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COVID-19 and children

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Abstract

In December 2019, the world became aware of an epidemic of a very severe infection caused by a new coronavirus. Later, WHO declared a pandemic. The pediatricians were ready for the worst. The novel infection was expected to promptly spread among the most vulnerable population, children. But the clinicians soon understood that the situation is unbelievable: adults develop severe disease and die, while the children remain almost excluded from the infection spreading. 9 months have passed in the "new reality". The humankind was learning to respond to the new infection challenge by empirical search for the potential therapeutic and diagnostic solutions and conducting wide clinical studies in parallel. A few questions have been answered because of consolidated and/or isolated actions of researchers and clinicians at the national, regional, and international levels. However, most aspects of how the new coronavirus affects the humans, including children, is still unclear and our knowledge of these aspects cannot be transferred in the routine practice. This review presents latest understanding of the course of the novel coronavirus infection in children, its treatment and outcomes.

Key words: children, COVID-19, SARS-CoV-2, anosmia, hyposmia, ageusia, dysgeusia, decreased cognitive functions, ferritin, D-dimer, Hac1, troponin, *pro*BNP, creatinine.

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COVID-19 и дети

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Резюме

В декабре 2019 г. началась эпидемия тяжелой инфекции, вызванной новым представителем семейства коронавирусов, позже объявленная Всемирной организацией здравоохранения пандемией. Педиатры приготовились к самому худшему – быстрому распространению новой коронавирусной инфекции (КВИ) среди самых уязвимых – детей, однако вскоре осознали, что впервые столкнулись с невероятной ситуацией, когда тяжело заболевали и умирали люди взрослые, а дети оставались практически вне распространения инфекционного процесса. В течение 9 мес. жизни в новой реальности человечество училось реагировать на новый инфекционный вызов в процессе его развития, чаще эмпирически нащупывая возможные лечебные или диагностические интервенции и параллельно широким фронтом осуществляя клинические исследования. В результате иногда разрозненных, иногда консолидированных действий ученых и клиницистов на страновом, региональном и международном уровнях на некоторые вопросы уже получены ответы, однако бóльшая часть информации, касающейся воздействия нового коронавируса на организм человека, в т. ч. ребенка, пока еще недоступна для внедрения в рутинную практику. В данном обзоре представлены современные представления о течении, лечении и исходах новой КВИ у детей.

Ключевые слова: дети, COVID-19, SARS-CoV-2, аносмия, гипосмия, агевзия, дисгевзия, снижение когнитивных функций, ферритин, D-димер, HAc1, тропонин, *pro*BNP, креатинин.

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Pediatricians know coronaviruses very well as causative agents of seasonal viral infections in children [1]. Most of these infections are caused by group 1 alpha-coronaviruses (HCoV-229E, HCoV-NL63) or line A group 2 beta-coronaviruses (HCoV-OC43, HCoV-HKU1). Such infections have been described in both children and adults in the second half of the 20th century and in the beginning of the 21st century. For example, a case of a boy from the United Kingdom was published in the 1960s. Group 1 alpha-coronavirus was identified in this patient. This coronavirus was first described as B814 isolate but was later defined as HCoV-229E. Another clinical case described US medical students (from the University of Illinois) who had similar symptoms of an acute respiratory infection with the same confirmed pathogen. A case of bronchiolitis in 7- and 8-month infants was published

in the Netherlands in 45 years. The condition was caused by the HCoV-NL63 coronavirus from the same subgroup of group 1 alpha-coronaviruses. In 1967 – 1972, the US National Institutes of Health reported several cases of ARI in adults that were caused by HCoV-OC43, a line A group 2 beta-coronavirus. A case of pneumonia in a 71-year-old Hong Kong resident caused by HCoV-HKU1, a line A group 2 beta coronaviruses, was published in 2004. In general, all the described cases had a moderate course and no lethal outcomes. Most patients were male [1].

The Russian and foreign pediatricians face a few cases of coronavirus infections in children with mild acute respiratory symptoms every season in the routine clinical practice. However, some children with coronavirus infection may develop a Kawasaki syndrome within 2 – 3 weeks. This complication is more often observed in Asian patients (approximately ⅔ of the cases) [2]. Veterinarians also regularly treat coronavirus infection in pets. The animals mostly show gastrointestinal symptoms and are infected with different types of coronaviruses as compared to humans [3].

