



# COVID-19 in cystic fibrosis patients

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## Abstract

Since the beginning of the COVID-19 epidemic, the European cystic fibrosis society (ECFS) has decided to launch a special ECFS-COVID-19 program to collect information on the of COVID-19 characteristics in the patients with cystic fibrosis (CF). The results of the program should help timely and efficiently provide the patients with CF with the necessary care. Initially, it was assumed that COVID-19 would be severe in CF patients. **The aim.** To assess the prevalence and characteristics of COVID-19 in patients with cystic fibrosis (CF) in the Russian Federation (RF). **Methods.** 6 cases (4 children and 2 adults) of COVID-19 in Russian CF patients were analyzed. **Results.** There are 405,843 infected with SARS-CoV-2 in Russia, the incidence of coronavirus infection in Russia was 1.4 cases per 1 thousand people. According to the Ministry of Health of the RF, as of December 2019, there were 3,931 patients with CF (2,823 children and 1,108 adults). The incidence of COVID-19 was 1.5 per 1000 patients with CF (1.4 : 1,000 for children and 1.8 : 1,000 for adults). The incidence was not higher than in the General population. The diagnosis of COVID-19 was confirmed in 4 boys and 2 women, 3 of the patients were infected with *Pseudomonas aeruginosa* and 2 – with *Achromobacter spp.* Mild disease was seen in 5 patients including all the children. Pneumonia was registered in 3 patients. One child with COVID-19 had abdominal syndrome. 2 patients – 1 adult and 1 child – needed in-patient care. Additional antibiotics were given to 4 patients, 2 of them received i/v antibiotics. One adult patient was on the lung transplantation waiting list. This woman had long-term oxygen therapy and BiPAP noninvasive respiratory support before the infection with SARS-CoV-2, FEV<sub>1</sub> was 24%<sub>pred</sub>. **Conclusion.** Despite the fact that patients with CF are at risk of severe COVID-19, to date, in the described cases, COVID-19 infection has not led to a significant deterioration of the symptoms of CF. Not a single fatal outcome in Russian patients with CF has been recorded.

**Key words:** cystic fibrosis, COVID-19, incidence, pneumonia, antibacterial therapy.

**Conflict of interests.** The authors declare the absence of conflict of interests.

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# COVID-19 у больных муковисцидозом

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## Резюме

С начала эпидемии COVID-19 Европейским обществом по муковисцидозу (*European Cystic Fibrosis Society* – ECFS) инициирована специальная программа наблюдения ECFS-COVID-19 для сбора информации по особенностям течения COVID-19 у пациентов с муковисцидозом (МВ). Ожидается, что данная программа должна помочь своевременно и качественно оказывать необходимую помощь пациентам с МВ. Первоначально предполагалось, что на фоне МВ COVID-19 протекать будет тяжело. **Целью** исследования явилась оценка распространенности и течения COVID-19 у пациентов с МВ в Российской Федерации. **Материалы и методы.** Проанализированы 6 (4 ребенка и 2 взрослых) случаев заболевания COVID-19 у российских пациентов с МВ. **Результаты.** В Российской Федерации SARS-CoV-2 инфицированы 405 843 человека, заболеваемость коронавирусной инфекцией составила 1,4 случая на 1 тыс. населения. Учитывая численность пациентов в регистре МВ (по данным Министерства здравоохранения Российской Федерации, на декабрь 2019 г. в регистр включен 3 931 пациент: 2 823 ребенка и 1 108 взрослых), заболеваемость SARS-CoV-2 составила около 1,5 на 1 тыс. пациентов с МВ (1,4 : 1 000 – для детей и 1,8 : 1 000 – для взрослых), что не превышает таковую в общей популяции. Заболеваемость COVID-19 на 01.08.20 среди пациентов с МВ составила 3,8 (0,38 %) на 1 тыс. пациентов (2,1 : 1 000 – для детей и 8,8 : 1 000 – для взрослых). Диагноз COVID-19 подтвердился у 4 детей (все мальчики) и 2 взрослых женщин, при этом 3 больных были инфицированы *Pseudomonas aeruginosa*, 2 – *Achromobacter spp.* В легкой форме заболевание протекало у 4 из 6 пациентов, включая всех детей, пневмония зарегистрирована у 3 пациентов. У одного из 4 детей с COVID-19 отмечался абдоминальный синдром при отсутствии респираторных проявлений; 2 пациента (1 взрослый и 1 ребенок) нуждались в стационарном лечении. Антибактериальная терапия назначена 4 пациентам, двум из них – внутривенно. Одна взрослая пациентка, объем форсированного выдоха за 1-ю секунду у которой составлял 24 %<sup>долж.</sup>, зарегистрирована в листе ожидания на трансплантацию легких, до заражения SARS-CoV-2 у нее проводились длительная кислородотерапия и неинвазивная респираторная поддержка BiPAP. При подтверждении коронавирусной инфекции она была выписана из больницы. **Заключение.** Несмотря на то что пациенты с МВ находятся в группе риска тяжелого течения заболевания, на сегодняшний день в описанных случаях COVID-19 инфекция не привела к значительному ухудшению состояния по основному заболеванию. У российских пациентов с МВ не зарегистрировано ни одного летального исхода.

