physical function** | 0,41* | 0,57** | 0,44* | 0,62** |
| **Final score** | 0,42* | 0,59** | 0,42* | 0,58** |

**Note.** * — p <0,05; ** — p <0,01; **** — p <0,0001

improvement in stiffness ($p < 0.01$) and limited physical activity ($p < 0.001$). Moreover, only group 1 demonstrated significant reduction in the mentioned WOMAC values, obtained three months later, vs. results for the first 14 days ($p < 0.01$), evidencing the more significant efficiency of periarticular ozone therapy in combination with rehabilitation exercises, if compared to rehabilitation exercises alone or combined with physical therapy.

Assessment of laboratory results showed lower CRP and RF values after the rehabilitation therapy; however, there were no statistically significant difference between groups ($p = 0.08$).

On day 14 of rehabilitation therapy, patients with gonarthrosis after KJ TEP demonstrated lower concentrations of LPO products (DC and MDA) in all three groups vs. baseline; however, 25 % reduction in DC levels was recorded only in group 2 after rehabilitation exercises in combination with physical therapy ($p < 0.05$). MDA levels reduced by 4 % ($p > 0.05$) after periarticular ozone therapy, whereas a set of rehabilitation exercises, either alone or with physical therapy, resulted in significant reduction in its concentration by 14 % ($p < 0.05$) and 16 % ($p < 0.05$), respectively. After three months of therapy, significant reduction in DC and MDA levels in group 1 by 41 % ($p < 0.01$) and by 43 % ($p < 0.01$) was observed vs. baseline, respectively; and in group 2 — by 34 % ($p < 0.05$) and 20 % ($p < 0.05$). Group 3 patients did not demonstrate significant reduction in these values at the mentioned time points.

It has been shown that the use of a set of rehabilitation exercises combined with magnet therapy results in significantly higher activity of APS enzymes within the shortest period of time (14 days): plasma CAT activity increased by 15 % ($p < 0.01$), SOD levels rose by 25 % ($p < 0.01$) vs. baseline. Patients in this group had persistently higher APS activity three months later; however, there was no significant difference vs. data for the first 14 days of rehabilitation therapy. At three months, marked increase in CAT and SOD activity was observed in group 1 vs. baseline ($p < 0.01$) and first two weeks of rehabilitation ($p < 0.01$). After three months of rehabilitation exercises, patients in group 3 demonstrated minor reduction in enzyme activity of the antioxidant system ($p > 0.05$) vs. first 14 days.

The comparison of clinical functional and laboratory data was followed by a correlation analysis in order to assess the correlations between qualitative parameters of the status of gonarthrosis patients before and after rehabilitation therapy. It has been shown that with ageing, patients have lower blood SOD ($r = –0.45$, $p < 0.05$), whereas there were no age-related effects for CAT activity ($r = –0.16$, $p > 0.05$). There was positive correlation between MDA and increased BMI ($r = 0.32$; $p < 0.05$), irrespective of the rehabilitation method. Then we analysed the correlation between clinical functional parameters of WOMAC and post-therapy LPO and APS status.

Fourteen days after rehabilitation therapy initiation, patients in group 2 demonstrated that lower WOMAC pain levels and limited physical activity were associated with plasma MDA concentrations ($r = 0.32$, $p < 0.05$ and $r = 0.32$, $p < 0.05$, respectively) and elevated SOD activity ($r = –0.32$, $p < 0.05$ and $r = –0.32$, $p < 0.05$, respectively).

Long-term data (three months after rehabilitation initiation) for group 1 patients, who had a cycle of periarticular ozone therapy, showed that low WOMAC values were associated with lower LPO process intensity (MDA and DC levels) and antioxidant system activation (SOD and CAT activity) (see Table 3).

## Discussion

KJ TEP is a method to get rid of pain and improve physical functioning; it is most efficient at the later stages of OA. However, the positive result of surgery in a majority of patients can be completely negated without active rehabilitation measures in the post-surgery period [1], which correlates with the findings in this study. All patients referred to rehabilitation therapy were complaining of pain, morning stiffness for approx. 30 minutes and limited mobility in the operated KJ.

Given the above, adequate rehabilitation remains an important aspect of the management of post-endoprosthetic patients. Currently, there are numerous approaches to physical therapy of patients undergoing KJ TEP [7], aiming to strengthen muscles, reduce swelling, increase mobility of the affected limb, and normalise walking. Patients in this study (n = 40) were indicated a set of physical therapy (magnet therapy and electrophoresis of KJ region) for 10 days combined with a set of rehabilitation exercises. A combination of magnet therapy and electrophoresis is known to affect free-radical mechanisms, thus considerably reducing the intensity of LPO processes due to APS activation [7]. The findings in this study confirmed it: the short-term therapy (14 days) resulted in significant reduction in DC levels by 25 % ($p < 0.05$) and MDA levels by 16 % ($p < 0.05$); as well as marked increase in plasma CAT activity by 15 % ($p < 0.01$) and CAD activity by 25 % ($p < 0.01$) vs. baseline. An assessment of the clinical functional status of group 2 patients showed a significant reduction in WOMAC parameters (pain, stiffness, limited physical activity) in 14 days ($p < 0.001$); the positive result lasted for three months after therapy initiation ($p < 0.001$).

Over the past decade, ozone/oxygen mix injections to the joint projection to treat OA have been gaining popularity. Positive effects of periarticular ozone therapy in OA patients have already been demonstrated in numerous clinical trials and is associated with a sharp, short-term rise in free radicals in the injection site, triggering a cascade of consecutive reactions to induce expression of genes, which encode APS enzymes [2-3]. As compared to groups 2 and 3, patients in group 1 showed the best long-term result measured using the WOMAC scale (significant reduction of pain and stiffness, improved physical activity), and changes in the main parameters of APS, evidencing more pronounced efficiency of periarticular ozone therapy combined with rehabilitation exercises, vs. rehabilitation exercises alone or in combination with physical therapy.

Therefore, ozone-oxygen injections in periarticular tissue are based on marked anti-inflammatory and analgetic effect due to pronounced antioxidant action. Although ozone-oxygen injections do not provide fast positive effects vs. traditional physical therapy, the use of ozone therapy provides for long-lasting, long-term positive effects in patients with gonarthrosis after KJ TEP.

However, this study was limited to a period of three months, which can have affected the study results. Besides, there is no information on OA phenotyping (age-related, metabolic, post-traumatic, biomechanical, mixed) [8] and comorbidities, which might have an impact on clinical functional parameters of efficiency of the rehabilitation therapy and intensity of free radical oxidation processes, antioxidant protection activity, and might limit our conclusions.

## Conclusion

Periarticular ozone therapy provides for a more long-lasting positive result vs. traditional rehabilitation methods: pain relief, improvement in stiffness and physical activity, as seen on the WOMAC scale, by significantly reducing the LPO processes due to APS activation. Thus, correction of oxidative stress typical for degenerative dystrophic joint conditions is an element of the pathogenetic justification of the use of this therapy in the comprehensive rehabilitation of patients with gonarthrosis after KJ TEP.

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**Author Contribution:**

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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# МОЛЕКУЛЫ АДГЕЗИИ В ОЦЕНКЕ ГОДОВОГО ПРОГНОЗА У МОЛОДЫХ БОЛЬНЫХ, ПЕРЕНЕСШИХ ОСТРЫЙ КОРОНАРНЫЙ СИНДРОМ

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# Adhesion Molecules in Assessment of Annual Prognosis in Young Patients with Acute Coronary Syndrome

**Резюме**

**Цель.** Изучение места и роли адгезивных молекул (E-, L-, P-селектинов, молекул межклеточной и сосудистой адгезии 1 типа — ICAM-1, VCAM-1) в развитии неблагоприятного годичного прогноза у молодых пациентов с острым коронарным синдромом (ОКС). **Материал и методы.** В проспективное наблюдение продолжительностью 12 месяцев были включены 95 пациентов (90 мужчин, 5 женщин, средний возраст 41,00 [39,00-43,00] год) с ОКС, перенесших чрескожное коронарное вмешательство (ЧКВ). Оценивали конечные точки (первичная — смерть от сердечно-сосудистой патологии, вторичные комбинированные — нефатальные острый инфаркт миокарда и острое нарушение мозгового кровообращения, экстренные госпитализации ввиду сердечно-сосудистых причин — нестабильная стенокардия, аритмии, сердечная недостаточность). Методом иммуноферментного анализа в 1-е (до ЧКВ) и на 7-е сутки госпитализации (после ЧКВ) определяли концентрации в крови E-, L-, P-селектинов, молекулы межклеточной адгезии 1 типа (ICAM-1), сосудистой молекулы адгезии 1 типа (VCAM-1). **Результаты.** В течение 12 месяцев 22 (23,16 %) пациента имели оцениваемые конечные точки: смерть — у 2 (2,1 %) пациентов, нефатальный инфаркт миокарда — у 6 (6,32 %), госпитализация в связи с нестабильной стенокардией — у 14 (14,73 %). У пациентов с ОКС с неблагоприятным годовым прогнозом количество лейкоцитов, уровни P-селектина и ICAM-1 в 1-е сутки (до ЧКВ), L- и P-селектинов на 7-е сутки после ЧКВ были существенно выше, чем у пациентов с благоприятным годовым периодом. По данным многофакторного анализа, предикторами неблагоприятного годового прогноза у молодых пациентов с ОКС являлись уровни лейкоцитов (p=0,020) и ICAM-1 (p=0,010) в 1-е сутки (до ЧКВ); L-селектина — на 7-е сутки после ЧКВ (p=0,040). **Заключение.** У молодых пациентов с ОКС наиболее значимыми факторами, определяющими неблагоприятное течение острых форм ишемической болезни сердца в течение первых 12 месяцев, являются уровни лейкоцитов крови и ICAM-1 в 1-е сутки (до ЧКВ), L-селектина — на 7-е сутки после чрескожного коронарного вмешательства.

***Ключевые слова:*** *острый коронарный синдром, молодой возраст, молекулы адгезии, прогноз*

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### Abstract

**Aim.** To study the place and role of adhesive molecules (E-, L-, P-selectins, intercellular and vascular adhesion molecules of type 1 — ICAM-1, VCAM-1) in development of unfavorable one-year prognosis in young patients with acute coronary syndrome (ACS). **Material and methods.** A 12-month prospective follow-up included 95 patients (90 men, 5 women, mean age 41.00 [39.00-43.00] years) with ACS who underwent percutaneous coronary intervention (PCI). The endpoints were evaluated (primary — cardiovascular death, and combined secondary — nonfatal acute myocardial infarction and acute cerebrovascular accident, emergency hospitalization due to cardiovascular causes — unstable angina, arrhythmias, heart failure). Blood concentrations of E-, L-, P-selectins, ICAM-1, VCAM-1 were determined by enzyme immunoassay on the 1st (before PCI) and on the 7th day of hospitalization (after PCI). **Results.** During 12 months, 22 (23.16 %) patients had estimated endpoints: death in 2 (2.1 %) patients, nonfatal myocardial infarction in 6 (6.32 %), hospitalization due to unstable angina in 14 (14.73 %). In ACS patients with unfavorable annual prognosis, the levels of leukocytes, P-selectin and ICAM-1 on day 1 (before PCI), L- and P-selectins on day 7 (after PCI) were significantly higher than in patients with favorable annual period. According to multivariate analysis, predictors of unfavorable annual prognosis in young ACS patients were the levels of leukocytes (p=0.020) and ICAM-1 (p=0.010) on day 1 (before PCI) and L-selectin on day 7 after PCI (p=0.040). **Conclusion.** During the first 12 months in young ACS patients the most significant factors of unfavorable prognosis are the levels of blood leukocytes and ICAM-1 on day 1 (before PCI), and L-selectin on the 7th day after percutaneous coronary intervention.

***Key words:*** *acute coronary syndrome, young age, adhesion molecules, prognosis*

### Conflict of interests

Co-author of the article Yagoda A.V. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Yagoda A.V. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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CI — confidence interval, ACS — acute coronary syndrome, OR — odds ratio, PCI — percutaneous coronary intervention, ICAM-1 — intercellular adhesion molecule, type 1, ROC — receiver operating characteristic, VCAM-1 — vascular cell adhesion molecule, type 1

## Introduction

Wide use of advanced interventional therapies, efficient drugs and developed mapping of patients with acute coronary syndrome resulted in significant reduction in the rate of cardiovascular complications during the hospital period [1]. At the same time, patients surviving acute coronary syndrome are still at risk of cardiovascular events, especially during the first year after the index event [1, 2]. In this context, of interest is the so-called residual risk of cardiovascular complications, which is interpreted also based on parameters of non-specific inflammation [1, 3].

An inflammatory reaction in acute coronary syndrome patients presents with elevated levels of white blood cells, fibrinogen, C-reactive protein, cytokines, adhesion molecules and a number of other pro-inflammatory factors [4]. It is assumed that the inflammation intensity during the first day of acute coronary syndrome (ACS) is the determinant of the post-hospital clinical outcome [5]. At the same time, the study of prognostic capabilities using adhesion molecules, i.e. factors, which are induced as a response to inflammation, provided quite controversial results. For example, it has been established that higher circulating levels of intercellular adhesion molecule, type 1 (ICAM-1), vascular cell adhesion molecule, type 1 (VCAM-1), and P-selectin correlate with unfavourable clinical events within 12 months after the acute coronary process [5, 6, 7]. Other studies demonstrated opposite findings: lack of any association between high ICAM-1, E- and P-selectin levels with a risk of recurrent cardiovascular events [8, 9]. It can be assumed that these differences in study results are caused by abundance of mechanisms of ACS development, obstructive and non-obstructive coronary artery atherosclerosis or presence of intact coronary arteries, as well as differences in patient age, comorbidities, i.e. factors, which greatly affect biomarker concentration.

It is worth mentioning that patients, whose ischaemic heart disease manifested in the young age, differ from older age groups in the structure of the risk factors, clinical presentation and prognosis [10]. At the same time, cases of obstructive atherosclerotic damage to coronary arteries in young people are not uncommon [11]. The prognostic value of adhesion molecules, which play a significant role also in atherosclerotic damage through cell-cell interaction mediation between endothelium, monocytes, smooth muscle cells, platelets, in young patients remains unclear and is of tremendous clinical interest.

Therefore, it is advisable to measure the concentration of adhesion molecules in addition to routine inflammation markers — WBC, C-reactive protein, fibrinogen — in young patients with ACS in order to predict the risk of poor outcome, based on a one-year follow-up; one year is a period, when the majority of cardiovascular recurrences occur. A study of adhesion molecules in combination with other inflammation markers can provide a more accurate patient stratification depending on the risk of poor prognosis, which can have not only medical, but also socioeconomic significance.

**The objective** of this study was to study the place and value of adhesion molecules (E-, L-, P-selectins, ICAM-1, VCAM-1) in the development of poor year-long prognosis in young patients with acute coronary syndrome.

## Materials and methods

The study included 100 patients (93 men, 7 women, mean age: 41.00 [39.00–43.00] years), hospitalised with ACS. Inclusion criteria: signed informed consent form; acute coronary syndrome within 24 hours before hospitalisation, which is caused by atherosclerotic events (type 1 myocardial infarction, unstable angina, classes IB and IIIB under the classification by E. Braunwald); male and female subjects aged 25 to 44 years old. Exclusion criteria: type 2–5 acute myocardial infarction; unstable angina, classes A and C, and unstable angina, class IIB under the classification by E. Braunwald; patients after cardiopulmonary resuscitation or electrical cardioversion on disease onset; acute and chronic inflammatory conditions (period exacerbation); clinically significant comorbidity (with hepatic, renal, cardiac, and respiratory insufficiency); autoimmune diseases and cancer. Withdrawal criteria: refusal to participate at any time during the study. The study protocol was approved by the Local Ethics Committee at the Stavropol State Medical University.

***Table 1.*** *Initial characteristics of young patients with acute coronary syndrome*

| Indicator | Patients n (%) |
|---|---|
| Men | 93 (93 %) |
| Women | 7 (7 %) |
| Acute coronary syndrome with ST segment elevation | 43 (43 %) |
| Acute coronary syndrome without ST segment elevation | 57 (57 %) |
| Myocardial infarction type 1 with ST segment elevation | 43 (43 %) |
| Myocardial infarction type 1 without ST segment elevation | 14 (14 %) |
| Unstable angina pectoris of class IIIB | 43 (43 %) |
| Anamnesis of angina pectoris | 45 (45 %) |
| Anamnesis of myocardial infarction,<br>including with PCI | 35 (35 %)<br>14 (14 %) |
| Burdened hereditary anamnesis | 59 (59 %) |
| Smoking | 71 (71 %) |
| Excess body weight | 41 (41 %) |
| Obesity | 39 (39 %) |
| Arterial hypertension | 22 (22 %) |

**Comments:** PCI — percutaneous coronary intervention.

Baseline patient characteristics are presented in Table 1.