Thus, humanity has lived with the idea that coronaviruses do not pose a danger to people, including children, until the early 2000. In 2003 – 2004, China has seen an outbreak of atypical pneumonia caused by SARS-CoV, a line B group 2 beta-coronavirus. This outbreak prompted a fresh look at this family of RNA viruses. The coronavirus infections are considered life-threatening after the outbreak of Middle East respiratory distress syndrome 8 years later in Saudi Arabia. This syndrome was caused by MERS, a line C group 2 beta coronavirus. The mortality rate was about 10% during the first outbreak and reached 40% during the second one. The fatal cases included patients under 18 years old. Thus, the current pandemic can be called the "third arrival" of the most dangerous varieties of coronaviruses (lines B and C group 2 beta-coronaviruses).

The attitude of humankind towards the new epidemic is different, though. The degree of respect (or fear) of the new infection is so high that the name of the pathogen and the disease itself was chosen differently [4]. The atypical pneumonia of the first outbreak was called **SARS** (**S**evere **A**cute **R**espiratory **S**yndrome), and the coronavirus that caused it was named **SARS-CoV**. The second was an outbreak of **MERS** (**M**iddle **E**ast **R**espiratory **S**yndrome) caused by a coronavirus called MERS-CoV. The current coronavirus was named **SARS-CoV-2** (**S**evere **A**cute **R**espiratory **S**yndrome **C**orona**V**irus-2). The new infection was named nCoV-2019 first and then renamed into **COVID-19** (**CO**rona**VI**rus **D**isease that arose in 20**19**). And that is an interesting fact.

In the early months of the new outbreak, the main presentation of COVID-19 was believed to be pneumonia, so the term "coronavirus pneumonia" was used as a synonym. Today, it is clear that SARS-CoV-2 causes multiple organ damage, so this term should only be used to describe one of the affected systems or one of the symptoms of the disease.

The role of the receptor for SARS-CoV-2, a type 2 angiotensin converting receptor, or ACE2, is described in detail in the literature [5]. This receptor is expressed in various organs and systems – lungs, intestines, kidneys, blood vessels, as well as in the oral mucosa. This explains both the multidirectional action of the virus, and the fact that the inflammation triggered by it affects various target organs (as mentioned above, not only and not so much the lungs).

In the first months of the pandemic, some publications stated that patients taking ACE inhibitors (as well as statins) may need to switch to other hypotensive drugs because their current drugs might facilitate the penetration of the new coronavirus into the host cells [6]. The Russian cardiologists and therapists published such opinions, as well. In May 2020, a review was published that ACE inhibitors, on the contrary, can protect elderly patients with hypertension and reduce their risk of hospitalization by 40% [7]. No such protective effect was found for young patients, including those under 18 years of age, for unknown reasons.

Bronchial asthma has been named another risk factor for a severe course of the disease in the beginning of the pandemic [8]. But clinicians, including Russian pediatricians [9], did not observe the high susceptibility of children with asthma to the new infection. This was explained in a publication in *Allergy Clinical Immunology* in the end of April 2020 [10]. It said that patients with allergic asthma have reduced expression rate of the *ACE2* gene in their airway cells and are less susceptible to the infection. Fortunately, asthma has an allergic (atopic) nature in more than 90% of pediatric cases. This means that children are less susceptible to the novel coronavirus disease.

Later other receptors were found that the virus used to penetrate the host cells. A publication in *Allergy Clinical Immunology* [11] on May 7, 2020 confirmed that mediators of T2 inflammation in patients with allergic rhinitis or asthma (with high production of T2 cytokines and expression of their genes) modulate the activity of both ACE2 and TMPRSS2, which also facilitate the entry of SARS-CoV-2 into the cells. However, these actions are multidirectional. One cytokine, IL13 (but not IL-4 and IL-5), reduces the expression of ACE2 and increases the expression of TMPRSS2 in epithelial cells of the upper and lower respiratory tract *in vitro* (*ex vivo*). The epithelial cells were sampled during bronchoscopy in pediatric and adult patients. The genes of these receptors are located on different chromosomes, which may explain the multidirectional action of cytokines. In any case, the results of this study also partly explain the low incidence of COVID-19 in children and adults with atopic allergic diseases.