**Ключевые слова:** муковисцидоз, COVID-19, заболеваемость, пневмония, антибактериальная терапия.

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COVID-19 cases have been reported in many countries around the world since February 2020. WHO declared a pandemic on March 11, 2020 [1]. Isolated cases of COVID-19 were reported in the Russian Federation as early as at the end of January 2020. The incidence is growing steadily from the second half of March.

Patients with cystic fibrosis (CF) are at risk for bacterial respiratory tract infections due to dysfunction of the CFTR (chloride) channel caused by CFTR gene mutations [2]. By the Decree of the Government of the Russian Federation No.432 dated April 3, 2020, the routine medical exams and check-ups were suspended temporarily to ensure patient safety. The Order of the Healthcare Ministry of Russia No.198n dated March 19, 2020 recommended the management of healthcare institutions to postpone the scheduled in-patient medical services, if possible. In this regard, the health care professionals and the patient community were extremely concerned about changes in patient care and the threat of COVID-19. There was an urgent need to understand the risk of infection and the clinical course of coronavirus infection in CF patients. Outpatient CF treatment became highly relevant.

The updated reports from WHO [3] show that most patients (about 80%) recover spontaneously without the need for hospitalization. About one in five cases of COVID-19 is severe and is associated with respiratory failure or acute respiratory distress syndrome (ARDS), which can be lethal.

The disorders of the bronchopulmonary system in CF patients are characterized by airway obstruction, chronic bacterial infection, and inflammation. These processes damage the lung tissue and lead to bronchiectasis. Almost

all lethal outcomes are caused by respiratory disorders. The bronchopulmonary conditions increase the predisposition to *Pseudomonas aeruginosa* infection, which occurs in 53% of patients with CF [4].

Neutrophils are the primary cells of the inflammatory process in CF. They infiltrate the airways, damage the lung tissue, and cause the obstruction. Cytokine inflammation is also typical for CF [2, 5]. Thus, both CF and COVID-19 are characterized by neutrophilic inflammation and cytokine release, which determine the severity of damage to the respiratory tract and the vascular system [6].

The diagnostic criteria for the cytokine release syndrome in COVID-19 have not been developed yet. It should be suspected in patients with a rapid deterioration in lung function in combination with increased levels of C-reactive protein (CRP) and ferritin, cytopenia (thrombocytopenia and lymphopenia), coagulopathy (low platelet and fibrinogen levels and increased D-dimer level), signs of liver damage (increased activity of lactate dehydrogenase and aminotransferases) [7]. Dornase alpha is traditionally used in CF patients to eliminate the extracellular traps and digest the extracellular DNA that is present in the viscous bronchial secretions in large quantities.\* Dornase alpha is being studied as a potential component of combined therapy of COVID-19\* [7].

The European Cystic Fibrosis Society (ECFS) launched the ECFS-COVID-19 surveillance program in April 2020 to collect information on the course of COVID-19 in patients with CF. It was decided to collect the data through national registers. In our country, the national register of CF patients was created in 2011, and its data are included in the European Cystic Fibrosis Society Patient Registry.

\* Voronkova A.Ju. [Clinical efficacy and safety of dornase alfa ("Pulmozyme") in the treatment of children with cystic fibrosis]: Thesis for a candidate degree in medical sciences. Moscow; 2004 (in Russian).

Eight data reports have been published already [8]. The Organizing Committee of the Cystic Fibrosis Patient Registry in the Russian Federation decided to support the European surveillance program ECFS-COVID-19.