Coronary angiography results show that single-vessel coronary disease is diagnosed in 50 (50 %) patients; two damaged coronary arteries — in 31 (31 %) patients, while three and more coronary arteries were damaged in 19 (19 %) patients. All patients underwent stent placement in their symptoms-dependent artery. Standard laboratory and instrumental tests were performed, including blood WBC, C-reactive protein and fibrinogen on day 1 (before and after PCI). All patients had optimal drug therapy (according to the current clinical guidelines): DAPT, statins, angiotensin-converting enzyme inhibitors/ angiotensin receptor antagonists, β-blockers.

On day 1 (before PCI) and day 7 of hospitalisation (after PCI), all patients underwent plasma measurements of L-, E-, P-selectin, serum ICAM-1, VCAM-1 levels using ELISA test kits (Cloud-Clone Corp., China).

Over the next 12 months after admission, the following endpoints were evaluated: primary (cardiovascular-related deaths) and secondary (non-fatal acute myocardial infarction and acute cerebrovascular accidents, emergency hospital admission for cardiovascular causes: unstable angina, arrhythmias, cardiac insufficiency), as well as compliance.

Statistical data analysis was performed using StatTech, v. 4.2.7 (Russia). Normality of distribution was

checked using и the Kolmogorov-Smirnov test. Quantitative variables were presented with the median value and interquartile range (Me [Q25; Q75]), or mean ± standard error of mean (M±m). Qualitative parameters are presented as absolute values and percent. Differences between groups were identified using non-parametric Mann-Whitney U test or Student t-test for normal data distribution. A multivariate analysis was performed using the multivariate logistic regression analysis. ROC-analysis was used to evaluate the accuracy of the regression model and individual biomarkers. The level threshold was set in the cut-off point using the highest Youden's index. Odds ratios (OR) with 95 % confidence interval (CI) were calculated. Differences were statistically significant at $p < 0.05$.

## Results

The information on the prognosis one year after the index ACS was obtained from 95 (95 %) patients. Twenty-two (23.16 %) patients experienced adverse events (endpoints), which were recorded only during the post-hospital period. Over the follow-up period, two 2 (2.1 %) patients dies; six (6.32 %) developed non-fatal myocardial infarction, and 14 (14.73 %) were hospitalised for unstable angina. There were no cases of acute cerebrovascular accidents and/or arrhythmia requiring hospitalisation, cardiac insufficiency among the endpoints of the study.

Given a small amount of events in each endpoint, it was decided to introduce a combined endpoint, which would increase the statistical power of prognosis;

***Table 2.*** *Some markers of inflammation in blood of patients depending on annual prognosis*

| Indicator | Pick-up time | Unfavorable prognosis | | p |
|---|---|---|---|---|
| | | Yes (n=22) | No (n=73) | |
| White blood cells, $\times 10^9$/l | 1 day (before PCI) | 12,26 ±3,67 | 10,32 ±3,33 | **0,021** |
| | 1 day (after PCI) | 9,55 [8,79; 10,46] | 8,29 [6,90; 9,80] | 0,071 |
| C-reactive protein, mg/l | 1 day (before PCI) | 4,50 [3,12; 5,92] | 5,60 [3,50; 11,58] | 0,161 |
| | 1 day (after PCI) | 6,30 [3,53; 5,57] | 4,50 [3,75; 5,20] | 0,292 |
| Fibrinogen, g/l | 1 day (before PCI) | 4,04 [3,40; 9,11] | 3,64 [3,18; 4,90] | 0,562 |
| | 1 day (after PCI) | 4,46 [3,71; 5,57] | 4,50 [3,75; 5,20] | 0,941 |
| L-selectin, ng/ml | 1 day (before PCI) | 249,50 [122,00; 504,00] | 257,00 [112,00; 404,00] | 0,411 |
| | 7 day (after PCI) | 556,00 [314,00; 891,25] | 230,00 [104,00; 554,00] | **0,010** |
| P- selectin, ng/ml | 1 day (before PCI) | 406,00 [261,50; 703,62] | 250,70 [136,70; 411,30] | **0,010** |
| | 7 day (after PCI) | 545,25 [285,75; 691,25] | 206,20 [166,50; 311,70] | **0,010** |
| E- selectin, ng/ml | 1 day (before PCI) | 31,30 [19,47; 38,68] | 29,10 [21,50; 43,50] | 0,952 |
| | 7 day (after PCI) | 39,00 ±18,65 | 31,27 ±15,45 | 0,058 |
| ICAM-1, ng/ml | 1 day (before PCI) | 1664,20 [962,30; 2341,30] | 864,00 [698,80; 1358,40] | **0,010** |
| | 7 day (after PCI) | 1426,20 [905,88; 1868,20] | 1049,50 [817,20; 1358,40] | 0,177 |
| VCAM-1, ng/ml | 1 day (before PCI) | 530,00 [420,00; 595,52] | 468,00 [395,00; 550,00] | 0,215 |
| | 7 day (after PCI) | 1192,55±326,92 | 1136,93±437,10 | 0,581 |

**Comments:** PCI — percutaneous coronary intervention, ICAM-1 — intercellular adhesion molecule 1, VCAM-1 — vascular cellular adhesion molecule 1. Data with normal distribution is presented as M±m, Me [Q25; Q75]

*Table 3. Results of multivariate analysis by logistic regression*

| Indicator | Regression coefficient (B) | Exponent B | 95 % CI | p |
|---|---|---|---|---|
| White blood cells on day 1 (before PCI) | 0,205 | 1,228 | 1,036-1,455 | **0,020** |
| ICAM-1 on day 1 (before PCI) | 0,001 | 1,001 | 1,001-1,002 | **0,010** |
| L-selectin on day 7 (after PCI) | 0,002 | 1,002 | 1,001-1,003 | **0,040** |
| Constant | -5,888 | - | - | - |

**Comments:** CI — confidence interval, PCI — percutaneous coronary intervention, ICAM-1 — intercellular adhesion molecule 1.

this combined endpoint included death, acute myocardial infarction, and unstable angina. Depending on the outcome over the one-year follow-up period, patients were divided into two groups: group 1 (n = 22) — with poor one-year prognosis, and group 2 (n = 73) — with favourable one-year period.

Of note, there were no significant differences in traditional cardiovascular risk factors, past medical history, clinical variant of index ACS, severity of coronary damage, and compliance ($p > 0.05$).

Comparison of inflammation parameters in the study groups demonstrated statistically significant differences in WBC, P-selectin and ICAM-1 levels on day 1, L- and P-selection on day 7 of the disease (Table 2). C-reactive protein, fibrinogen, E-selectin, and VCAM-1 during the acute stage of the disease did not have any impact on recurrent cardiovascular events.

The identified statistically significant parameters observed in patients with poor one-year outcome were included into a multifactorial analysis. Logistic regression demonstrated an independent contribution to one-year poor prognosis from three out of five factors: WBC and ICAM-1 measured on day 1, and L-selectin, measured on day 7. P-selectin levels, both on day 1 (before PCI) and day 7 after PCI, did not have independent effects on poor one-year prognosis. Characteristics of each factor included into the model are presented in Table 3. Based on regression coefficients, WBC and ICAM-1 measured on day 1, and L-selectin, measured on day 7, had direct correlation with the probability of poor one-year prognosis.

At the next stage of the study, a model was generated which combined all independent prognostic factors:

$$P = \frac{1}{1 + 2.72^{-(-5.888 + 0.205X1 + 0.001X2 + 0.002X3)}},$$

Where P is the probability of identifying one-year poor prognosis; 2.72 is the base of the natural logarithm; –5.888 is the mathematical constant; 0.205, 0.001 and 0.002 are respective coefficients; $X_1$ is blood WBC before PCI ($10^9$/L); $X_2$ is pre-PCI ICAM-1 level (ng/mL); $X_3$ is L-selectin concentration on day 7 after PCI (ng/mL). The resulting regression model is statistically significant ($p < 0.001$).

We have conducted ROC analysis, which allowed us to find the limit of log function P. The resulting curve is presented in Figure 1. The area under ROC curve is 0.76±0.05 (95 % CI 0.65–0.86), indicating good quality of the model.

The cut-off limit threshold, which corresponded to the highest Youden's index, was 0.35, with sensitivity and specificity of 77.3 % and 72.6 %, respectively. Therefore, if the calculated P vale falls within the range from 0.35 to 1, then the poor one-year prognosis is highly likely. If P value is 0 to 0.35, then the probability of the poor one-year prognosis is low.

ROC analysis was used to identify the diagnostic accuracy of some biomarkers — WBC, ICAM-1 levels on day 1 (before PCI) and L-selectin concentration on day 7 after PCI (Fig. 2). For WBC, the identified limit of $10.6x10^9$/L possessed satisfactory sensitivity (77.3 %), but insufficient specificity (57.5 %). For ICAM-1 and L-selectin, the limits associated with prognosis were 1,240.0 ng/mL (sensitivity 63.6 %, specificity 79.5 %)

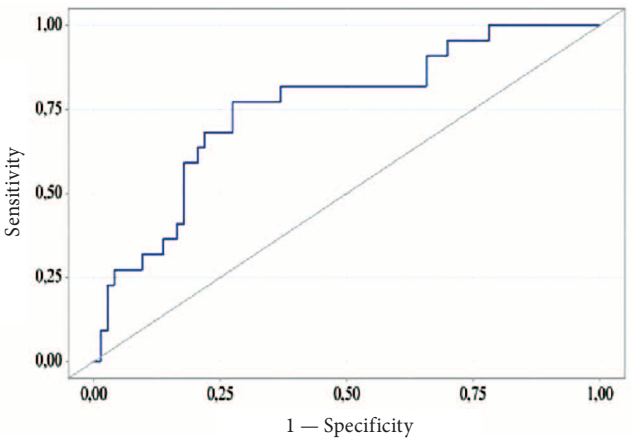


***Figure 1.*** *ROC curve for model of predicting an unfavorable annual outcome in young patients with acute coronary syndrome*

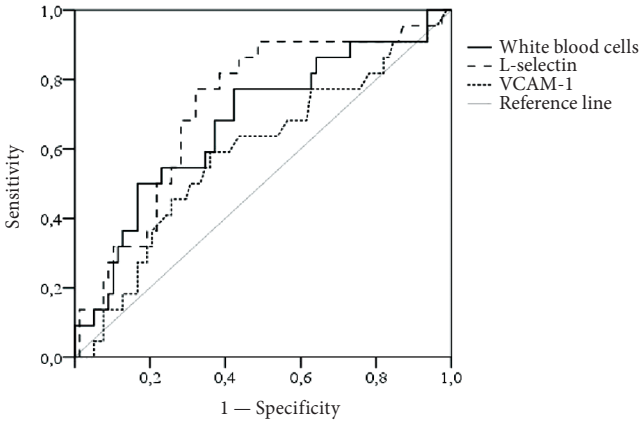


***Figure 2.*** *ROC curves of diagnostic accuracy of inflammatory markers*
**Comments:** VCAM-1 — vascular cellular adhesion molecule 1.

and 314.00 ng/mL (sensitivity 77.3 %, specificity 65.8 %), respectively. Thus, unlike WBS values, adhesion molecules are more specific in indicating chronic inflammatory condition typical for atherosclerosis.

It has been shown that, in young patients with ACS, pre-PCI WBC of over $10.6x10^9$/L is associated with c 4–5-fold increase in the risk of recurrent cardiovascular conditions during the next year (OR 4.64; 95 % CI 1.55–13.84), pre-PCI ICAM-1 of over 1,240.0 ng/mL — with 5–6-fold increase in the risk (OR 5.82; 95 % CI 2.08–16.25), and L-selecting of more than 314 ng/mL (on day 7 after PCI) — with 6–7-fold increase in the risk (OR 6.8; 95 % CI 2.23–20.48).

## Discussion

A high patient response rate (95 %) made it possible to conduct a correct analysis of factors affecting one-year prognosis. The absence of adverse cardiovascular events during hospitalisation is probably a result of the use of endovascular methods: revascularisation was performed in all patients included in the study. During the post-hospital period (one-year follow-up), the combined endpoint, including cardiovascular-related death, myocardial infarction and emergency hospitalisation with unstable angina, was recorded in 22 (23.16 %) patients, corresponding to the literature data (14.6–24.8 %) [1, 12, 13]. It is obvious that the residual risk of cardiovascular events during the first year after ACS remains high, and even advanced optimal therapies cannot compensate it.

Poor one-year prognosis in young patients with ACS was associated with high levels of WBC, P-selection and ICAM-1 on day 1, and L- and P-selectins on day 7. It is likely that higher concentrations of the mentioned adhesion molecules indicate the intensity and persistence of inflammation, causing more marked endothelial dysfunction and resulting atherosclerotic process destabilisation with elevated blood-clotting.

Absence in this study of prognostic significance of other inflammation markers, particularly of C-reactive protein, fibrinogen, E-selectin, VCAM-1 may be a result of their measurement timing. It is reported that C-reactive protein, used as a marker of poor prognosis, should be measured later, before discharge or a month after the index event [14].

The multivariate analysis demonstrated that independent predictors of poor one-year prognosis in young post-ACS patients are WBC and ICAM-1 levels on day 1 (before PCI), L-selectin — on post-PCI day 7. According to earlier information, WBC count was associated not only with larger myocardial infarction area and complications, but also with reduced therapy efficacy and patient survival rates during three to six months after infarction [4]. At the same time, it was demonstrated that in old patients with ACS, elevated blood WBC levels were not a risk factor for recurrent atherothrombotic events during one-year post-hospital follow-up [15]. Accordingly, it is worth noting that in old patients with ACS, low L-selectin levels have prognostic significance, indicating functional depletion of WBC [6]. In this study, young patients with ACS had high L-selectin levels on day 7 after coronary angioplasty as a marker of poor one-year prognosis. It is obvious that poor ACS prognosis in young patients is characterised with elevated WBC levels and their long-lasting activity, ensuring L-selectin generation. The prognostic potential of high ICAM-1 levels is probably independent of age: lower ICAM-1 levels found in this study on day 1 as an independent predictor of poor outcome in young patients with ACS was also a predictor of recurrent ACS in old patients, including after stent placement [13].

Measuring WBC, ICAM-1 on day 1 and L-selectin on day 7 makes it possible to clarify the risk of recurrent cardiovascular conditions and to minimise risk underestimation in young patients. Not also specific markers, but also timeline for their measurement, are crucial for patients with ACS.

These results can be used in clinical settings to improve classification of risks of poor one-year outcome in post-ACS young patients; it can be later used as novel targets in the therapy of acute IHD.

Study limitations A number of exclusion criteria used, particularly acute inflammatory conditions and recurrences of chronic conditions, clinically significant comorbidity (with hepatic, renal, cardiac, and respiratory

insufficiency), autoimmune diseases and cancer, could have independently contributed to the model of one-year prognosis in young patients with ACS. The resulting data can be extrapolated for young patients with ACS, provided it transforms to type 1 myocardial infarction and/or unstable angina, class IIIB (under the classification by E. Braunwald).

## Conclusions

Poor course of ischaemic heart disease during the first 12 months after the PCI with stent placement was reported in 22 (23 %) young patients with ACS. In patients with poor prognosis, WBC, P-selectin and ICAM-1 levels on day 1 (before PCI) and L- and P-selectin levels on day 7 after PCI were significantly higher than in patients with favourable one-year prognosis. The multivariate analysis demonstrated that predictors of poor one-year prognosis in young patients with ACS are WBC ($p = 0.020$) and ICAM-1 ($p = 0.010$) levels on day 1 (before PCI) and L-selectin concentration on day 7 after PCI ($p = 0.040$). Limit thresholds for WBC and ICAM-1 on day 1 (before PCI) and L-selectin on day 7 were established, which are associated with 4–7-fold increase in the risk of recurrent cardiovascular events. These data allow recommending inclusion of adhesion molecules to an additional examination of young patients with ACS, making it possible to identify the risk group of poor course of the disease during the first year after PCI with stent placement.