The fact that men were diagnosed with COVID-19 and died more frequently than women was observed in Wuhan, other Chinese provinces, and in the adjacent and far away countries even before the pandemic was declared. The cases of coronavirus infection that were referenced in the beginning of this article describe mainly male patients. The ratio of sick men to women was about 2 : 1, and the risk of dying was significantly higher in men than in women during the outbreak in China. The mortality was 1.7% in women and 2.8% in men in China. The risk of intensive care or death was more than 2 times higher among men

than among women – 32 and 15%, respectively – in Hong Kong hospitals. This inequality was also noted in other regions of the world. However, the long-term consequences are usually worse in women than in men due to the social and psychological factors. This justifies the need for rehabilitation technologies after recovery that will be discussed at the end of the article. In any case, these facts forced *D.Gemmati et al.* to conduct a study, which explained that double X chromosomes in women are a protection against the new coronavirus. The gene of one of the receptors that the virus uses to enter the cell (ACE2, but not TMPRSS2) is located on the "female" chromosome [12]. In addition, X chromosome contains the gene that mediates both the cellular and humoral immunity and inflammation.

Another study clarified the differences in clinical symptoms at the onset of the disease. The study was published by *R.Zang et al.* and evaluated the expression of receptors for SARS-CoV-2 – ACE2 and TMPRSS2/TMPRSS4 – in enterocytes of the small intestine [13]. The authors have shown that the expression rate of ACE2 in the small intestine is maximal as compared to other human organs and tissues. The expression rate is much higher than in alveolocytes of the lungs. This may explain that COVID-19 starts with intestinal symptoms frequently, especially in children. The authors emphasized that the coronavirus is inactivated in the large intestine and the feces do not contain active and infectious forms of the virus. However, the fecal-oral route of infection cannot be excluded, since the experiment did not study the properties of the virus that is excreted with feces in the case of frequent stools (whether it is inactivated fully in a short time).

The epidemiological features of this viral infection have been analyzed in detail in many publications, including the Russian ones [14, 15]. Replication of the pathogen takes 2 – 3 times longer as compared to the seasonal influenza virus. Therefore, isolation and physical distancing in compliance with sanitary and hygienic requirements are highly effective, including for children. "Physical distancing" is a preferred term over "social distancing" because social isolation just does not happen in the "new reality". People stay connected not a bit less and maybe even more than before the pandemic thanks to the Internet and other means of communication. At the same time, the definition of the safe distance is being discussed today. Is 1.5 meters enough or is it better to maintain a distance of 5 meters or more? A scientific study showed that the minimum distance should be 5 – 6 meters. The results were even published, but then the publication was retracted. So, this study is not cited here.

An important fact about masks is that children under 3 years old are NOT recommended to wear masks at all. It is obvious that babies will not be able to describe breathing difficulties or adjust their breathing difficulties caused by the mask! Moreover, pediatricians agree that only children over 6 should wear masks [16].

COVID-19 quickly turned into a nosocomial infection, and today it is most dangerous for healthcare practitioners (more than 1,800 doctors from 64 countries have died already), as well as for adults who work or live in closed groups (nursing homes, hospitals, and so on), especially the elderly. At the same time, only one real outbreak in a children group have been described. It happened in a French high school in the first months of the pandemic.

One question has been discussed heatedly from the beginning of the pandemic: are children infected less often than adults, or are they infected with the same frequency but have much less pronounced clinical symptoms? The Chinese researchers wrote from the very beginning of the outbreak in China that children become infected and sometimes develop the symptoms, but much more rarely and milder than adults [16].

The scientists explain the supposed relative resistance of children to SARS-CoV-2 with several factors. Obviously, from the epidemiological point of view, children have a reduced risk of infection due to less travel, communication, and transportation. The low morbidity in children might be associated with higher levels of circulating ACE2 or other characteristics of the receptors [17]. Children may also have some features of innate immunity that disappear with age [18, 19]. Other possible reasons include a more favorable state of the mucous membrane of the respiratory tract due to the lower destructive active effects of cigarette smoke and air pollution, and a smaller number of chronic diseases, in contrast to adults. The maturity of the immune system may explain the unfavorable type of triggered immune response, which is associated with the development of acute respiratory distress syndrome in adult patients. And finally, the key factor might be that the children are regularly vaccinated, including live weakened vaccines that stimulate the innate immunity.

In any case, this fact has not been explained unambiguously from a scientific point of view yet.