Initially, COVID-19 was assumed to take a severe course in patients with CF. However, the studies have shown that the disease is less common and is often mild in CF patients.

A multinational report to characterize SARS-CoV-2 infection in people with cystic fibrosis included 40 patients from 8 countries – Australia, Canada, France, Ireland, Netherlands, New Zealand, UK, and USA. The report showed (as of April 13, 2020) that the incidence of COVID-19 in patients with cystic fibrosis (0.07%) was lower than the average prevalence in the studied countries (0.15%) [9].

Another study described 30 cases of COVID-19 in CF patients (Lombardy (Italy), France, Germany, Spain). No deaths have been reported by April 15, 2020. The absence of fatal outcomes among CF patients by April 2020 may be associated with the relatively low incidence of COVID-19, the effective self-isolation methods, as well as with the young age of patients. But it is too early to make any final conclusions [10].

Study objective: To assess the prevalence and course of COVID-19 in patients with cystic fibrosis (CF) in the Russian Federation.

## Materials and methods

We analyzed 6 Russian patients with CF (4 children and 2 adults) with COVID-19. Inclusion criteria: diagnosis of cystic fibrosis, a positive PCR-test for SARS-CoV-2 coronavirus RNA (or a positive test by another method), or a positive enzyme-linked immunosorbent assay for anti-SARS-CoV-2 IgG immunoglobulin [11]. Exclusion criteria: no laboratory confirmation of COVID-19 and no signed informed consent. The characteristics of patients with cystic fibrosis and COVID-19 are shown in Table 1.

## Results

Per the study objective, 6 cases of COVID-19 among patients with cystic fibrosis were analyzed. 2 patients were over 18 years old.

### Case No.1

A boy born in 2015 lives in Moscow and is under the care of the CF department of the Children's Clinical Multidisciplinary Center of the Moscow Region and the Morozov Children's City Clinical Hospital. The child was diagnosed with CF at the age of 3 months based on the positive neonatal screening and the positive sweat test on a Nanodact device (120 mmol/L against the upper reference level of 50 mmol/L), confirmed by the genetic testing (a pathogenic homozygous variant of the *CFTR* *F508del* gene). The child had left-sided upper lobe pneumonia at 3 months of age. He was hospitalized for pseudo-Bartter

syndrome at 4 months of age. At 2 years of age, the chest X-ray showed distorted vascular markings and a peribronchial infiltration in the upper medial part of the left lung. The infiltrative changes were resolved after the treatment. *S. aureus* (MSSA) and *K. pneumoniae* were identified in sputum cultures for a long time. *P. aeruginosa* was first identified in August 2017. Inhaled sodium colistimethate and oral ciprofloxacin were administered to eradicate the bacteria. *P. aeruginosa* was identified again in September 2018 and 2019. MRSA was first identified in December 2018 and was detected in the cultures until May 2019, despite the antibiotics. *P. aeruginosa* was detected intermittently since September 2019. The boy received courses of inhalation therapy with sodium colistimethate 2 million units 2 times a day, oral ciprofloxacin for respiratory infection, and an alternate course of azithromycin. The basic therapy also includes dornase alpha, pancreatic enzymes, vitamins, ursodeoxycholic acid, and kinesiotherapy. No severe exacerbations of the chronic bronchopulmonary process and no hospitalizations were reported last year. The child was examined by an otolaryngologist for nasal polyps and by an allergist for allergic rhinitis associated with a history of sensitization to alder, birch, and house dust.

At the beginning of May 2020, the child developed abdominal pains, followed by vomiting and fever up to 39.3 °C the next day. The O<sub>2</sub> saturation was 98%. The child was examined by a pediatrician, who diagnosed an acute intestinal infection. The fever and abdominal pain persisted for 2 days. The doctor prescribed Enterofuril, sorbents, and daily azithromycin. Oropharynx and nasal swabs for PCR for COVID-19 were taken from all family members because both parents had malaise and subfebrile body temperature previously. The child received a positive result the next day. The second test also turned out to be positive, and the next two were negative. The child was dismissed after 21 days from the onset of the illness. The tests of both parents were negative.

### Case No.2

A child born in 2018, a resident of the North Caucasus Federal District, has been under the care of the Clinic of the Research Institute of Pediatrics of Federal State Autonomous Institution of the Ministry of Health of the Russian Federation of the Ministry of Health "National Medical Research Center for Children's Health" since August 2018 (the age of 4 months). The diagnosis was established by the neonatal screening and sweat test and confirmed by genetic testing (a homozygous pathogenic variant of the *CFTR* *W1282X* gene).