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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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# ХРОНИЧЕСКИЙ ГЕПАТИТ В У СПОРТСМЕНОВ ВЫСШИХ ДОСТИЖЕНИЙ

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# Chronic Hepatitis B In Elite Athletes

**Резюме**

Спортсмены, как и другие представители общей популяции, подвержены риску инфицирования вирусами гепатитов. **Цель исследования** — охарактеризовать клинико-вирусологическую картину хронического гепатита В (ХГВ) у спортсменов и оценить эффективность противовирусной терапии. **Материалы и методы.** В исследование были включены 42 спортсмена высших достижений с ХГВ. Проанализированы результаты клинико-лабораторных (включая вирусологические) показателей и данные инструментальных методов обследования. Эффективность противовирусной терапии оценивали по вирусологическому, серологическому, биохимическому ответам и уменьшению выраженности фиброза печени. **Результаты.** 35,7 % спортсменов периодически отмечали тяжесть в правом подреберье, 19 % — незначительную слабость. У двух третей (66,7 %) спортсменов были выявлены диффузные изменения печени, у 19,4 % — увеличение ее размеров и/или спленомегалия, у 29,0 % — умеренный или выраженный фиброз печени. Активность АЛТ была повышена у 31,0 %. ДНК вируса гепатита В была обнаружена в сыворотке крови у всех спортсменов, при этом в 73,8 % случаев ее уровень составлял ≥ 200 МЕ/мл. На фоне приема аналогов нуклеоз(т)идов была получена авиремия и нормализация активности аминотрансфераз во всех случаях (через 3,0 месяца и 4,5 месяца, соответственно), стабилизация или уменьшение выраженности фиброза печени у 90,9 % спортсменов (через 24,0 месяца). Возобновление виремии отмечено в 7/17 случаев из-за прекращения приема препарата. **Заключение.** Клиническая картина ХГВ у спортсменов отличается минимальной симптоматикой. После относительно короткого периода противовирусная терапия аналогами нуклеоз(т)идов показала высокую эффективность в достижении вирусологического и биохимического ответов, а также в уменьшении выраженности фиброза печени. Отмеченные случаи возобновления виремии связаны с прерыванием приема препаратов.

***Ключевые слова:*** *спортсмены, хронический гепатит В, противовирусная терапия, аналоги нуклеоз(т)идов, фиброз печени*

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## Abstract

Athletes, as well as other general population groups, are at risk of infection with hepatitis viruses. **The aim** of the study was to characterise the clinical and virological picture of chronic hepatitis B (CHB) in athletes and to evaluate the efficacy of antiviral therapy. **Materials and Methods.** Forty-two elite athletes with CHB were included in the study. The results of clinical and laboratory (including virological) parameters and data of instrumental methods of examination were analysed. The efficacy of antiviral therapy was evaluated by virological, serological, biochemical responses and reduction of liver fibrosis severity. **Results.** 35.7 % of athletes periodically reported heaviness in the right hypochondrium, and 19 % experienced mild weakness. Diffuse changes in the liver were detected in two-thirds (66.7 %) of the athletes. Additionally, 19.4 % exhibited liver enlargement and/or splenomegaly, while 29.0 % showed moderate or significant liver fibrosis. Elevated ALT activity was observed in 31.0 % of the athletes. Hepatitis B virus DNA was found in the blood serum of all athletes, with 73.8 % of cases showing a viral load of ≥200 IU/mL. During treatment with nucleos(t)ide analogs, aviremia and normalization of aminotransferase activity were achieved in all cases within 3.0 and 4.5 months, respectively. Stabilization or reduction in the severity of liver fibrosis was observed in 90.9 % of athletes after 24.0 months. Viremia recurrence was noted in 7 out of 17 cases due to drug discontinuation. **Conclusion.** The clinical presentation of CHB in athletes is characterized by minimal symptoms. After a relatively short period, antiviral therapy with nucleos(t)ide analogs demonstrated high efficacy in achieving virological and biochemical responses, as well as in reducing the severity of liver fibrosis. Cases of viremia recurrence were associated with discontinuation of the medications.

***Key words:*** *athletes, chronic hepatitis B, antiviral therapy, nucleos(t)ide analogs, hepatic fibrosis.*

### Conflict of interests

Co-author of the article Ilchenko L.Yu. is the editor-in-chief of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. The decision to publish the article was made by the editorial board without the participation of the editor-in-chief. The authors have not declared any other conflicts of interest

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### Conformity with the principles of ethics

The study was approved by the local ethics committee of the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation (protocol № 213 dated December 13, 2021).

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ALT — alanine aminotransferase, NA — nucleoside analogues, anti-HBc — hepatitis B core antibody, anti-HBe — hepatitis B e-antigen antibody, anti-HBs — hepatitis B surface antigen antibody, HVB — hepatitis B virus, DNA — deoxyribonucleic acid, AVT — antiviral therapy, peg-IFNα — pegylated interferon alpha, TDF — tenofovir disoproxil fumarate, TE — transient elastometry, HF — hepatic fibrosis, CHB — chronic hepatitis B, ETV — entecavir, HBe Ag — hepatitis B e-antigen, HBsAg — hepatitis B surface antigen.

## Introduction

High-level sports (top-class sports) are a part of sports, accounting for approximately 2 % of sportsmen and targeting high sport results during the official national and international sport competitions [1]. These competitions include world championships, Olympic and continental games, most prestigious sport leagues. High-level sports are associated with constantly rising sport results as well as new records, sometimes even phenomenal ones. At the same time, sportsmen require complete mobilisation of emotional resources and all functional capabilities of their bodies. High sports achievements are based on methodological organisation of the training system, which comprises various stages of the training and competition process.

Viral hepatitis B is associated with high morbidity and mortality in the general population. According to the World Health Organisation, in 2019, 296 million people had chronic hepatitis B (CHB) globally, and over 800,000 people die of complications, such as hepatic cirrhosis and hepatocellular carcinoma [2]. In the Russian Federation, the number of hepatitis B virus (HBV) carriers and patients with CHB is about 3 million people [3, 4].

Given the global incidence of viral hepatitis B, sportsmen are also at risk of catching this disease. In a majority of cases, HBV is transmitted during activities not related to sports, e.g. unprotected sex, drug injections, including anabolic steroids and psychoactive drugs, shared use of personal belongings, body tattoos and piercing [5].

Nonetheless, there is a risk of transmitting the virus during some types of sports. Contact sports are believed to bear the highest risk of HBV transmission [6-8]. Besides, the risk for a sportsman to catch HBV depends on the country of their origin, especially for sportsmen living in endemic regions.

The actual incidence of CHB among professional sportsmen is unknown due to the minimal amount of data in scientific literature. In a recent Russian study, HBsAg (hepatitis B surface antigen) was found in two out of 384 blood samples drawn from professional sportsmen [5]. Results of a study conducted in Tehran demonstrated that the rate of HBsAg in fighters was 1.2 %, volleyball and football players — 0.5 % [9]. At the same time, it is worth mentioning that these studies reported a high detection rate of anti-HBc (hepatitis B core antibody) (7–13.9 %), which is a surrogate marker of latent HBV infection [5, 9].

Potential effects of CHB for the health and quality of life of an infected athlete can hardly be overestimated. Although hepatic complications can be uncommon among sportsmen, physical and mental disorders can be present at early stages of the disease, interfering with reaching high results [10].

Therefore, medical professionals attending to sportsmen should be aware of the risk of infection during sport activities and should be able to consult sportsmen in this matter, know measures to prevent hepatitis, and make decision on the therapy and access of the infected sportsman to training and competitions.

**The objective** of this study is to characterise the clinical presentation of CHB and to assess the efficacy of the antiviral therapies in professional athletes.

## Materials and methods

The retrospective prospective observational study included 42 professional sportsmen with CHB, who were followed up by the specialists of the Centre for Diagnostics and Therapy of Chronic Viral Hepatitis in 2011–2024. Sportsmen with markers of HIV infection, hepatitis C, hepatitis D were excluded from the study.

During the initial visit, all patients gave their consent for participation in the study, treatment and publication of anonymous results.

This study was approved by the Local Ethics Committee at N. I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation (Minutes No. 213 dated December 13, 2021).

Source documents were used to analyse the clinical virological, biochemical and instrumental data. Sportsmen also had their blood drawn and HBV phenotype identified.

The efficacy of antiviral therapy was evaluated on the basis of virological (HBVdeoxyribonucleic acid (DNA) < 50 IU/mL), serological (HBsAg clearance/seroconversion, HBeAg clearance/seroconversion (HBV e-antigen) in HBeAg-positive patients), biochemical (normalised activity of alanine aminotransferase (ALT)) response and reduced hepatic fibrosis (HF) activity.

Both standard laboratory and instrumental test methods were used. Serological markers of HBV (HBsAg, anti-HBs (hepatitis B surface antigen antibody), HBeAg, anti-HBe (hepatitis B e-antigen antibody)) were measured by ELISA. HBV DNA in blood was detected using polymerase chain reaction. HBV genotype was identified using a phylogenetic analysis of available nucleotide sequences or ELISA test for HBsAg subtypes in cases when no HBV DNA could be found. Aixplorer SuperSonic Imagine device (France) was used for abdominal ultrasound. HF was evaluated during transient elastometry (TE) at Fibroscan® (502 Touch Echosens, France). METAVIR classification was used to identify the stage of fibrosis (stage F0-1 — 7.2 kPa and less; F2 — 7.3 to 9.5 kPa; F3 — 9.6 to 12.5 kPa; F4 — 12.6 kPa and above) [11].

Statistical processing was performed using SPSS software (version 26.0; SPSS Inc., USA). Numerical clinical data were compared with the help of Mann — Whitney test (independent groups). Wilcoxon test was used to analyse the changes in numerical data during therapy. Parameter correlation was assessed using Spearman's correlation coefficient (r). Serum HBV and HBsAg levels were analysed after log transformation. A statistically significant value was $p < 0.05$.

## Results

### *Clinical virological pattern*

The study group included mostly male subjects (30/42; 71.4 %). The age of sportsmen varied from 15 to 45 years old (median age: 25.0 [20.0–33.0] years old). There were no statistically significant differences in the mean age between male and female subjects: 25.0 [20.0–31.0] and 25.5 [19.5–36.5] years old, respectively ($p = 0.596$).

31.0 % (13/42) of sportsmen were candidates for master of sports, 42.9 % (18/42) — masters of sports, 11.9 % (5/42) — international masters of sport. The mean sporting experience was 12.5 [7.4–21.1] years old.

Information on the first HBsAg detection was recorded during an extended medical examination; and the duration of antigen presence in blood was 6.0 [2.0–10.3] years. Sportsmen denied having a history of acute hepatitis and did not undergo hepatitis B vaccination.

Sportsmen were involved in various sports; over a half of them (52.4 %; 22/42) were contact sportsmen (Table 1).

Clinical presentations of CHB in sportsmen were minimal. Fifteen (35.7 %) sportsmen noted periodic feeling of weight in their right hypochondrium, while eight (19.0 %) mentioned mild weakness.

HBV genotype was identified in 69.0 % (29/42) of cases. Genotype D was prevailing (26; 89.7 %) as compared to genotypes A (2; 6.9 %) and C (1; 3.4 %).

During the initial visit, the majority of sportsmen (92.9 %; 39/42) were HBeAg negative. Elevated ALT values were recorded in 13/42 (31.0 %) of cases: up to three upper limits of normal (ULN) — in 11, 3–5 ULN — in 1 and over 10 ULN — in 1.

Serum HBV DNA was observed in all sportsmen, with the levels ≥ 200 IU/mL reported in 31 (73.8 %); the highest value was $10^8$ IU/mL. HBV DNA levels in contact and semicontact/non-contact sportsmen did

***Table 1.*** *Characteristics of athletes by sports affiliation*

| **Contact sports** | | **Semi-contact/ non-contact sports** | |
|---|---|---|---|
| Type of sport | n | Type of sport | n |
| Freestyle wrestling | 6 | Athletics | 6 |
| Judo | 6 | Ski racing | 2 |
| Taekwondo | 3 | Chess | 2 |
| Greco-Roman wrestling | 2 | Pentathlon | 1 |
| Boxing | 1 | Canoeing | 1 |
| Kickboxing | 1 | Powerlifting | 1 |
| Rugby | 1 | Bobsleigh | 1 |
| Sambo | 1 | Basketbal | 1 |
| Football | 1 | Badminton | 1 |
| | | Mountaineering | 1 |
| | | Rock climbing | 1 |
| | | Stand shooting | 1 |
| | | Shot put | 1 |
| **Total** | **22** | **Total** | **20** |

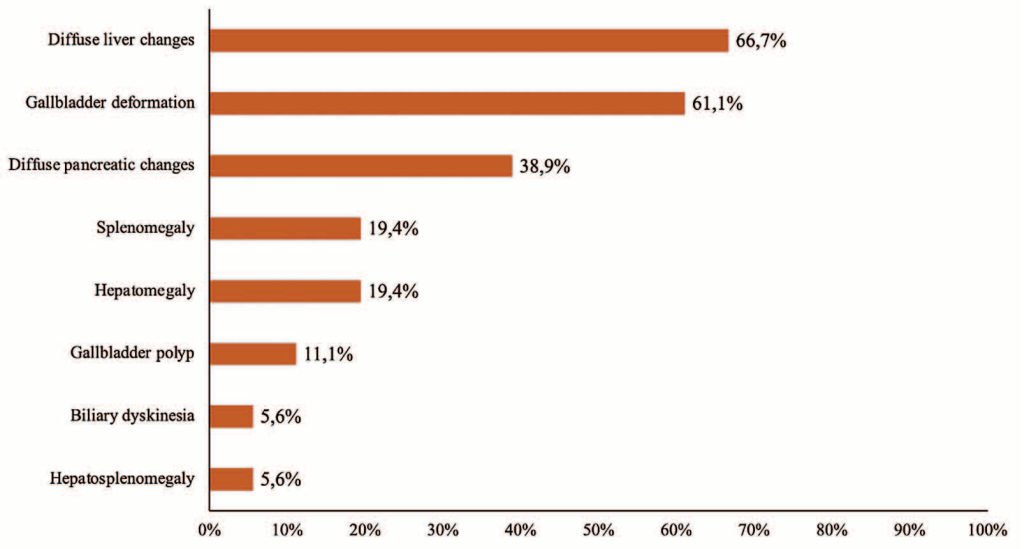


***Figure 1.*** *Echographic signs of abdominal organ pathology in athletes*

not differ (2.8 [2.0–3.6] $log_{10}$ IU/mL and 3.1 [2.5–3.7] $log_{10}$ IU/mL, respectively; p = 0.350).

Abdominal ultrasound in 36 sportsmen revealed abnormal signs in the majority of cases (85.1 %; 31/36) (Figure 1).

Two thirds (66.7 %; 24/36) of sportsmen had diffuse changes in their liver. Hepatomegaly or splenomegaly was reported in 19.4 % (7/36) of cases. Over one third of sportsmen (38.9 %; 14/36) has diffuse changes in their pancreas.

Gall bladder and bile passage abnormalities were reported in 63.8 % (23/36) of cases. Of these, deformed gall bladder was observed in 61.1 % (22/36), gallbladder polyps — in 11.1 % (4/36) and biliary dyskinesia — in 5.6 % (2/36) of cases.

Liver TE was performed in 30 sportsmen, and METAVIR stage F0-1 HF was diagnosed in 22 (71.0 %) cases, F2 — in 6 (19.3 %), and F3 — in 3 (9.7 %) cases.

There were no differences in fibrosis severity between male and female athletes (6.1 [5.3–7.6] kPa and 6.1 [4.0–7.2] kPa, respectively; p = 0.527).

Comparison of semicontact/non-contact sportsmen with contact sportsmen showed more severe HF in the latter group (4.6 [4.3–6.9] kPa and 6.4 [5.6–7.8] kPa, respectively; p = 0.039).

## *Antiviral therapy efficacy*

Eighteen sportsmen (10 male and eight female athletes) were treated with AVT. The baseline characterics of sportsmen are presented in Table 2.

The patients were treated with the following products: 9 — entecavir (ETV), 6 — tenofovir disoproxil fumarate (TDF), 1 — pegylated interferon alpha (peg-IFNα), 2 — peg-IFNα with subsequent replacement with nucleoside analogues (NA).