Previously, it was believed that special attention should be paid to children of any age, since they play a huge role in the spreading the disease, including by excretion of the pathogen with feces [20]. From this point of view, the fecal-oral route of transmission was considered no less important as compared with the airborne and contact routes for SARS-CoV-2. This fact was especially relevant in areas where outbreaks of hepatitis A and rotavirus gastroenteritis are frequent and where wastewater can easily become a source of an outbreak of the novel coronavirus infection when it mixes with the groundwater. However, as mentioned above, it was found later that the virus is inactivated at the level of the large intestine and is excreted with feces in an inactive form [21]. Therefore, the fecal-oral route is most likely not the principal route in the spread of infection, but only one of the probable ones.

The opposite can be said about the possibility of children spreading the infection as asymptomatic carriers. The studies of the ways of spreading COVID-19 in Russia and other countries indicate that children become infected in families, in cluster sites, and not vice versa [9, 22–26]. That is why it is so important to follow the sanitary and hygienic measures in everyday life, in families, to teach the children hygiene from an early age.

COVID-19 is a severe illness in adult patients. Several authors [27] associate it with early functional depletion of innate (NK-cells) and acquired ($CD8^+$ cytotoxic lymphocyte) immunity. Although some researchers do not agree that the virus induces suppression of innate immunity [28]. Today all agree that the serious illness in adults is

associated with the so-called "cytokine storm". This reaction is similar to a pathological immune response in some rheumatic diseases (the so-called MAS – macrophage activation syndrome, or secondary HLH – secondary hemophagocytic lymphohistiocytosis, when a systemic inflammatory response is activated and damages multiple organs and systems) [29]. The key phrase above is "similar to", so COVID-19 patients cannot be treated as patients with a rheumatic disease and hemophagocytic syndrome, for example. Therefore, the treatment strategies for COVID-19 are both similar and different to those used in adult or pediatric rheumatology. And again, today it is obvious that not all adults develop the disease, or rather, the clinical symptoms in people of the same age and lifestyle can be completely different – from asymptomatic carriage to a critically serious condition. The factors that determine the course of the disease are still unclear. Some of these factors have already been described (those associated with a genetic predisposition) and some are still being studied.

The following observation also confirms that a cytokine storm is crucial in people vulnerable to SARS-CoV-2. The study showed that levels of fecal calprotectin are increased in patients with diarrhea (but without an inflammatory bowel disease) associated with COVID-19 [30], regardless of the presence of the virus in stool samples. The authors believe that it confirms that SARS-CoV-2 triggers the systemic inflammatory response and justifies the use of anti-cytokine therapy. The systemic inflammatory response apparently proceeds in 2 steps. The first is active viral shedding, but without the symptoms. The symptoms appear in the second step and are determined by the inflammatory changes in different organs and systems, i.e. the "cytokine storm". The patient is releasing almost no viral particles at this point. By the way, the ACE2 levels are sharply increased in patients with active inflammatory bowel disease (without treatment), which makes them vulnerable to SARS-CoV-2 [31], in contrast to patients with asthma and allergies.

There is another difficulty regarding the pediatric population. The children were not getting COVID-19 in large numbers for months, but then frightening messages suddenly appeared. On April 27, 2020, the UK Society of Pediatric Intensive Care issued the PICS Statement [32]. The global pediatric and parenting communities were informed about the increasing number of children with a new multisystem inflammatory disease associated with positive tests for SARS-CoV-2 (although not all patients had this connection confirmed by laboratory tests for the virus at admission). The disease proceeded as toxic shock syndrome and atypical Kawasaki disease (with abdominal pain, gastrointestinal symptoms, and heart damage). The patients had high levels of CRP, ferritin, troponin, proBNP, and red blood cell counts, as well as changes in the coronary arteries.