The child has a history of severe pseudo Bartter syndrome. *P. aeruginosa* was identified in culture from the upper respiratory tract, and the child received intravenous antibiotics therapy. The basic therapy included dornase alpha (inhalation), enzyme replacement therapy (Creon), ursodeoxycholic acid, vitamins, and inhaled colistimethate sodium.

The child had febrile fever for one day with no other symptoms in mid-May 2020. The SARS-CoV-2 infection was confirmed in his parents and his 4-month sister. The SARS-CoV-2 infection was confirmed by PCR in the patient. The chest X-ray showed no infiltrative changes. The blood lymphocyte level was 58%.

The treatment was outpatient and included azithromycin 10 mg/kg per day for 7 days in addition to the current medications. The control smears for PCR were taken on May 29 and 31, and the results were negative.

*Table 1*  
*Characteristics of the patients with cystic fibrosis and COVID-19*  
*Таблица 1*  
*Характеристика пациентов с муковисцидозом и COVID-19*

Parameter	Patients					
	1	2	3	4	5	6
Age, years	13	4	32	24	2	1
Sex	Male	Male	Female	Female	Male	Male
Pancreatic insufficiency	+	+		+	+	
FEV <sub>1</sub> before COVID-19, %			24	54		
BMI before COVID-19	15,2	15,8	19,8	16,7	19,4	16,9
Lung bacteriological status for 12 months:						
• <i>P. aeruginosa</i>		+	+		+	
• <i>S. aureus</i>	+	+				+
• <i>Achromobacter</i> spp.			+	+		+
• MRSA		+				
			Respiratory failure	Vasculitis		
Comorbidities						
CF treatment > 3 months:						
• Dornase alpha	+	+	+	+	+	+
• Inhalations with 7% NaCl	+	+				+
• Inhaled antibiotics		+	+	+		
• Tablet antibiotics			+	+		
• Inhaled GCs			+	+		
• Azithromycin		+	+	+		
Course of COVID-19:						
• Pneumonia	+		+	+		
• ARVI		+	+	+	+	+
• Abdominal syndrome		+				+
• Others						
			Hemoptysis			
Symptoms:						
• fever	+	+	+	+	+	+
• pharyngitis	+			+		
• rhinitis	+					
• increased cough	+		+	+		+
• diarrhea		+				+
• vomiting		+				
• abdominal pain		+				+
• fatigue		+	+	+		
Course of the disease						
• mild	+	+		+	+	+
• severe			+			
Treatment:						
• in-patient			+			+
• outpatient	+	+		+	+	
Therapy:						
NSAIDs			+	+		
Oral antibiotics	Azithromycin, Cefixime	Azithromycin	Azithromycin	Ciprofloxacin, Minolexine, Azithromycin	Azithromycin	
Duration (days)	15	≤ 7	14	10	≤ 7	16
Intravenous therapy			Meropenem / Ceftazidime / Amikacin			Ampicillin / Sulbactam
Hydroxychloroquine				+		
Antivirals						Interferon α2b
NIV (BiPAP, CPAP)			BiPAP			
CT lesion volume, %			25			
Diagnostics:						
• PCR (nasal and oropharyngeal swabs)	+	+		+	+	+
• Serum (antibodies)			+			
Outcome:						
• Recovery	+	+	+	-		+
• Ongoing treatment				+	+	

Note: FEV<sub>1</sub>, forced expiratory volume during the 1<sup>st</sup> second; BMI, body mass index; MRSA, Methicillin-resistant *Staphylococcus aureus*; CF, cystic fibrosis; GCs, glucocorticoids; ARVI, acute respiratory viral infection; NSAID, non-steroid anti-inflammatory drugs; NIV, noninvasive ventilation; BiPAP, Biphase Positive Airway Pressure; CPAP, Constant Positive Airway Pressure; CT, computed tomography; PCR, polymerase chain reaction.



Case No.3

A child (boy) born in 2019, living in Moscow, is under the care of the Morozov Children's City Clinical Hospital. Cystic fibrosis was diagnosed at the age of 2 months based on positive neonatal screening and positive sweat test and was confirmed by genetic testing (F508del/E92K). The fecal level of pancreatic elastase-1 was 96 µg/g.