One out of three sportsmen treated with peg-IFNα demonstrated complete virological and biochemical response, and AVT was discontinued after 48 weeks. The other two sportsmen switched to ETV and TDF after 24 and 48 weeks of peg-IFNα therapy, respectively, because of persistent high viral load and elevated aminotransferases.

Thus, NA preparations were indicated in 17 sportsmen (ETV — 10, TDF — 7). The length of AVT with NAs was six to 118 months, mean value: 15.0 [10.0–32.0] months.

After NA therapy, all sportsmen demonstrated positive response (i.e. undetectable HBV DNA levels). The mean time from therapy initiation to this result was 3.0 [2.0–5.0] months and did not differ between sportsmen on ETV or TDF (2.5 [2.0–5.0] months and 3.0 [2.0–5.0] months, respectively, p = 0.582). The latest aviremia was recorded in one sportsman at nine months of TDF therapy.

It has been shown that the time to virologic response depends on the initial viral load: a higher HBV DNA levels were associated with a longer time to aviremia (r = 0.617; p = 0.014).

In one case, TDF therapy resulted in HBeAg seroconversion nine months after therapy initiation. No HBsAg clearance was observed; however, its level slightly dropped from 4.0 $log_{10}$ IU/mL to 3.8 $log_{10}$ IU/mL after 18.0 [12.0–40.0] months of therapy.

All sportsmen demonstrated normal ALT activity 4.5 [2.0–9.0] months after therapy initiation. There were no differences in the time to biochemical response with ETV or TDF therapy (5.0 [2.0–12.0] months and 4.0 [2.5–7.0] months, respectively, p = 0.748).

TE was used in 11 cases after 24.0 [12.0–30.0] months of AVT to assess changes in HF. The mean TE values reduced from 6.2 [5.5–10.5] kPa to 5.7 [4.3–7.1] kPa. The majority of sportsmen (10/11) demonstrated fibrosis stabilisation or reduction. Only one sportsman out of seven with baseline stage F0-1 developed HF stage F2.

***Таблица 2.*** *Характеристика спортсменов на старте ПВТ*
***Table 2.*** *Characterization of athletes at the start of antiviral therapy*

| Parameters | Athletes n=18 |
|---|---|
| Gender, n<br>Male<br>Female | <br>10<br>8 |
| Age, years | 25,0 [20,0-34,0] |
| Type of sport, n<br>Contact<br>Semi-contact/ non-contact | <br>9<br>9 |
| HBeAg-positive, n | 3 |
| HBV DNA, $log_{10}$ IU/mL | 3,3 [3,1-4,2] |
| ALT, IU/L<br>ALT>40 IU/L, n(%) | 50,5 [25,0-59,4]<br>10 (55,6) |
| AST, IU/L<br>AST>40 IU/L, n(%) | 37,5 [25,0-45,0]<br>7 (38,9) |
| HBsAg, $log_{10}$ ME/ml | 4,1 [3,8-4,6] |
| TE, kPa | 5,6 [4,3-7,8] |
| METAVIR stage of fibrosis, n<br>F0-1<br>F2<br>F3 | n=14<br>10<br>1<br>3 |

As for the sportsmen with baseline stage F3, there was one case of improvement to stage F2 and two cases of improvement to stage F1. Also, one sportsman with baseline stage F2 demonstrated improvement to stage F1.

Seven out of 17 sportsmen had HBV DNA on the average eight months after the therapy initiation.

The viral load varied from 150 IU/mL to 650 IU/mL, and no elevated ALT was observed. Viremia recurrence was associated with a short-term break in NA therapy during sport events (the duration of AVT suspension is unknown). Once AVT with previous drugs was resumed, aviremia was achieved on the average in 5.0 [3.0–6.0] months in all cases.

## Discussion

Like the rest of the population, sportsmen are susceptible to HBV infection; however, studies of the characteristics of the clinical virological pattern and efficacy of AVT in sportsmen with CHB have never been conducted before. Our study included 42 professional sportsmen with CHB aged 15 to 45 years old.

Hepatitis B virus is justifiably included into the group of vaccine preventable diseases, the spread of which is efficiently controlled with specific prevention, i.e. vaccination. In Russia, hepatitis B vaccination was added to the National Immunisation Schedule in 2001. However, all sportsmen in the CHB study group originated from the regions, where (for some reason, primarily for religious reasons) no hepatitis B immunisation was performed. These data correlate with the results of an earlier study in 384 highly qualified athletes. According to questionnaires and medical records, only 45 (11.7 %) subjects had been vaccinated against hepatitis B [5].

The clinical presentation of CHB in sportsmen is minimal: 35.7 % of sportsmen complained of feeling of weight in their right hypochondrium and 19 % mentioned mild weakness. However, it is worth noting that an ultrasound examination revealed diffuse changes in the liver of 24 subjects, while seven had hepatomegaly or splenomegaly. Besides, there were four cases of mild to moderate HF diagnosed with TE (METAVIR stage F2–F3). Organic lesions of the liver in CHB patients can cause limitations related to the athlete's health and worsen their competitive results.

Unfortunately, there is insufficient information on the clinical characteristics of CHB in professional sportsmen in the available medical references in English (PubMed, Cochrane Library, UpToDate, Medscape, Sports Med Open, Br J Sports Med., etc.), and we are unable to compare our results with similar findings in foreign athletes.

Despite minimal clinical signs in sportsmen, CHB is a long-lasting, progressive conditions with a high risk of hepatic cirrhosis and cancer. To prevent these complications, the only option is timely AVT initiation.

There are currently no guidelines on the use of AVT in professional athletes. However, horizontal transmission of this infection via damaged skin during trainings and competitions has been reported [6, 7].

There is still no evidence of the lowest threshold of HBV DNA, below which HBV-infected athletes are considered safe to take part in competitions and protect other team members and rivals. Studies should be conducted to identify the viral load, below which the virus is not transmittable from an athlete to an athlete. Since there are no additional data, foreign scientists use the criteria applicable to medical professionals engaged in high-risk procedures, i.e. 200 IU/mL, in order to minimise the risk of HBV transmission among professional sportsmen [12]. Pending a relevant regulation, it is suggested to use it for AVT therapy in athletes with CHB [12].

During the observation, seventeen sportsmen received NA AVT (ETV or TDF). The results demonstrated high efficacy of these drugs: all patients achieved aviremia and normal ALT activity after a relatively short period of time (3.0 months and 4.5 months, respectively). As compared to other studies in non-athletes, the mean time from AVT initiation to aviremia was longer and made approximately 10 months [13]. A number of previous studies and this study established direct correlation between time to aviremia and baseline viral load [14, 15]. In athletes with CHB, AVT was initiated at lower viremia level (over 200 IU/mL), that is why they relatively rapidly achieved a non-detectable levels of HBV DNA. There were no differences in ETV and TDF therapy as to the time to virological and biochemical response. ETV and TDF also demonstrated good effects for improved liver morphology: HF stabilised or improved in the majority of athletes undergoing therapy. Timely CHB therapy considering the viral load not only reduces the risk of infection among professional athletes, but also contributes to improved hepatic enzyme levels and hepatic fibrosis status, allowing them to demonstrate high sport results.

At the same time, it is interesting to note that viremia recurred in seven patients on the average eight months after AVT initiation. ETV and TRF are known to be products with a high genetic barrier to resistance; and viremia recurred at early stages of the therapy, so drug resistance can be ruled out.

Excessive physical stress in sportsmen with CHB causes more severe damage to hepatic tissue than in athletes without CHB, and it can affect AVT efficacy [16]. Also, it can be expected that athletes may suspend NA therapy for a short period of time during trainings and competitions. In all cases, AVT was resumed with the same products and at the same doses, and in all cases aviremia was achieved in 5.0 months. It is essential that doctors in sports medicine explain to athletes that NA preparations prevent CHB complications and are not on the WADA List of Prohibited Substances and Methods; these preparations can be used on a daily basis [17].

## Conclusions

Athletes with CHB have few symptoms; however, damage to their liver observed at ultrasound and TE can affect health and sport results. Antiviral therapy with NAs can efficiently inhibit virus replication, normalise cytolytic enzymes and reduce HF severity. Viremia recurrence during therapy emphasises the importance of consultations by doctors in sport, so that athletes are compliant also during their sport activities.

**Вклад авторов:**

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**Нгуен Т.Х.:** концепция и дизайн исследования, сбор и обработка материала, анализ полученных данных, написание текста.

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**Мельникова Л.И.:** сбор и обработка материала.

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**Author Contribution:**

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

**Nguyen T.H.:** concept and design of the study, collection and processing of material, analysis of the obtained data, writing the text

**Ilchenko L.Yu.:** the concept and design of the study, editing the text

**Kyuregyan K.K.:** concept and design of the study, analysis of the obtained data.

**Melnikova L.I.:** collection and processing of material.

**Nguyen C.C.:** analysis of the obtained data.

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# МУЛЬТИМОРБИДНЫЙ ПАЦИЕНТ С ПЕРВИЧНЫМ ИММУНОДЕФИЦИТОМ. ДИАГНОСТИКА, ЛЕЧЕНИЕ

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# Multimorbid Patient with Primary Immunodeficiency. Diagnostics, Treatment

**Резюме**

Первичный иммунодефицит — патология иммунной системы, проявляющаяся в снижении либо отсутствии одного или нескольких звеньев системы иммунитета. Ранее считалось, что первичный иммунодефицит является редкой патологией, но последние статистические данные свидетельствуют об обратном. По этой причине врачам всех специальностей (особенно специалистам первичного звена) следует быть настороженным в вопросах диагностики и тактики ведения пациентов с данным заболеванием. Первичные иммунодефициты манифестируют различными клиническими проявлениями: инфекционными, онкологическими, аутоиммунными, аллергическими и др. Чаще всего дебют представлен рецидивирующими инфекциями и/или хронической диареей, но возможны и альтернативные варианты. В диагностике данных состояний стоит учитывать «настораживающие» признаки иммунодефицитов, а также результаты лабораторных исследований, таких как лимфо-/нейтропения, снижение сывороточных иммуноглобулинов и другие специфические тесты. Лечение первичного иммунодефицита базируется на пожизненной заместительной терапии иммуноглобулинами, а также лечении и профилактике клинических проявлений данного состояния. В статье приводится обсуждение клинического случая взрослого мультиморбидного пациента с первичным иммунодефицитом — несемейной агаммаглобулинемией. У пациента наблюдаются инфекционные (хронический бронхит), онкологические (базальноклеточный рак кожи) и другие клинические проявления заболевания (вторичная панкреатогенная энтеропатия). В разборе клинического случая делается акцент на ключевые детали в постановке диагноза «первичный иммунодефицит» у взрослых. Рассматривается вопрос ведения пациента в амбулаторных условиях с учетом основной патологии и обострения сопутствующих хронических заболеваний. Кроме этого, подчеркивается важность преемственности таких пациентов на амбулаторном и стационарном звеньях.

***Ключевые слова:*** *первичный иммунодефицит, общая вариабельная иммунная недостаточность, агаммаглобулинемия*

**Конфликт интересов**

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

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## Abstract

Primary immunodeficiency is a pathological condition of immune system, expressed in the absence or decrease certain parts of immune system. It was generally believed that primary immunodeficiency is a rare pathology but recent findings indicate the opposite. For that matter all types of specialists (especially family doctors) should be well informed. Primary immunodeficiency manifests with various clinical forms, like infectious, oncological, autoimmune, allergical etc. It should be well-known that primary immunodeficiency often debutes with chronic infections and diarrhea, but other sparks are also possible. As for the diagnostics, "red flags" should be taken into account, in addition to laboratory findings, such as lympho-/neutropenia, decrease in immunoglobulins and other specific tests. The therapy for primary immunodeficiency is based on substantial, vital treatment with immunoglobulins, along with prevention and treatment of comorbidities. The article discusses clinical case of an adult multimorbid patient with primary immunodeficiency, non-hereditary agammaglobulinemia with an emphasis on complexity of stating the final diagnosis in adulthood. The peculiarity of the patient is an absence of family history in immunodeficiency. He suffers from infectious (chronic bronchitis), oncological (basal cell carcinoma) and others (pancreatogenic enteropatia) clinical manifestations. It is observed, how family doctors could approach the treatment of the main pathology considering the intensification of comorbid chronic diseases. Futhermore, such patients should be managed ambulatory with full awareness of the stationary treatment and vice versa.

***Key words:*** *primary immunodeficiency, common variable immunodeficiency, agammaglobulinemia*

## Conflict of interests

The authors declare no conflict of interests

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## Conformity with the principles of ethics

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IgA — immunoglobulin A, IgG — immunoglobulin G, IgM — immunoglobulin M, IRAK-4 — interleukin-1 receptor-associated kinase 4, IUIS — International Union of Immunological Societies, NBN — Niymegen breakage syndrome, HIV — human immunodeficiency virus, CCH — city clinical hospital, Ig — immunoglobulin, LN — lymph nodes, $FEV_1$ — forced expiratory volume per 1 second, PID — primary immunodeficiency, PIDS — primary immune deficiency state, CRP — C-reactive protein, PFT — pulmonary function test, FLC — functional lung capacity, EGDS — esophagogastroduodenoscopy

# Introduction

Primary immunodeficiencies (PIDs) are genetically determined life-threatening conditions, associated with defects of one or several components: cellular or humoral immunity, phagocytosis, complement system. By now, 176 hereditary disorders leading to persistent immune dysfunctions have been identified.

O. Bruton was the first to mention PID in the mid-20th century. His paediatric patient with recurrent infections of upper and lower respiratory tract practically had no serum protein gamma fractions. The child's condition improved after immunoglobulin as replacement therapy.

For the purpose of further studies of primary immunodeficiencies, the International Union of Immunological Societies (IUIS) was formed in the 1970s.

Globally, approximately one in every 2,000 people has PID, therefore, this condition is an orphan disease. Orphan diseases are conditions with the incidence of less than one per 2,000 newborns [1]. However, the rarity of this pathology is controversial. According to preliminary estimates, the global incidence of PID can be six million people, whereas currently there are just 27,000 confirmed cases in PID registries [2]. The incidence of these conditions varies a lot, and in some countries it is over the average rate; however, it is believed that the detectability of PID is greatly underestimated. According to specialists, in Europe the number of patients with PID is at least 638,000, but only 15,052 cases are currently registered (2.27 %). In Africa, up to 902,631 people may have PID, but the current number of registered cases is just 1,016.

In 2020 in the Russian Federation, data of 2,472 patients registered in the primary immune deficiency state (PIDS) database were analysed; most of the patients were underage (61 %) [3]. It was shown that the average incidence of all PIDs in Russia was 1.5 per 100,000 of population. The annual number of children born with PID is at least one in every 16–17 thousand newborns; and since 2010 the number of patients with confirmed PIDs has risen significantly. The lowest mortality in all PID cases is 4–5.5 %, while the highest death rate was recorded in the group of children in early years [3].

Currently, there are 415 disease entities and syndromes described and included in PIDs. Clinically, they are usually divided into nine main groups, depending on the primary damage to a component of the immune system [4]:

1) Humoral defects (including impaired antibody formation)
2) Combined cell and humoral immunity insufficiency
3) Qualitative and quantitative phagocyte defects
4) Complement system defects
5) Syndrome-like PIDS (including defective deoxyribonucleic acid (DNA) reparation)
6) PID with immune dysregulation
7) Innate immunity defects
8) Autoinflammatory diseases
9) Phenocopies

The characteristics of PID variants are presented in Table 1.