*Achromobacter xylosoxidans* was identified in one culture at the age of 3 months. The antibiotic therapy included intravenous meropenem + amikacin + oral ciprofloxacin for 2 weeks, and inhaled fluimucil-antibiotic IT for 3 months. Only *S. aureus* (MSSA) was detected in the subsequent cultures. The basic therapy includes inhaled dornase alpha, 3% NaCl, ursodeoxycholic acid, and vitamins A, D, E, K. The boy received enzyme replacement therapy at a minimum dosage up to 1 year of age. The therapy was canceled after a repeated fecal level of pancreatic elastase of more than 200 µg/g.

The grandmother had ARVI symptoms 1 week before the COVID-19 onset in the boy. The grandmother's PCR test for COVID-19 was positive. The child had an acute onset of the disease with a fever up to 38.8 °C. He was examined by a pediatrician the next day, and a swab from the throat and nose was taken for the PCR test. Cough and hoarseness developed a day later. The smear was positive, and the child was hospitalized on the 3<sup>rd</sup> day of illness.

His state was of moderate severity upon admission. Pale skin, symptoms of intoxication, and decreased appetite were noted. The respiratory system showed difficulty in nasal breathing with mucous discharge and moderate pharyngeal hyperemia. The cough was rare and unproductive. The child had no dyspnea at rest. The breathing was harsh, no wheezing. The results of the total blood counts are shown in Table 2.

Urinalysis: all parameters were within the reference range. The blood biochemistry showed an insignificant elevation of AST (40 U/L) and the lipase level of 71 U/L. Other parameters were within the reference range. The tests for the coronavirus (COVID-19) were positive on days 4, 11, and 16.

**Table 2**  
**Results of the general blood test of a child born in 2019**  
**(clinical observation No.3) in dynamics**  
**Таблица 2**  
**Результаты общего анализа крови ребенка 2019 года**  
**рождения (клиническое наблюдение № 3) в динамике**

Parameter	Day of the illness		
	3 <sup>rd</sup> (admission)	8 <sup>th</sup>	13 <sup>th</sup>
Hemoglobin, g/L	116	119	116
Hematocrit, %	37.9	40	39.7
Red blood cells, 10 <sup>12</sup> /L	4.58	4.84	4.8
White blood cells, 10 <sup>9</sup> /L	7.2	11.5	6.4
Neutrophils, %	13.5	3.7	18.9
Lymphocytes, %	82.8	92.5	77
Monocytes, %	3.7	3.8	4.1
Platelets, 10 <sup>9</sup> /L	328	441	450
ESR, mm/h	22	5	2

Note: ESR, erythrocyte sedimentation rate.

The chest X-ray on the 4<sup>th</sup> day of illness showed a slight heterogeneous decrease in pneumatization of the right upper internal parts without clear contours. The pulmonary vascular markings were increased and distorted, prominence of the interstitial pattern was increased. The right root was dilated, poorly structured, and not visible on the left behind the shadow of the mediastinum. The chest X-ray on the 11<sup>th</sup> day of illness showed no focal infiltrative changes. The pulmonary vascular markings were increased and distorted.

Diagnosis: COVID-19, the virus was confirmed. SARS-CoV-2 infection, moderate right-side pneumonia, RF-0.

IV ampicillin/sulbactam for 9 days, and rectal suppositories with interferon alpha-2b 500,000 IU/day were prescribed. The mother had a positive smear on day 18. The child was discharged with improved symptoms and isolated at home.

Case No.4

A boy born in 2006 and living in the Leningrad Region is under the care of the Leningrad Regional State Budgetary Health Care Institution "Children's Clinical Hospital".

The diagnosis of cystic fibrosis was established by a positive sweat test and the reduced level of pancreatic elastase. The child had recurrent bronchitis from 7 months or age. At the age of 10 months, he had surgery for congenital heart disease, a ventricular septal defect. *S. aureus* is identified in the cultures from 2 years of age. In 2019, computed tomography showed bronchiectasis in S 2, 3, 4, 5 of the right lung and S 5 of the left lung. Spirometry indices were normal: FEV<sub>1</sub> – 85%; SatO<sub>2</sub> – 95%. The child has 3 – 4 exacerbations per year associated with ARVI and received oral antibiotics. The basic therapy included pancreatin, ursodeoxycholic acid, inhaled dornase alpha, vitamins D, A, E, K, and nutritional support.

The coronavirus disease was mild with symptoms of fever, pharyngitis, rhinitis, and increased cough. The X-ray revealed right lower lobe pneumonia. The PCR test for coronavirus by (COVID-19) was positive. Azithromycin for 5 days and the cefixime for 10 days were prescribed in addition to the basic therapy of CF.

Case No.5

The patient was born in 1987. She has been under the care of the Research Institute of Pulmonology and the D.D.Pletnev City Clinical Hospital under the Moscow Department of Health since 2009.

The patient had bronchitis from early childhood. CF was diagnosed at the age of 15 based on the clinical picture. She had recurrent bronchitis from early childhood. A right-sided upper lobectomy was performed in 1995. The respiratory tract was infected with *P. aeruginosa* since 1995. The diagnosis was confirmed by a positive sweat test (sweat chlorides 62,76 mmol/L). The genetic testing identified pathogenic variants of the *CFTR* gene: *CFTR*dele2,3 and 3849+10kbC>T. In recent years, the patient's condition deteriorated: the number of respiratory episodes increased, she developed shortness of breath, hemoptysis, reduced periods of remission after antibiotic therapy, and more frequent need for such treatment. The patient is on noninvasive ventilation in a protective mode since the summer of 2015 as the

part of kinesitherapy. The patient developed hypoxemic respiratory failure in the autumn of 2017 and was prescribed oxygen therapy. A gastrostomy was installed in January 2019. The patients gained about 10 kg of body weight within a year of nocturnal hyperalimentation. The patient was included in the waiting list for lung transplantation due to respiratory failure, low respiratory function ( $FEV_1$  within 20 – 27% of the reference value since 2016), and more frequent episodes of bronchopulmonary exacerbations in spring 2019. She receives daily inhalations of dornase alpha, a short-acting bronchodilator, budesonide/formoterol, and ambroxol, courses of inhaled tobramycin and colistimethate sodium, ursodeoxycholic acid preparations, omeprazole, and azithromycin as anti-inflammatory therapy. She also receives intravenous antibiotics 3 – 4 times a year and oral antibiotics every three months.

The cough, hemoptysis, and shortness of breath have become more severe in association with fever, and the volume of purulent sputum has increased to 100 mL/day since the second half of April 2020. Intravenous antibiotic therapy on an outpatient basis had no significant effect. This treatment failure, previous contact with a COVID-19 patient, and the severe baseline condition of the patient required inpatient treatment.

The general state was of moderate severity upon admission.  $SpO_2$  was 85% on room air and 92% with  $O_2$  – 4 L/min. The respiratory rate was 24 per minute. The blood pressure was 115/65 mm Hg. The heart rate was 88 per minute. Influenza was ruled out by the express test immediately upon admission, and nasal and oropharyngeal swabs were taken to test for COVID-19. The laboratory tests showed that the lymphocyte level was 15% with the number of leukocytes of  $7.6 \times 10^9$ , and the level of C-reactive protein was 83.0 mg/L. The chest CT (Figure 1) on April 29, 2020 showed that the volume of the right lung is reduced due to the upper lobectomy. The right upper part (S6) showed an area of pronounced pneumopleurofibrosis associated with a bullous transformation with a bulla size up to 52 mm.

The left upper lobe contained bullae up to 16 mm, one of them with a horizontal content level. Focal pneumosclerosis were seen in all parts of both lungs, but more on the right. Dilation of bronchi of III/IV degree with cylindrical and sacular bronchiectasis was reported in association with ground-glass

opacities, mainly in the middle and lower right lobes, as well as in the upper and lower left lobes. Bronchiectasis were of various sizes, with perifocal infiltration, and some contained fluid. The mediastinum was structurally intact and displaced to the right. The trachea and the main bronchi were not deformed. The heart was in the standard location; the configuration was intact. The heart chamber sizes were regular. The thoracic aorta was intact. The diaphragm is in the normal location, the contours are even and clear. The pleural cavities were intact. Lymphadenopathy was not reported. The soft tissues and chest bone structures were intact. Conclusion: History of right-sided upper lobectomy. CT picture of cystic fibrosis. Bullae in both lungs. CT signs of suspected COVID-19 infection (the correlation with clinical and laboratory data have not been established).