***Table 1.*** *Classification of primary immunodeficient states based on immunological disorders according to the International Union of Immunological Societies*

| Pathogenetic mechanisms | Examples of nosologies |
|---|---|
| Humoral defects (e.g. abnormal antibody formation) | X-linked agammaglobulinemia<br>Common variable immunodeficiency<br>IgG subclass deficiency |
| Combined deficiency of cellular and humoral immunity | Severe combined immunodeficiency<br>CD40 ligand deficiency |
| Qualitative and quantitative phagocytic cells defects | Severe congenital neutropenia (Kostmann syndrome)<br>Cyclic neutropenia<br>Chronic granulomatous disease |
| Congenital immunity defects | Ectodermal dysplasia<br>*Interleukin-1 receptor-associated kinase-4* (IRAK-*4*) *deficiency*<br>Chronic mucocutaneous candidiasis |
| Defects of complement system | hereditary angioedema<br>Deficiency of various components of complement |
| Primary immunodeficiency with immune dysregulation | Immunodeficiency with hypopigmentation<br>Familial haemophagocytic syndrome<br>X-linked lymphoproliferative syndrome<br>Autoimmune lymphoproliferative syndrome |
| autoinflammatory diseases | familial Mediterranean fever<br>TNF receptor associated periodic syndrome<br>Hyper-IgD syndrome<br>Criropyre-associated periodic syndrome |
| PIDS syndromic forms | Viscott-Aldridge syndrome<br>Nijmegen syndrome<br>Hyper-IgE syndrome<br>DiGeorge syndrome |
| PID phenocopies | Phenocopies associated with somatic mutations<br>Phenocopies associated with antibodies |

**Note. PID — primary immunodeficiency; PDS — primary immunodeficient states, IL — interleukins**. Adapted from Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL, Abel L. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol. 2013;33(1):1-7. doi: 10.1007/s10875-012-9751-7 [2]

In Russia, neonatal PID screening was introduced only on January 1, 2023 (Order of the Ministry of Health of the Russian Federation No. 274n dated April 21, 2022, On Approval of the Procedure of Medical Assistance to Patients with Innate and/or Hereditary Diseases). This was a breakthrough in the area of early identification of innate immunodeficiencies and timely medical assistance to these patients; however, screenings does not take into account all possible variants of immunodeficiencies.

## *Clinical presentation of primary immunodeficiencies*

Clinical signs of PID can be divided into several groups. In a majority of cases, PID manifestations are similar to those of infectious diseases. There can be both unexplained chronic recurrent infections and infections caused by low-virulence or rare agents. Infections can affect skin and mucous membranes, upper and lower respiratory tract, and gastrointestinal tract. In most cases, PID starts with chronic recurrent diarrhoea [5,6]. There is also connection between PID type and clinical form of a gastrointestinal disorder. Recurrent sinopulmonary infections with encapsulated bacteria, such as Haemophilus influenzae type B or Streptococcus pneumoniae, can be typical for antibody deficiency syndrome. Frequent viral, fungal or protozoal infections can evidence impaired T-lymphocyte function. Multiple staphylococcal skin infections and fungal infections are diagnosed in neutrophil dysfunction or elevated immunoglobulin E (IgE) concentration syndrome, while recurrent Neisseria infections are a typical manifestation of deficient complement C5, C6, C7, C8, C9 components. Mycobacterial infections are typical for interleukin 12 system disorders.

Other clinical presentations of PID include malignancies. As compared to the general population, the incidence of malignancies is higher in patients with PID.

Besides, PID can manifest as various autoimmune disorders (up to 22 % of cases) [7].

PIDs manifesting as typical syndrome complexes (Table 2) need special attention.

## *Primary immunodeficiency diagnostics*

Primary immunodeficiency diagnostics can be challenging for primary healthcare providers due to the lack of information and rarity of some forms [8]. Primary healthcare providers should be aware of manifestations of primary immunodeficiency in order to timely refer the patient to an immunologist.

The Jeffrey Modell Foundation (USA) published a guidance for practitioners titled “Ten warning signs of primary immunodeficiency”. Below are the warning signs of primary immunodeficiency in adults [8].

- Two or more cases of ear infection within one year
- Two or more complex cases of paranasal sinus infections within one year (without allergies)
- One or more pneumonia cases every year
- Chronic diarrhoea with loss of weight
- Recurrent viral infections
- Repeatedly required IV antibiotics to kill an infection

***Table 2.*** *Syndromal forms of PID with specific symptomatic complex*

| Syndromes | Defect in the immune system | Clinical features |
|---|---|---|
| DiGeorge syndrome | Thymus hypoplasia | congenital heart defects<br>hypoparathyroidism<br>facial abnormalities |
| Viscott-Aldridge syndrome | T- и B-lymphocytes dysfunction | Hemorrhagic syndrome (petechiae, ecchymosis, nasal bleeding, melena)<br>eczema<br>Recurrent infections |
| Louis Bar Syndrome | T- и B-lymphocytes dysfunction | Ataxia<br>telangiectasia |
| Nijmegen syndrome | Mutation NBN (NIJMEGEN BREAKAGE SYNDROME) Breakdown of the synthesis of the protein nibrine, associated with double-strand repair | Microcephaly<br>Change of facial skeleton by type “bird face”<br>Predisposition to malignancy |

- Persistent oral thrush or mycotic lesions of skin
- Severe abscesses of skin and internal organs
- Infections caused by otherwise non-pathogenic mycobacteria
- Family history of primary immunodeficiency.

Medical history and laboratory data, which should be considered in order to suspect PID and refer the patient to specific tests, are presented in Figure 1.

Given that the above signs are typical both for primary and acquired immunodeficiency, acquired immune defi-

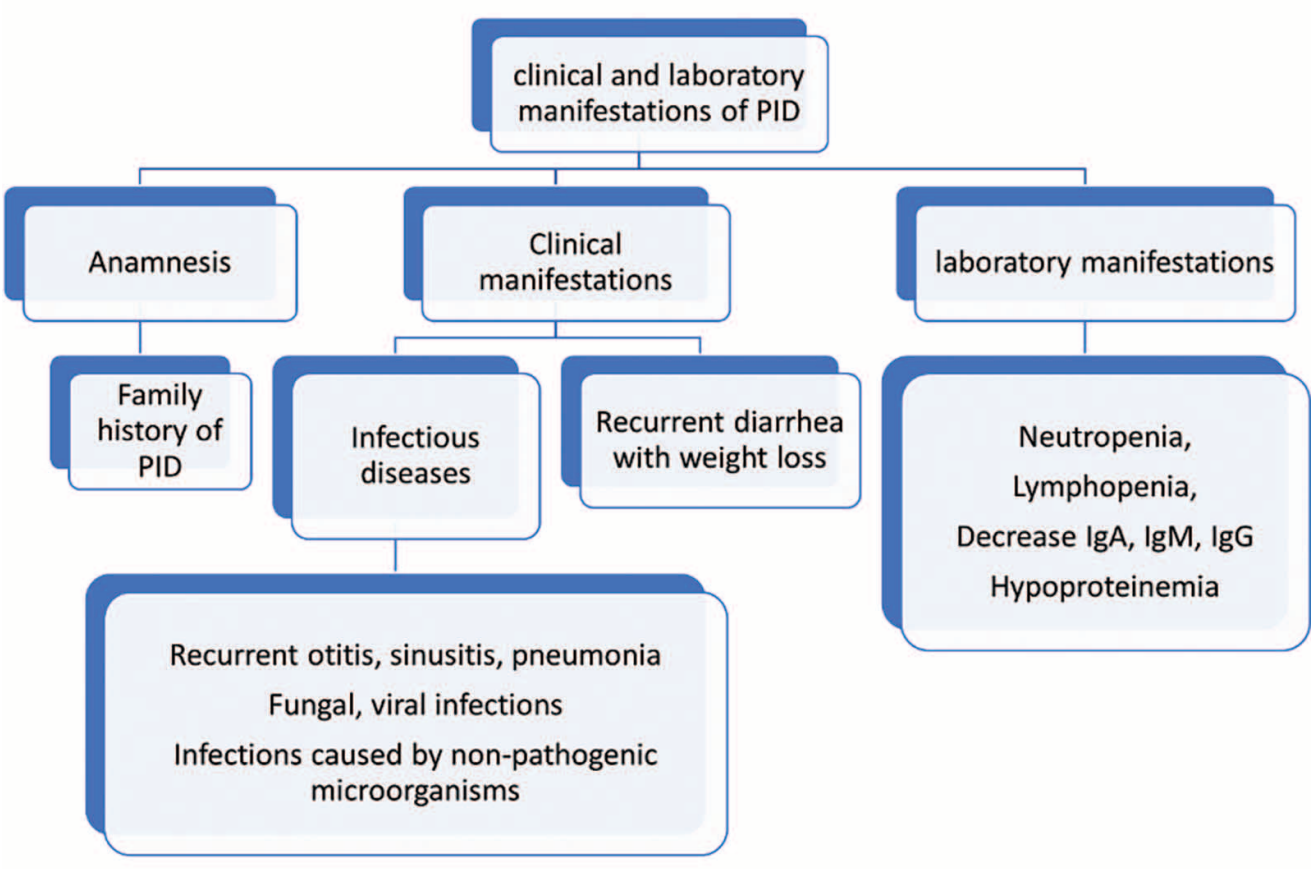


***Figure 1.*** *Clinical and anamnestic basis for primary immunodeficiency (PID) diagnostic search*

***Table 3.*** *Screening tests for PID detection*

| Suspected immune system defect | Laboratory abnormalities that make PID suspect | Clarifying methods of diagnostics |
|---|---|---|
| Humoral immunity | Serum immunoglobulins (IgA, IgM, IgG)<br>Titer of post-vaccination antibodies and/or isohemagglutinins<br>Serum total protein level | Detection of IgG subclasses<br>Determination of B-lymphocytes content and phenotyping with the help of monoclonal antibodies CD19 (CD20, CD21) |
| cellular immunity | Lymphopenia<br>Skin Delayed Hypersensitivity Tests | T-lymphocyte count (CD4, CD8) |
| phagocytes | Neutropenia or neutrophilia | Nitroblue tetrazolium test (NBT test) |
| complement | Anemia, leukopenia, thrombocytopenia, reduction of serum immunoglobulins (IgA, IgM, IgG) | Total hemolytic capacity of serum (CH50)<br>Content of complement components in serum |

**Note.** PID — primary immunodeficiency; IgG — Immunoglobulin G class; IgA — Immunoglobulin A class; IgM — Immunoglobulin M class, CD19,20,21 — co-receptor proteins on the surface of B lymphocytes; CD4,8 — co-receptor proteins on T-lymphocytes

ciency syndrome (AIDS) and diabetes mellitus should be ruled out in adult patients before disease-specific tests and examinations.

Besides, there are a number of laboratory screening panels to test for primary immunodeficiency, which were developed by the Working Group of the European Society for Immunodeficiencies (Table 3) [8].

## *Therapy of primary immunodeficiencies*

The general principles of PID management are presented below:

1) Replacement therapy with parenteral immunoglobulin
2) Prevention of infectious manifestations
3) Management of non-infectious manifestations
4) Correction of immune dysregulation complications.

The case study below is an example of PID detection using clinical symptoms and laboratory test results; it also describes further patient management, both in inpatient and outpatient settings.

Patient S., 36 y.o. According to the patient, there is no history of family diseases; all his relatives are healthy. He is a father to two healthy children. As a child, he frequently had acute respiratory diseases (ARD). When he was a child, he was diagnosed with chronic rhinosinusitis with over four recurrences annually. He was successfully treated with antimicrobial drugs; however, no long-lasting remission was achieved. In 2013, the patient underwent maxillary sinus microsurgery, which resulted in long-lasting remission. The last episode of maxillary sinusitis was recorded in 2019.

Besides, since childhood he has been having 4–6 events of diarrhoea a day, at a frequency of 3–4 times a year, associated with diffuse stomachache. The symptoms were treated with intestinal antiseptic drugs, rifaximin and probiotics.

In 1998, the patient was diagnosed with hypogammaglobulimenia; the treatment was non-specific and did not result in significant improvements; no documentary evidence was provided. In 2013, genetically non-confirmed reduction in IgA, IgG, IgM levels was reported (according to the patient, he does not have any documentary evidence). Attempted immunoglobulin therapy resulted in anaphylaxis and was discontinued.

In November 2017, the patient had severe recurrence of diarrhoeal syndrome with several daily episodes of loose stool, pain in epigastric, paraumbilical and colon area, as well as bloating and occasional rises in body temperature to subfebrile values. The patient was hospitalised to the gastroenterological ward, and gluten-sensitive enteropathy was suspected. Laboratory and instrumental test results did not confirm gluten-sensitive enteropathy; the patient was transferred to the infectious disease ward with gastrointestinal salmonellosis. His condition was treated with furasolidone, intestinal sorbents and infusion therapy, however, the symptoms did not resolve.

An examination in the infectious disease ward showed absolute lymphocyte depletion, reduction in various immunoglobulin fractions, and abnormal changes

***Table 4.*** *Patient's results of examination in infectious department in 2017*

| Methods | Results |
|---|---|
| complete blood count | absolute lymphocytopenia<br>relative monocytosis |
| biochemical blood test | ↑CRP |
| Immunogramm | ↓IgG |
| Colonoscopy with biopsy | significant diffuse inflammation with shortening of the intestinal villi;<br>absence or reduction of plasma cells↑ interepithelial lymphocytes |
| Stool test for disbiosis | bacterial imbalance<br>↓bifidobacteria, lactobacteria<br>↑lactosonegative Escherichia, staphylococci, conditionally pathogenic flora, yeast-like fungi |
| Gliadin antibodies | ↓IgA (0,2 г/л) |

**Note.** CRP-C-reactive protein; IgG- immunoglobulins G class; IgA- immunoglobulins A class, ↓ decrease, ↑ increase

(see Table 4), which was indicative of immunodeficient conditions. Once the main symptoms were arrested, the patient was transferred to the consultative diagnostic unit for allergology and immunology at the City Clinical Hospital No. 52 (Moscow) with a referral diagnosis "Common variable immunodeficiency".

A further examination in the allergology and immunology unit showed low serum immunoglobulins; lymphocyte immunophenotyping was performed, i.e. search for co-receptor protein on lymphocytes (CD), specific for each lymphocyte family. The result was as follows: high CD3-, CD19+ levels, moderately low CD3+, CD19-; CB3+, CD4+; CD3-, CD8+ levels.

The diagnostic search allowed making the following diagnosis "Primary immunodeficiency. Common variable immunodeficiency — agammaglobulinaemia".

Recommended therapy: IV normal human immunoglobulins at a dose of 10 g of protein/day for an indefinite period of time. This therapy did not trigger any allergic reactions in the patient.

Once PID was verified during the inpatient treatment in 2017, the patient was hospitalised only once, in 2020, when he had a flare-up of his chronic bronchitis. Then the patient was followed up in outpatient settings.

In February 2018, the patient was consulted by a gastroenterologist for recurrent diarrhoea, body weight loss (10 kg from November 2017), left-sided subcostal pain. The patient underwent an outpatient examination. The following diagnosis was made: Chronic gastritis with exocrine secretion and pancreatic insufficiency; secondary pancreatogenic enteropathy with malabsorption syndrome. Excessive bacterial growth syndrome. After the diagnostic procedures, multienzyme products, mandatory course of probiotics and intestinal antiseptic drugs were prescribed. The patient takes the drugs until the temporary positive effects are achieved (normal stool for 7–8 days); a course of administration is repeated if the symptoms return. The periodic therapy resulted in significant improvement, the patient had fewer and less severe episodes of diarrhoea.

In March 2019, the patient attended his GP complaining of productive cough, especially in the morning. Sputum was from mucoid to mucopurulent. The patient had cough from time to time, starting from 2016. Given the duration of these complaints, the patient was diagnosed with chronic bronchitis. Recommendations included levofloxacin 500 mg for 10 days, in combination with ipratropium/fenoterol as nebulizer therapy. In September 2019, the patient was hospitalised to the pulmonology ward with a severe flare-up of chronic bronchitis, manifesting with fever, shortness of breath when walking less than 100 m, weakness, cough with yellow-green sputum. The patient underwent a comprehensive pulmonary function test (PFT), chest X-ray (two views); sputum culture was not performed. Chest X-ray did not show any new focal or infiltrative shadows; the lung pattern was clear in all areas. PFT did not reveal any abnormalities. The therapy included vancomycin, bronchodilators and mucolytics.

The patient was discharged after six days in the hospital with positive changes and recommendations on drugs therapy:

- Glycopyrronium bromide 50 μg for inhalation, one inhale/day, for 21 days
- Fluconazole 50 mg, two capsules in the morning after meals, for 10 days
- Amikacin 1 g + 10.0 mL saline solution — solution for nebulizer inhalations, every eight hours, for one month
- Azithromycin 250 mg, one tablet once daily, for three months [9]
- Multienzyme preparations 10,000 U, one tablet TID, for 10 days
- Trimebutine 200 mg, one capsule BID, for 2–3 weeks
- Vancomycin 500 mg, four times daily per os, as a 14-day course
- Bifidumbacterinum, 10 doses TID, for two weeks.

In case of a flare-up of chronic bronchitis, nebulizer therapy with spirometry monitoring is indicated:

- Ipratropium bromide/fenoterol budesonide, 15–20 drops per 2.0 mL of saline solution, BID
- Budesonide 0.25 mg/mL 1 nebula, or 0.5 mg/mL 1/2 nebula, BID
- Ambroxol 40 drops per 2.0 mL of saline solution, BID.