CT scan on May 11, 2020 (Figure 2) showed persistent ground-glass opacities, primarily in the lower parts of the lungs. The upper left lobe contained bullae up to 16 mm, no fluid levels were detected. Otherwise, the CT findings were unchanged. Conclusion: CT signs of viral pneumonia. The intensity of typical COVID-19 signs complies with CT degree 1 (mild). History of right-sided upper lobectomy. CT picture of cystic fibrosis. Bullae in both lungs.

The PCR tests for COVID-19 with smears that were taken on the day of admission and on May 02, 2020 turned out to be negative. The patient had a serum test for IgM and IgG antibodies to the virus. The results confirmed COVID viral infection: IgM was 2.82 U/mL (the reference range is 0 – 0.99), IgG was 143.17 U/mL (the reference range is 0 – 10).

The 14-day therapy included intravenous meropenem, ceftazidime, tranexamic acid, and paracetamol; inhaled dornase alpha, budesonide/formoterol, and sodium colistimethate; oral azithromycin, ursodeoxycholic acid, omeprazole, and acetylcysteine. The patient also received noninvasive ventilation and oxygen therapy. The nocturnal hyperalimentation via the gastrostomy was continued.

The patient improved during the treatment. The body temperature steadily returned to normal, the systemic inflammation regressed, the intensity of purulent-obstructive bronchitis decreased, the hemoptysis was resolved, and the severity of respiratory failure decreased ( $SpO_2$  – 92%).

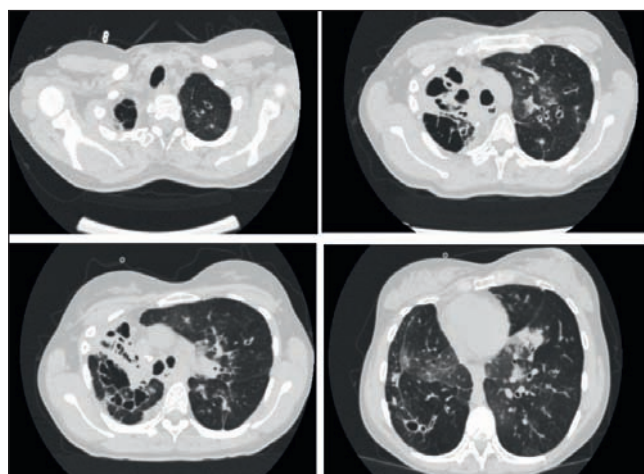


Figure 1. Computer chest tomography of the patients (case 5) dated 29.04.20

Рис. 1. Компьютерная томография органов грудной клетки пациентки (клиническое наблюдение № 5) от 29.04.20

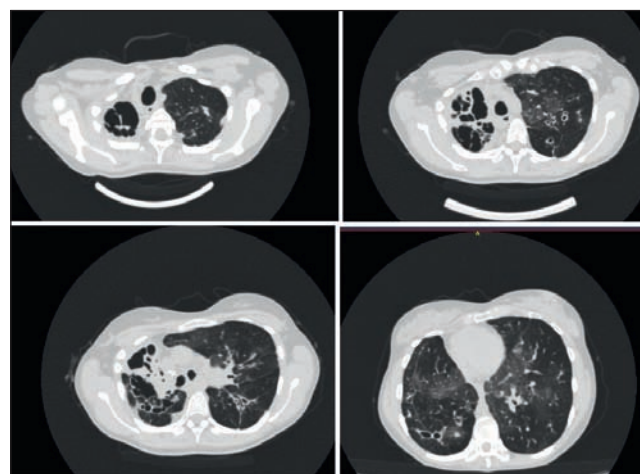


Figure 2. Computer chest tomography of the patients in dynamics (5 cases) dated 11.05.20

Рис. 2. Компьютерная томограмма в динамике (клиническое наблюдение № 5) от 11.05.20

## Case No.6

The patient was born in 1995. She has been under the care of the Research Institute of Pulmonology and the D.D.Pletnev City Clinical Hospital under the Moscow Department of Health since 2013.

She was diagnosed with cystic fibrosis at the age of 3 years based on the typical clinical picture (pancreatic insufficiency from the first weeks of life) and a positive sweat test. The patient had a respiratory tract infection with *P. aeruginosa* from 3 years of age, and *Pseudomonas alcaligenes/Achromobacter spp.* from 12 years of age. The patient received outpatient intravenous antibiotic therapy every three months, and oral antibiotic treatment twice a year. The patient received daily inhalations with hypertonic NaCl solution, dornase alpha, inhaled mannitol, budesonide/formoterol, thiamphenicol glycinate acetylcysteine, and receives oral prednisolone, pancreatin, ursodeoxycholic acid, ambroxol hydrochloride, vitamins, and alternate azithromycin.