In January 2020, the patient started complaining of cough with mucopurulent sputum, subfebrile body temperature. Chest X-ray: no focal and infiltrative changes in the lung field. PFT did not show any abnormalities (forced expiratory volume per 1 second ($FEV_1$): 95 %, functional lung capacity (FLC): 98 %). Since the flare-up was moderate, antibiotic therapy was conducted in outpatient settings, with positive dynamics. After 2020, the patient did not visit the hospital and was not hospitalised for exacerbations of chronic conditions. He was followed up by an allergologist-immunologist, pulmonologist and ENT specialist

In January 2023, the patient came for a consultation by the skin specialist, complaining of a skin lesion on his

right cheek. Examination revealed a hollow scar up to 5 mm on his right cheek. Dermatoscopy showed dendriform vessels on the periphery of the scar. Regional lymph nodes were nonpalpable. Biopsy was performed; a histological examination verified initial stages of nodular basal cell carcinoma. Curative surgery was performed (resection). Currently, the patient is followed up by the skin specialist; he comes to scheduled monitoring visits once every six months. The tumour did not recur.

***Final diagnosis: primary immunodeficiency. Common variable immunodeficiency — agammaglobulinaemia. Chronic bronchitis, long-lasting remission. Chronic pancreatitis with exocrine secretion insufficiency. Secondary pancreatogenic enteropathy with malabsorption syndrome. Excessive bacterial growth syndrome. Nodular basal cell skin carcinoma, post-surgery condition.***

The diagnosis was worded in mid-2023 by the GP on the basis of medical records from the skin specialist, allergologist-immunologist, pulmonologist.

At the case follow-up (September 2024), the patient complained of cough, occasionally loose stool; the management comprises the following measures:

1. Follow-up by GP, allergologist-immunologist, pulmonologist, ENT specialist, gastroenterologist, oncologist
2. Life-long replacement immune therapy with IV immunoglobulin once a month at a dose of 0.4 g/kg
3. Monitoring of pre-transfusion IgG, IgA, IgM levels once every three months (inpatient settings)
4. Routine sputum analysis, bacterial and fungal culture, chemotherapy sensitivity test once every three months
5. Spirometry, examination of diffusing lung capacity once every three months
6. Fibrocolonoscopy once a year
7. Stool culture for opportunistic and pathogenic flora in recurrent diarrhoeal syndrome
8. Complete blood count, C-reactive protein (SRP), fibrinogen, calprotectin once every three months
9. Ultrasound examination of abdomen and kidneys, retroperitoneal space, all lymph node groups once a year
10. Flu and pneumococcus vaccination.

## Discussion

The characteristic of the presented case study lies in the duration and challenges with diagnosis of primary immunodeficiency with onset in an adult; and also in the development of a management strategy for these patients, causing a lot of uncertainties among healthcare practitioners.

The diagnostic challenge in this case is the absence of the family history (parents, siblings and even children of the patient did not have this pathology), as well as in late onset of the immune pathology.

For a correct diagnosis, clinical disguises of immune deficiency should be taken into account: infections, cancer, autoimmune conditions, allergies, etc. It is essential to pay attention to a common clinical sign PIDS in addition to recurrent infections, which in this case gave a hint of the correct diagnosis, namely frequent episodes of diarrhoea with stomachache. This can be explained by the fact that the large lymph system of the gastrointestinal tract, being the primary protective barrier, grows thinner and leads to the damage to jejunum villi from foreign microorganisms. It results in inflammatory and osmotic diarrhoea. The autoimmune nature of the gastrointestinal tract involvement facilitates the development of diarrhoea. Once any other known origins (human immunodeficiency virus (HIV), infectious enterocolitis, Crohn's disease, intestinal tumour and TB, pseudomembranous colitis, gluten-sensitive enteropathy, etc.) have been ruled out, PID should be suspected [6]. A typical sign of PID in complete blood count is absolute lymphopenia; immunogram — low levels of all immunoglobulin fractions; colon biopsy — short villi and an elevated level of interepithelial lymphocytes, as well as impaired bacterial balance in stool samples. For the final diagnosis of PID, a number of additional tests and examinations are required, depending on the suspected group of immune deficiencies (see Table 3). In this case study, lymphocyte immunophenotyping was performed, the results of which gave an idea of the common variable immunodeficiency.

PID therapy requires adherence to the principle of the life-long continuous replacement therapy with immunoglobulins and immunogram monitoring once every three months [10]. Besides, all comorbidities should be treated, and the patient should be hospitalised in case of severe exacerbations. It is worth mentioning that cooperation between inpatient and outpatient teams is essential for the management of patients with PIDS. Inpatient healthcare providers should verify the diagnosis of PID and offer professional services in urgent cases. In outpatient settings, the current patient's condition is corrected, and laboratory and instrumental results are monitored.

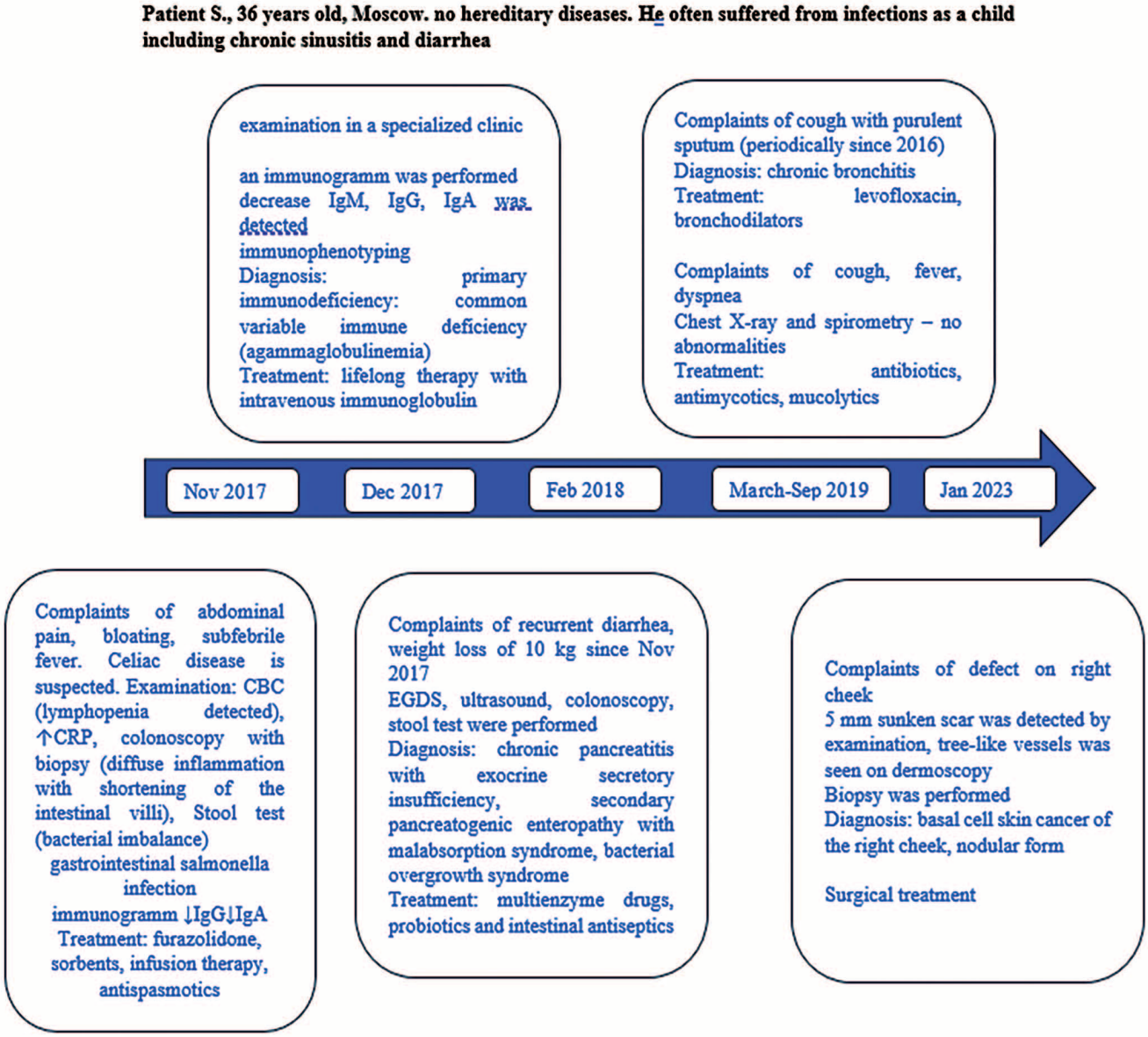


***Figure 2.*** *Timeline of observation of a patient with primary immunodeficiency*
**Note.** Ig — immunoglobulin, CBC — clinic blood cells, CRP — C-reactive protein, EGDS — esophagogastroduodenoscopy

In this patient, the prognosis is favourable due to an optimal level of serum immunoglobulins maintained with monthly intravenous infusions; there are no reports of any serious flare-ups of chronic conditions; and the patient is highly compliant with the therapy.

## Conclusion

An approach to the diagnosis and management of PIDS is a complex cross-disciplinary task. One should not forget about late onset of the disease, possible disguises of this pathology, compulsory life-long replacement therapy with immunoglobulin and serum immunoglobulin monitoring, as well as regular follow-ups by healthcare providers involved in the therapy of comorbidities.

**Вклад авторов:**

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

**Ларина В.Н.**: разработка концепции и дизайна рукописи, анализ и интерпретации данных, редактирование текста, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, ответственная за все аспекты работы

**Кудина Е.В.**: анализ и интерпретации данных, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, подготовка текста рукописи, ответственная за все аспекты работы

**Матвейчук Т.А.**: обзор публикаций по теме статьи, интерпретация данных, подготовка текста рукописи, работа с литературой, ответственная за все аспекты работы

**Шерегова Е.Н.**: обзор публикаций по теме статьи, сбор, анализ и интерпретация данных, организационное и ресурсное обеспечение публикации, ответственный за все аспекты работы, итоговые выводы, окончательное утверждение рукописи для публикации

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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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# КЛИНИЧЕСКИЙ СЛУЧАЙ ПЕРВИЧНОЙ НАДПОЧЕЧНИКОВОЙ НЕДОСТАТОЧНОСТИ: ТРУДНОСТИ ДИАГНОСТИКИ, ТЕРАПЕВТИЧЕСКАЯ ТАКТИКА

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# Clinical Case of Primary Adrenal Insufficiency: Diagnostic Difficulties, Therapeutic Tactics

**Резюме**

Туберкулезное поражение надпочечников — редкая причина первичной надпочечниковой недостаточности (ПНН), характеризующаяся недостаточной выработкой глюкокортикоидов, минералокортикоидов и андрогенов. Неспецифическая симптоматика ПНН затрудняет своевременную диагностику и лечение, что нередко приводит к жизнеугрожающему состоянию — аддисоническому кризу. В данной статье представлено клиническое наблюдение пациентки 67 лет. В течение 8 месяцев пациентка отмечала постепенное нарастание общей слабости, снижение аппетита. При обращении в клинику по месту жительства в июне 2022 г. был установлен диагноз «синдром раздраженного кишечника». Состояние при госпитализации в терапевтическом отделении в октябре 2022 г: выраженная общая слабость, появление боли в животе, мышечные боли, тошнота, рвота. Учитывая вышеперечисленные симптомы, был заподозрен аддисонический криз. Не дожидаясь результатов диагностического поиска, пациентке было назначено введение гидрокортизона 100 мг внутривенно струйно 4 раза за сутки. По результатам исследований, у пациентки была подтверждена первичная надпочечниковая недостаточность, вызванная туберкулезным процессом. Пациентке была назначена заместительная гормональная терапия, проведена беседа о принципах самостоятельной коррекции гормональной терапии и рекомендована консультация врачом-фтизиатром для решения вопроса об инициировании противотуберкулезной терапии. На фоне терапии (межлекарственного взаимодействия) и диагностических процедур (бронхоскопия) и при отсутствии коррекции заместительной гормональной терапии у пациентки развился аддисонический криз. После купирования острого состояния, пациентка повторно консультирована врачом-эндокринологом: принято решение увеличить дозировку заместительной гормональной терапии на фоне лечения противотуберкулезными препаратами. Представленный клинический случай демонстрирует не только особенности диагностики и подбора заместительной терапии при лечении ПНН, но и необходимость повышения осведомленности врачей различных специальностей об алгоритме и тактике ведения пациентов с признаками аддисонического криза.

***Ключевые слова:*** *туберкулез надпочечников, первичная надпочечниковая недостаточность, аддисонический криз, болезнь Аддисона*

**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

**Соответствие принципам этики**
Информированное согласие не требуется в силу невозможности идентифицировать пациента

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**Abstract**
Tuberculous adrenal insufficiency is a rare cause of primary adrenal insufficiency (PAI), characterized by insufficient production of glucocorticoids, mineralocorticoids, and androgens. Nonspecific symptoms of PAI complicate timely diagnosis and treatment, which often leads to a life-threatening condition, Addisonian crisis. This article presents a clinical observation of a 67-year-old female patient. For 8 months, the patient noted a gradual increase in general weakness, and decreased appetite. When visiting a local clinic in June 2022, she was diagnosed with irritable bowel syndrome. Condition on admission in the medical ward in October 2022 was manifested as severe general weakness, abdominal pain, muscle pain, nausea, vomiting. Given the above symptoms, Addisonian crisis was suspected. Before the results of diagnostic tests were obtained, the patient was given hydrocortisone 100 mg intravenously by jet stream 4 times per day. Based on the test results, the patient was diagnosed with primary adrenal insufficiency caused by a tuberculosis process. The patient was prescribed hormone replacement therapy, she was advised on the principles of independently adjusting the hormone therapy; a consultation with a TB specialist was also recommended to decide on initiating anti-tuberculosis therapy. The patient developed an Addisonian crisis due to a combination of factors: the treatment (the drug interaction), the impact of diagnostic procedures (bronchoscopy) and due to no correction of the prescribed hormone replacement therapy. After the acute condition was relieved, the patient was re-consulted by the endocrinologist who decided to increase the dosage of hormone replacement therapy and continue the treatment with antitubercular agents. This clinical case has demonstrated the specifics of diagnostics and selection of replacement therapy in the treatment of PNI. It has also shown that doctors of various specialties have to be better informed about the algorithm and tactics of managing patients with symptoms of Addisonian crisis.

***Key words:*** *adrenal tuberculosis, primary adrenal insufficiency, Addison crisis, Addison's disease*

**Conflict of interests**
The authors declare no conflict of interests

**Conformity with the principles of ethics**
Informed consent is not required due to the impossibility of identifying the patient

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PAI — primary adrenal insufficiency, ACTH — adrenocorticotropic hormone, CRH — corticotrophin-releasing hormone, DHA-S — dehydroepiandrosterone sulfate, BP — blood pressure, Ab — antibodies, CT — computer tomography, IBS — irritable bowel syndrome

## Introduction

Primary adrenal insufficiency (PAI) is a rare endocrine conditions affecting 100–140 people per million. Currently, autoimmune adrenal cortex deficiencies are more common in clinical practice, whereas tuberculous damages are observed maximum in 10 % of confirmed cases [1]. Although replacement therapy considerably improves prognosis, 50 % of patients are at residual risk of a dangerous, life-threatening condition — addisonian crisis, which is a result of therapeutic errors [2]. Therefore, early diagnosis and therapeutic strategy are relevant for various healthcare professionals, because non-specific symptoms hinder early diagnosis, and errors in patient management can cost the patients their lives.

## Aetiology and pathogenesis

Deficient production of adrenal cortex hormones is caused by impaired functions at various levels of the hypothalmic-pituitary-adrenal axis (Figure 1).

Adrenal insufficiency resulting from adrenal cortex damages is called primary. If a pathologic process develops in the pituitary gland, then this clinical condition is called secondary adrenal insufficiency. There is also tertiary adrenal insufficiency, meaning changes in hypothalamus functions. Secondary and tertiary adrenal insufficiency often have common clinical presentation. Adrenal insufficiency can be innate or acquired **(Table 1)**.

Acquired primary adrenal insufficiency is often caused by an autoimmune process; the second most common cause of acquired PAI is an infection, mostly TB [1, 2].