The patient deteriorated in early May 2020. The symptoms included increased coughing and shortness of breath, and body temperature of 38.0 °C. COVID-19 was diagnosed in the patient's father, who lives with her. The repeated swabs (PCR) from the nose and oropharynx tested positive and confirmed the diagnosis of COVID viral infection.

The treatment was outpatient, considering normal oxygen status ( $\text{SpO}_2$  – 97%),  $\text{FEV}_1$  – 58%, and insignificant symptoms of intoxication. The therapy included daily azithromycin, ciprofloxacin, and minolexin together with inhalations of dornase alpha twice daily.

The patient improved. The body temperature steadily returned to normal on the 5<sup>th</sup> day of therapy, and the respiratory symptoms improved.

## Discussion

405,803 patients with SARS-CoV-2 have been registered in Russia by May 31, 2020. By this date, 6 CF patients with COVID-19 were identified. Their medical history is discussed in this article. 15 cases of the coronavirus infection were registered in patients with CF (6 children and 9 adults) by August 01, 2020.

3,931 patients (2,823 children and 1,108 adults) with cystic fibrosis were registered in Russia in the register of the Ministry of Health of the Russian Federation as of December 2019. The incidence of COVID-19 among them was 1.5 per 1,000 patients (0.15%) (1.4 : 1,000 for children and 1.8 : 1,000 for adults), which is higher than 0.07% in Europe on April 13, 2020, according to a European study [12].

At first, COVID-19 was reported in children with CF more often as compared to the adults (4 vs 2). This fact can be explained with the predominance of children among CF patients of the Russian Federation [3]. In European countries, adults account for 50% or more of the CF population [8]. The COVID-19 statistics have changed in Russia by August 01, 2020. The proportion of adults with CF and COVID-19 is now higher, as it is in other countries.

According to WHO, COVID-19 is rare and milder in the general pediatric population [13]. This trend is also observed in patients with cystic fibrosis. The state of 5 out

of 6 patients that are discussed in this publication was mild (including all children). Pneumonia was diagnosed only in 3 patients. One of the four children had abdominal syndrome, which is typical for children [13]. 2 patients (adult and child) required hospitalization. 4 patients received antibiotic therapy, 2 of them – intravenously. One adult patient was on NIV. This patient suffered from hypoxemic respiratory failure and received long-term oxygen therapy prior to the infection with SARS-CoV-2. In general, our findings comply with the reported course of COVID-19 in CF patients in other countries [9, 10].

According to the data from the European Cystic Fibrosis Society ECFS-COVID-19 surveillance program as of May 27, 2020, COVID-19 cases in CF patients have been reported in 13 out of 35 countries that participate in the data collection. 79 patients were reported, including 72 cases with a detailed description (34 men and 38 women, 16 children), including Russian patients. 17 patients were asymptomatic, 27 had mild disease, 7 had severe disease, and 3 were critically ill. In total, 41 patients were hospitalized. 6 of them needed intensive care, 2 were ventilated, and 3 died [12].

As of July 29, 2020, 128 cases of the disease were registered in 18 countries (men : women – 69 : 59) out of 38 European countries that submitted information to the ECFS-COVID-19 program. These cases included 33 children (<https://www.ecfs.eu/covid-cf-project-europe>). 80 patients had mild disease, 6 patients were severe, and 5 patients were critically ill. No other fatal outcomes were reported, so 3 patients died in total. 22 patients were asymptomatic. 68 patients were hospitalized, 3 were on mechanical ventilation, and 1 patient needed ECMO. The five most common symptoms were fever, cough, fatigue, increased amount of sputum, and headache.

## Conclusion

Thus, both foreign and Russian data show that most patients with CF develop a mild course of COVID-19. The incidence of COVID-19 is not higher than in the general population, which is associated with both the young age of patients, their early and strict isolation, skills in preventing infection, and, possibly, with basic therapy. Different researchers suggest that the following drugs protect patients with CF from the severe course of COVID-19: dornase alpha, azithromycin used for anti-inflammatory purposes against chronic *P. aeruginosa* infection, and frequent courses of antibiotic therapy [9, 10]. Further data will help to draw more accurate conclusions.

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