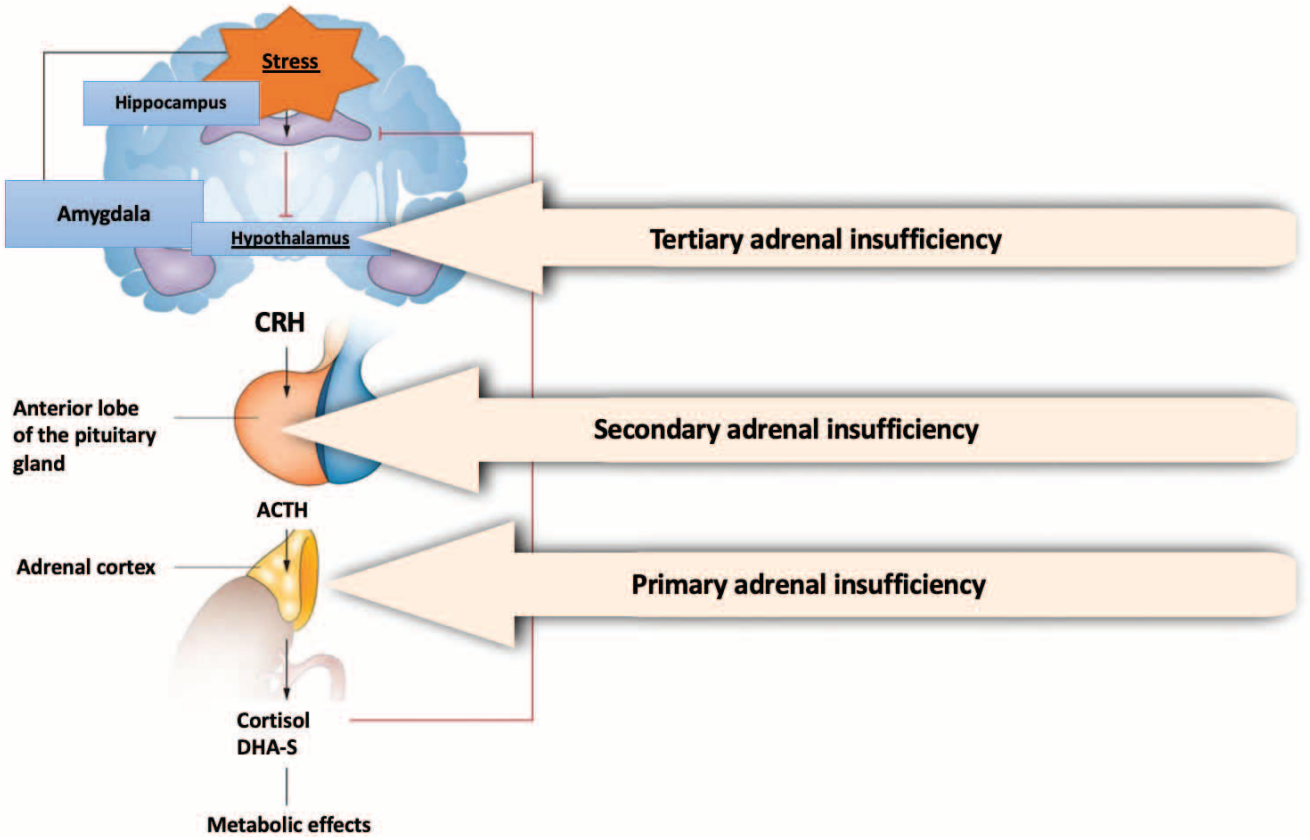


***Figure 1.*** *Hypothalamic-pituitary-adrenal axis and types of adrenal insufficiency according to the level of lesion*

**Note:** ACTH — adrenocorticotropic hormone, CRH — corticotropin-releasing hormone, DHA-S — dehydroepiandrosterone sulfate (Adapted from Papadopoulos, A. S., & Cleare, A. J. (2011). Hypothalamic–pituitary–adrenal axis dysfunction in chronic fatigue syndrome. Nature Reviews Endocrinology, 8(1), 22–32.doi: 10.1038/nrendo.2011.153) [3]

***Table 1.*** *Causes of primary adrenal insufficiency*

| Causes of primary adrenal insufficiency | |
|---|---|
| **Congenital causes** | **Acquired causes** |
| • Congenital adrenal cortex dysfunction (the most common cause of primary adrenal insufficiency in children, 80%)<br>• Congenital insensitivity to adrenocorticotropic hormone (isolated glucocorticoid deficiency)<br>• Congenital adrenal hypoplasia<br>• Adrenoleukodystrophy<br>• Mitochondrial diseases<br>• Vollmann's disease | • Autoimmune damage to the adrenal glands<br>• Damage to adrenal tissue:<br>  Infections<br>  Metastasis<br>  Hemorrhage<br>• Medical causes (rifampicin, ketoconazole, anticancer drugs, certain aromatase inhibitors, protein kinase inhibitors, diagnostic drugs, general anesthesia drugs)<br>• Total adrenalectomy<br>• Unilateral adrenalectomy with contralateral adrenal atrophy<br>• Infiltrative diseases (hemochromatosis, amyloidosis, sarcoidosis) |

**Notes:** PAI — primary adrenal insufficiency. Adapted from the clinical guidelines of the endocrinology association "Primary adrenal insufficiency" 2021 [1].

## Clinical presentation

Clinical presentation of primary adrenal insufficiency is a result of reduced glucocorticoid and mineralocorticoid levels. At the beginning of the pathologic process, the clinical manifestations are unclear, which can delay timely diagnosis. *Non-specific* symptoms are: loss of body weight, developing general weakness, musculoskeletal pain, abdominal discomfort, anxiety, depression. *Specific* and pathognomonic symptoms of PAI are skin and mucosa hyperpigmentation due to an elevated production of proopiomelanocortin, a biological precursor of chromatophorotropic hormones. Hyperpigmentation is clearly visible in natural skin folds, point of contact with clothes, and near post-surgery scarring. Proopiomelanocortin is also a precursor of lipotrophic hormones, facilitating subcutaneous tissue lipolysis, which is an additional factor of body weight loss [1].

Clinical presentations of *addisonian crisis* are marked general weakness, hypotonia, nausea, vomiting, abdominal and muscle pain.

## Diagnostic algorithm

The PAI diagnostic algorithm is presented in Figure 2.

## Management

**Addisonian crisis management.** Adrenal insufficiency is a life-threatening condition. **When addisonian crisis is suspected, replacement therapy should be initiated immediately, and there is no need to wait for laboratory test results** [1]. According to clinical guidelines, patients demonstrating signs of addisonian crisis should have hydrocortisone or prednisolone injections at equivalent doses. If hydrocortisone or prednisolone therapy is impossible, dexamethasone should be considered. (Dosage regimens are presented in 2021 Clinical Recommendations: Primary Adrenal Insufficiency) [1].

**Replacement therapy.** Once the acute condition has been relieved, the patient requires long-term therapy selected.

Replacement therapy in PAI patients is based on several principles:

**1. Characteristics of replacement therapy.** The dose regiment of replacement therapy mirrors the characteristic expression of adrenal cortex hormones in a healthy individual. The most active production of cortisol is known to be taking place in the morning, while aldosterone has a pulsating cycle of production, and this is taken into account when selecting a dose. Therefore, in order to compensate for the glucocorticoid component, hydrocortisone is administered in the morning, a half to two thirds of the daily dose; and one third is administered in the afternoon, thus mimicking the physiological production of this hormone. As for the compensation of the mineralocorticoid component, its purpose is to prevent

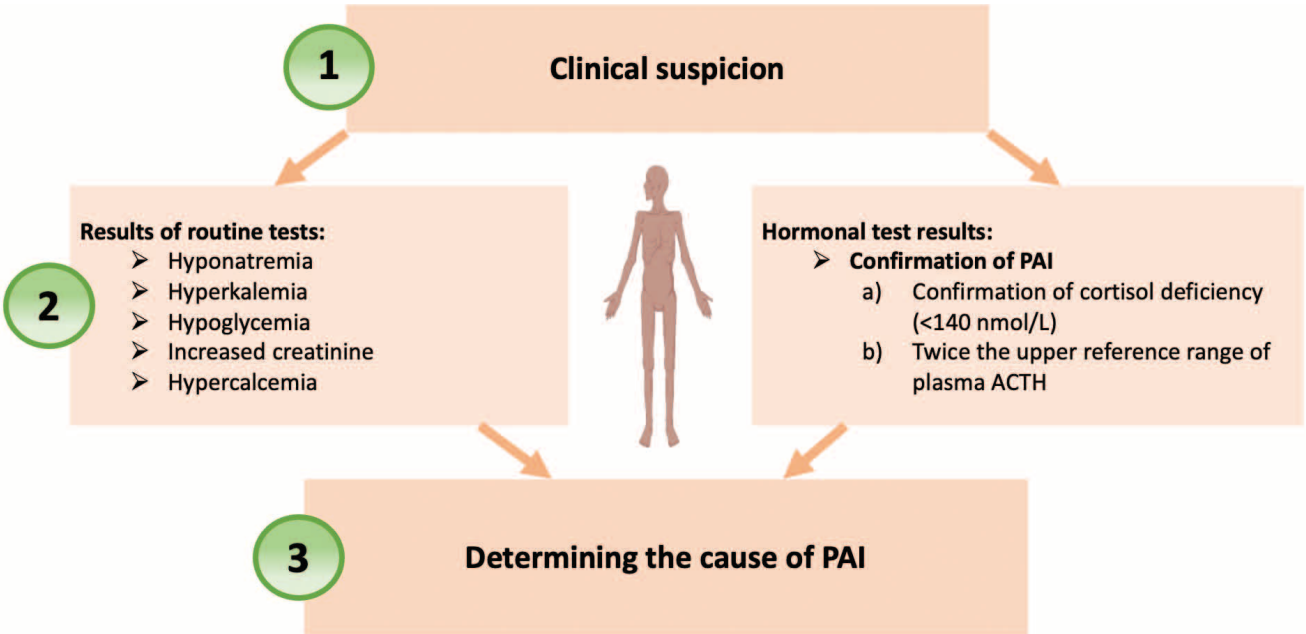


***Figure 2.*** *Algorithm for diagnosing PAI. Adapted from the clinical guidelines of the endocrinology association "Primary adrenal insufficiency" 2021 [1].*

**Note:** PAI — primary adrenal insufficiency, ACTH — adrenocorticotropic hormone

hyponatraemia and dehydration. Fludrocortisone is used in this case, and the dose is selected depending on the blood pressure values.

**2. Assessment of replacement therapy efficacy**. Since there are no objective parameters to assess the adequate replacement therapy, internal medicine specialists have to rely on clinical presentation. The efficacy criteria of the replacement therapy are:

- Normalised blood pressure
- Improved general condition and emotions
- Appetite, improved skin colour.

The following are the signs of possible overdose:

- Uneven colour
- Rapid gain of weight
- Osteopenia.

**3. Training the patients in the principles of replacement therapy dose correction**. Another important aspect in the therapy is training both the patient and their close ones during the initial and follow-up visits. Diagnosed PAI requires understanding that the replacement therapy is life-long, and in some cases the patient will need dose adjustments. Any event associated with release of stress hormones must be medicated. Patients are recommended to carry hydrocortisone injections with them in order to arrest an addisonian crisis, a pendant, a memo and any other available attributes, which can facilitate timely medical assistance [1]. Dose should be adjusted in the following situations: fever, gastroenteritis or trauma, surgery (a manor or a major intervention), addisonian crisis. (Dosage regimens are presented in 2021 Clinical Recommendations: Primary Adrenal Insufficiency) [1].

## Case study

A female patient, 67 y.o., was admitted to the medical ward of the hospital of the Central Union of Consumer Cooperatives of the Russian Federation (Moscow) on October 4, 2022. She was complaining ofgeneral weakness, nausea, loss of 35 kg of body weight over seven months, iliac pain, insomnia.

**Past medical history:** the patient first complained of weakness in March 2022. Blood pressure (BP): 150/90 mm Hg, weight: 86 kg. Antihypertensive therapy was not administered. In June 2022, general weakness progressed; blood pressure dropped to 100/60 mm Hg; and body weight reduced to 71 kg with no changes in the lifestyle. She started complaining of nausea and vomiting and called for medical assistance at the hospital at the place of residence, where she was diagnosed with *irritable bowel syndrome*. Since 2022, here general condition deteriorated; BP: 80/40 mm Hg; the patient started complaining of iliac pain, insomnia, no appetite, nausea, and was admitted to the medical ward of the hospital of the Central Union of Consumer Cooperatives of the Russian Federation for further diagnostics and therapy (Fig. 3).

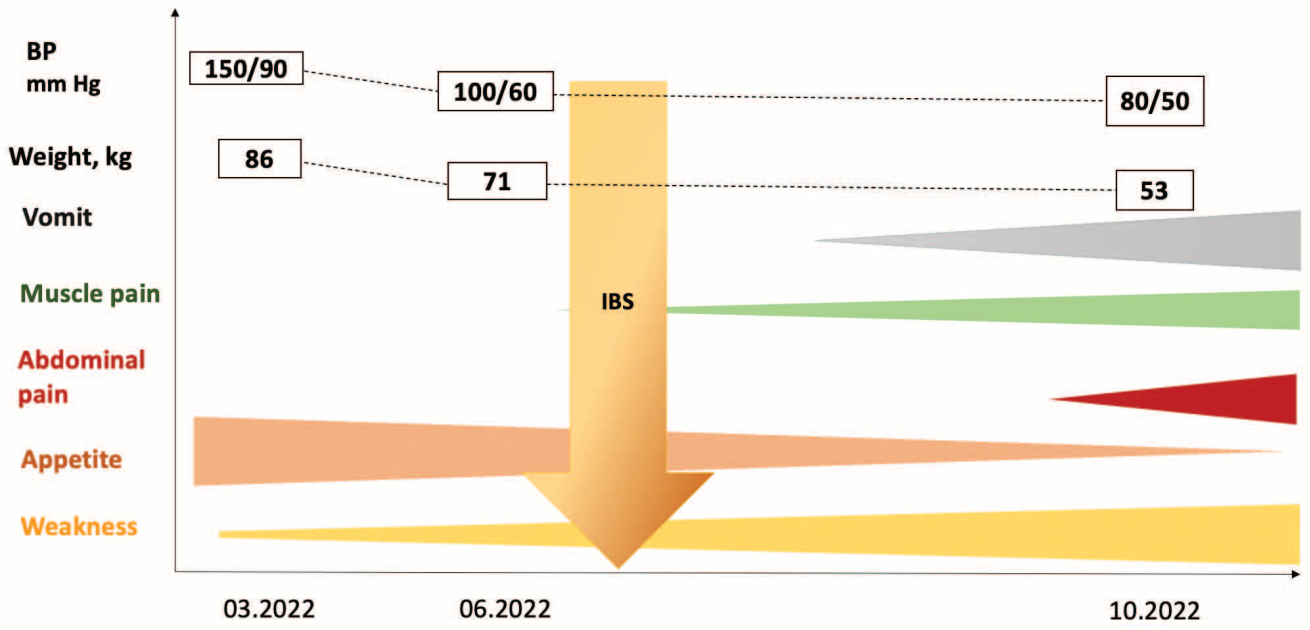


***Figure 3.*** *Patient's medical history*
**Note:** BP — blood pressure, IBS — irritable bowel syndrome

**Life history:** a citizen of Turkmenistan, high education, widow. Allergies: denies. Family history: her brother died of lung TB in 2014. It is known that until 2014 she was a tutor for deaf and mute children and came for regular medical check-ups; chest X-ray did not show any abnormalities.

**Initial examination:** moderately severe general condition, lucid. Body temperature: 36.7 °C. She can move unattended only near the bed. Skin examination shows regions of hyperpigmentation in natural folds of the body (Fig. 4a); skin tightness is extremely low. Visible mucosa: point hyperpigmentations on the tongue (Fig. 4b). No body hair in axillary creases and on the pubis. Subcutaneous fat is feebly marked (height: 165 cm, weight: 53 kg, BMI: 19.5). Respiratory rate: 18 respirations per minute. By percussion: clear pulmonary sounds in the projection of the lung tissue; by auscultation: vesicular breathing with individual dry rales in the interscapular space.

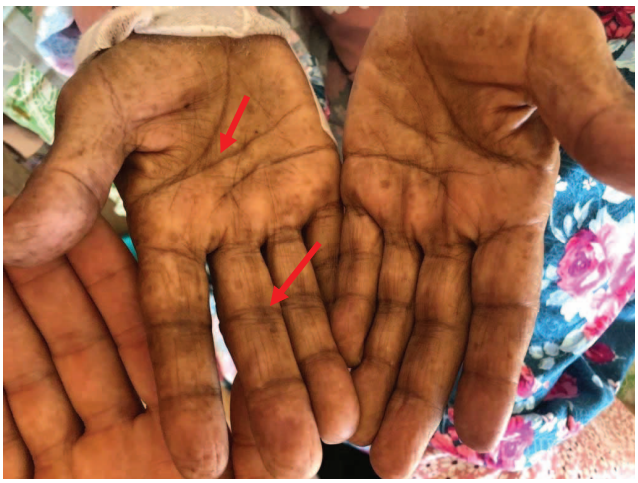

***Figure 4a.*** *Hyperpigmentation zones in natural body folds*

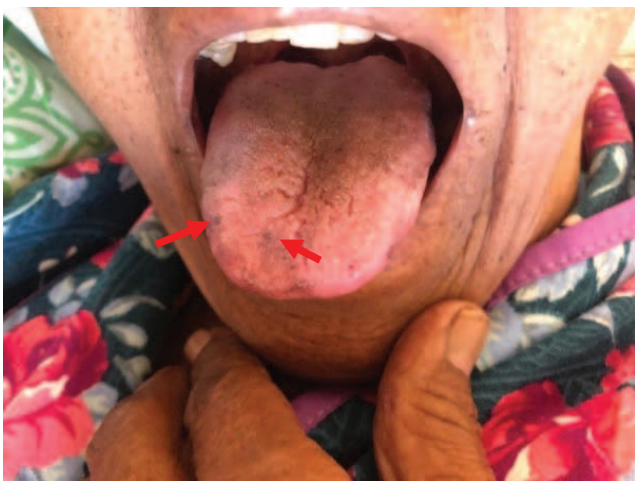

***Figure 4b.*** *Hyperpigmentation zones on the tongue*

Regular cardiac rhythm, muffled heart tones, no heart murmurs. A. radialis, a. dorsalis pedis pulse is symmetrical, with satisfactory volume. Pulse: 100 bpm, rhythic; BP: 80/50 mm Hg (D=S). When palpated, the abdomen is soft, sensitive in iliac region. The liver is within the costal arch. Bowel movements: tendency to constipations. Region of the kidneys: visually unremarkable. When palpated, the bladder is painless. Kidney punch is negative on both sides. Neurological status: speech and memory are normal, the patient is oriented to place and time, adequate, communicative.

**Examination results**

*ECG dd 05/10/2022:* Sinus, regular rhythm; heart rate: 69 bpm; electrical axis of the heart: vertical.

*Complete blood count dd 05/10/2022:* HCT — 36.6 % (35–47), Hb — 12.9 g/dL (11.7–16.1), RBC — 4.60 mln/μL (3.8–5.2), platelets — 309 ths/μL (150–400), WBC — 4.5 ths/μL (4.5–11), ESR — 14 mm/h (< 30), K — 4.7 mmol/L (3.5–5.1), creatinine — 48 mmol/L (49–50), glucose — 3.7 mmol/L (4.1–6.0), albumin — 36.8 g/L (37.5–50.1).

*Urinalysis dd 05/10/2022:* colour — light-yellow; clarity — not completely clear; specific density — 1.020, pH — 5.0, protein — 0.0, KET — 0.0, WBC — 0.0, salt — 0.0, bacteria — 0.0, mucous — +.

*Blood biochemistry dd 05/10/2013*: AST — 35 U/L (< 31), **glucose — 3.7 mmol/L** (4.1-6.0), **Na — 120 mmol/L** (136–145), **Cl — 88 mmol/L** (101–110), **creatine kinase — 1211 U/L** (<167).

First, the critically low sodium levels stand out, which is a life-threatening condition. Considering that the patient had pronounced asthenic syndrome, abdominal syndrome, skin and mucosa hyperpigmentation, hypoglycaemia, hyponatraemia, chloropenia, hypotonia, *addisonian crisis was suspected*. High creatine kinase levels show active myolysis in the patient, hence her complaints of muscle pain.

According to the clinical guidelines [1], the patient was prescribed hydrocortisone 100 mg as intravenous push four times daily, not waiting for laboratory test results for cortisol and adrenocorticotropic hormone (ACTH).

Hormone test results dd 05/10/2022: dehydroepiandrosterone sulfate (DHA-SO4) < 0.08 μmol/L (0.8–4.9), cortisol < 27.6 nmol/L (blood drawn before 10 am, reference range: 101.2–535.7), ACTH — 769.0 pg/mL (< 46), renin (plasma) — 121.1 μIU/mL (4.4–46.1), aldosterone — 15.0 pg/mL (25.2–392).

Plasma ACTH levels is more than 16-fold (!) higher than the upper limit of normal, while cortisol level is

below 140 nmol/L, which is a criterion to diagnose primary adrenal insufficiency. Also, elevated renin is a compensatory response to low aldosterone levels, according to the mechanisms of renin-angiotensin-aldosterone system (RAAS) functioning.

Once the acute condition was resolved, the following replacement therapy was initiated: hydrocortisone 10 mg in the morning, 5 mg at lunchtime, 5 mg in the evening; fludrocortisone 25–50 mg in the morning, with dose adjustment depending on well-being.

If a patient is diagnosed with PAI, diagnostic search should continue in order to identify the cause of adrenal damage [1]. According to the diagnostic algorithm of PAI, the autoimmune origin of adrenal insufficiency should be ruled out in the first instance. For this purpose, a test for anti-steroid-producing adrenal cell antibodies (AB) was performed.

*Test for anti-21-hydroxylase AB:* < 1:10 (reference range: <1:10). Therefore, anti-21-hydroxylase AB test came back negative.

Once the autoimmune origin of adrenal insufficiency was ruled out, adrenal computer tomography (CT) was performed (Fig. 5a).

*Adrenal computer tomography*. Adrenals: regular position; both adrenals are diffusely thickened up to 14 mm, with uneven structure due to numerous calcifications. Surrounding fat tissue: unremarkable. Kidneys: regular position and shape, not enlarged. Contours are clear, uneven. Parenchyma structure is even. The renal collecting system is not dilated. No stones. Paranephric fat tissue: unremarkable. Inferior vena cava is distinguished and normal. Aorta: calcified walls. Retroperitoneal lymph nodes are not enlarged. Destructive bone changes in the lumbar spine, visible pelvic and hip bone sections are not detected.

*Conclusion.* CT signs of adrenal calcifications.

Given the CT pattern of adrenal calcifications and the family history of the patient, the decision was made to continue the diagnostic search for TB. According to the scientific references, enlarged adrenals are often a sign of an active infectious process, whereas minor atrophic changes and visible calcifications in adrenal cortex evidence a chronic process, which is most likely inactive [4].

Chest computer tomography (Fig. 5b).

Chest CT: S2 of the right lung shows focal cord-like thickening adjacent to the costal pleura; the surrounding pulmonary tissue is unchanged. S1 of the right lung has a single focus with unclear even margins. Apical adhesions on both sides. The lung pattern is trackable and is not deformed. The lumen of the trachea, main and segmental bronchi is trackable and is not deformed. Pleural spaces do not hold any effusion or free gas. Mediastinal organs and soft tissue: clinically unremarkable.

Conclusion. CT signs of focal changes in the upper lobes of both lungs; differentiation should be made between focal TB and post-infection changes.

To rule out TB, the patient underwent Mantoux test, DST and sputum analysis for M. tuberculosis.

Mantoux test and DST results: papules of up to 30x30 mm with subcutaneous haemorrhage and marked swelling.

Sputum analysis for M. tuberculosis: negative.

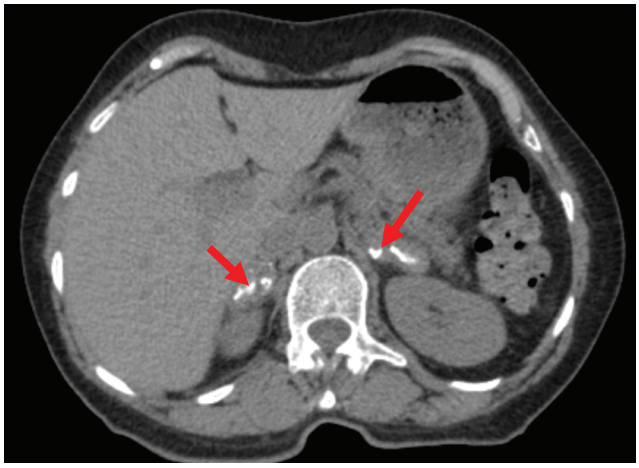

***Figure 5a.*** *Computed tomography (CT) of the adrenal glands*
***Arrows indicate multiple adrenal calcifications***

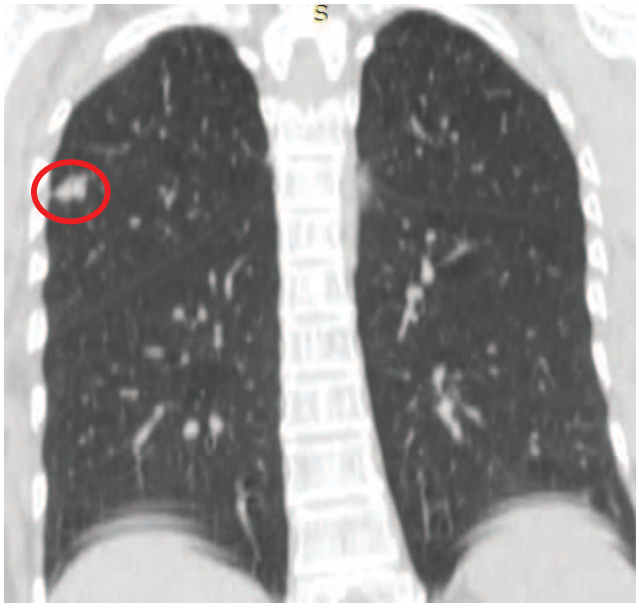

***Figure 5b.*** *Computed tomography of the chest organs*
***A single focus with blurred smooth contours of the apical segment of the left lung is highlighted in color***

Once M. tuberculosis infection was confirmed, the patient was referred to a TB specialist. Diagnosis: *Focal TB of the right lung, M. tuberculosis infiltration phase. M. tuberculosis (–). Adrenal tuberculosis. Primary adrenal insufficiency, medically compensated.*

Upon discharge, the patient was prescribed replacement therapy with hydrocortisone: hydrocortisone 10 mg in the morning, 5 mg at lunchtime, 5 mg in the evening; fludrocortisone 25 mg in the morning; she was also provided with recommendations on dose adjustment depending on various real-life situations and possible scheduled therapy according to clinical guidelines (in case of addisonian crisis, fever, severe emotional stress, minimally invasive surgeries, etc.). Besides, scheduled hospitalisation to TB hospital was recommended.

On July 24, 2023, the patient was hospitalised to the National Medical Research Centre for Phthisiopulmonology and Infectious Diseases of the Ministry of Health of the Russian Federation for antituberculosis therapy (rifampicin 450 mg in the morning before meal; isoniaside 300 mg in the morning after meal; pyrazinamide 1,500 mg in the morning after meal; ethambutol 1,200 mg after lunch). After bronchoscopy on August 2, 2023, the patient started complaining of nausea, vomiting, general weakness again. In inpatient settings, the patient was prescribed prednisolone tablets; since no significant therapeutic effects were observed, the patient visited the hospital of the Central Union of Consumer Cooperatives of the Russian Federation for replacement therapy adjustment regarding PAI and dose selection for antituberculosis therapy initiation.

Rifampicin is a potent cytochrome P-450 inducer, engaged in adrenocorticosteroid metabolism, resulting in accelerated glucocorticoid metabolism and reduced glucocorticoid effects [5, 6]. Therefore, the dose was increased for the duration of antituberculosis therapy.

The patient was discharged in satisfactory condition, with stable haemodynamics. The following replacement therapy with hydrocortisone was selected: 15 mg in the morning, 7.5 mg at lunchtime, 7.5 mg in the evening; fludrocortisone: 50 mg in the morning. The patient underwent a repeated training in self-correction of the hormone therapy. The antituberculosis therapy recommended for six months: isoniaside 300 mg in the morning; pyrazinamide 1,500 mg in the morning; ethambutol 1,200 mg at lunch.

The patient completed the antituberculosis therapy and is followed-up by a TB specialist (visits at least two times a year) and thyroid specialist (consultations twice a year).

## Discussion

Primary adrenal insufficiency and addisonian crisis are often ignored by medical professionals due to their non-specific symptoms. Clinical presentation, i.e. body weight loss, general weakness, abdominal discomfort can mislead clinicians, and patients are referred to a wrong ward with clinical signs of acute abdomen, irritable bowel syndrome, etc. In this case study, the patient was followed up for irritable bowel syndrome at the place of her residence, and only after her condition deteriorated, and the patient was hospitalised with symptoms of addisonian crisis, the correct diagnostic hypothesis was made. PAI was finally diagnosed eight months after the onset of clinical symptoms.

Despite rare cases of tuberculosis as a cause of PAI, clinicians should take into account the patient's epidemiological anamnesis and include TB verification methods (DST, Mantoux test, chest CT, Quantiferon test, etc.) to the diagnostic algorithm.

In their clinical observation, Van Haren Noman S, Visser H et al. (2018) described adrenal tuberculosis. Upon hospitalisation, the patient was complaining of abdominal discomfort and weigh loss. The final diagnosis was made two months later after CT, the results of which showed enlarged adrenals. A hormone test, which confirmed adrenal insufficiency, was preformed after X-ray imaging. The authors also discuss challenges with PAI diagnosis due to non-specific symptoms and characteristics of simultaneous therapy of adrenal insufficiency and adrenal tuberculosis. In this case study, once antituberculosis therapy was initiated, hydrocortisone and fludrocortisone doses were increased three- and two-fold, respectively [6]. Besides, antituberculosis therapy initiation caused adrenal insufficiency decompensation, requiring repeated hospitalisation for addisonian crisis and subsequent correction of replacement therapy.

In selecting a dose of hormone replacement therapy, it is essential to take into account any comorbidities. Antituberculosis drugs accelerate glucocorticosteroid metabolism, reducing their blood levels, and clinicians have to adjust the dose empirically, based on the patient's well-being and blood pressure values [1].

Zhao N, Gao Y et al. (2021) described autopsy results of a patient, who died of addisonian crisis. A 45-year-old male patient was hospitalised with finger trauma and bleeding. On day 13 of hospitalisation, the patient's condition suddenly deteriorated: vomiting, blood pressure 104/70 mm Hg, hypoglycaemia, hyponatraemia (108.2 mmol/L (!)). Brain CT confirmed

brain swelling caused by hyponatraemia. Hormone test results: ACTH — 855.00 pg/mL, cortisol — < 1.00 mg/dL. A microscopic examination of the lung tissue sample showed caseous necrosis with calcifications and granulomas in the lower lobe of the right lung. The microscopic examination also showed caseous necrosis with calcifications in the left adrenal. The patient did not have typical skin hyperpigmentation and symptoms of PAI. This case study illustrates that the patient developed addisonian crisis amidst an acute clinical situation, which requires higher glucocorticosteroid production (trauma, bleeding). Most likely, symptoms of adrenal insufficiency before the incident were non-specific and did not raise red flags in the patients and his doctors. Adrenal insufficiency was not diagnosed before hospitalisation. In our case study, addisonian crisis was most likely caused not only by drug-drug interaction, but also by diagnostic procedures (bronchoscopy), which can also lead to decompensation.

After replacement therapy selection, the patient should be trained in the principles of hormone replacement therapy selection depending on various situations, which are physiologically associated with higher blood glucocorticoid levels (stress, fever, minor invasive interventions, diagnostic procedures, etc.) [1]. In this case study, drug-drug interactions between hormone replacement therapy and antituberculosis drugs were not taken into account, and doses were not adjusted, causing addisonian crisis [7].

## Conclusion

This case study illustrates challenges with timely diagnostics of adrenal insufficiency. Currently, there are up-to-date methods to reliably verify the diagnosis; and drug therapy regimens have been developed. However, referrals of patients with addisonian crisis to wrong wards show low level of awareness among medical professionals. A speedy diagnosis is still an issue among various doctors.

**Вклад авторов:**

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

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**Author Contribution:**

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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