On May 6, *Lancet* [33] published an article describing 8 children aged 4 – 14 years, mostly boys, who were admitted to intensive care units in London in mid-April with Kawasaki-like syndrome. 6 children were of Afro-Caribbean origin and 2 were Asian. Half of the children got COVID-19 from their family members. The tests for SARS-CoV-2 with nasopharyngeal swabs and bronchoalveolar lavage were negative upon admission. Children were admitted with high fever (up to 40 °C), various rashes, edema, conjunctivitis, pain in the extremities, and severe gastrointestinal symptoms, which quickly led to vasoplegic shock. They were refractory to resuscitation and required norepinephrine. Almost all patients (7 out of 8) required mechanical ventilation to stabilize their cardiovascular system (not for the relief of respiratory failure). Signs of systemic inflammation were also reported, including pericarditis, pleurisy, ascites; increased levels of CRP, procalcitonin, ferritin, triglycerides, and D-dimer. Other pathogens (adenoviruses and enteroviruses) were isolated in only one of 8 patients. The ECGs were normal, but echocardiography showed signs of coronary aneurysm one week after discharge in one child. Another child developed severe arrhythmia with refractory shock, which required extracorporeal support. The patient died later from a massive cerebrovascular infarction. The increased levels of myocardial enzymes indicated inflammation of the heart muscle in all patients. All children received intravenous immunoglobulins (2 g/kg) in the first 24 hours and antibiotics (ceftriaxone and clindamycin). 6 children also received 50 mg/kg aspirin. 12 more children were admitted to the ICU in different parts of London over the next 7 days after this publication, in the end of April. Again, almost all of them were initially negative for SARS-CoV-2. The Royal College of Pediatrics and Child Health in the United Kingdom has promptly issued RCPCH Guidance, the clinical guidance to treat such pediatric cases [34].

A week later, on May 4, 2020, the Head of the New York City Department of Health (*Daskalakis*) also sent out a notification about the new disease – Pediatric Multisystem Inflammatory Syndrome (PMIS), that is potentially associated with SARS-CoV-2 [35].

A fairly large number of publications on multisystem inflammatory syndrome in children appeared in the next 3.5 months [36–41]. Some of them highlighted the racial and ethnic differences among the patients. The article from France states that 57% of the children hospitalized with this diagnosis in Paris were from African communities; the average age of these children was 7.9 years [39]. At the onset of the disease, all children had gastrointestinal disorders, 57% had symptoms of shock, and 76% had myocarditis. All received treatment with intravenous immunoglobulins, 48% received steroids. The average duration of hospitalization was 8 (5 – 17) days. All children recovered. The absence of the viral RNA in the biological loci and the presence of IgG antibodies strongly indicated that the disease develops not at the time of viremia, but after 2 – 3 weeks from the introduction of infection.

These inter-ethnic differences between the children with multisystem inflammatory syndrome did not come as a surprise. Clear inter-ethnic differences have already been noted in morbidity and mortality from COVID-19 earlier in the United States [42]. For example, Latin American communities represent 39% of all communities in California, but they represent more than half (56%) of cases and 46% of deaths from COVID-19. 8.5% of the fatal cases were African Americans (6% of the state's popu-

lation). But Caucasians (37% of California's population) contribute less to morbidity (17.5%) and mortality (30%) as compared to the Latin American communities.

Many children who died from systemic inflammatory syndrome were African Americans, including those with obesity. Although many aspects remain unclear. The higher morbidity and mortality rates among the ethnic population of the United States is explained by the worse economic situation, including the lower availability of highly qualified medical care and a higher incidence of obesity among the Afro-Caribbean and Latin American citizens as compared to Caucasians. However, these data contravene the global statistics, because the morbidity and mortality from COVID-19 is incomparably higher in developed countries compared to the developing countries: at the end of May, when more than 5.3 million cases of the disease and 350,000 deaths (more than 100,000 in the USA alone) were recorded worldwide, only 80,000 cases were confirmed and 2,000 deaths were reported at the African continent! [43]. Although, according to the authors, the "economic storm" caused by the new coronavirus in the emerging economies has led to a much larger number of mental health issues as compared to physical health. 2% of the population was suffering from severe depression requiring serious medication in the "precovid period", and now this number seems to have increased significantly. This is clearly confirmed by the study by *M.Taquet et al.* that was published in *JAMA Psychiatry* on July 29, 2020 and describes the change in the mood of 16.5 – 24 year old students in the Netherlands during quarantine compared to the pre-quarantine period [44]. The authors noted a significant decrease in "mood homeostasis", increased depression, especially in those students who had a family history of mental health problems. This again draws attention to the need for serious rehabilitation, including psychological, of children, youth, people of older age groups who have survived quarantine, and especially those who have recovered from COVID-19. Also, the current situation, when lots of citizens from different countries were left without the basic means of subsistence, will inevitably lead to an increase in violence, primarily in families under the lockdown.

From our point of view, the pediatric systemic inflammatory syndrome is the analogue of the COVID-19 disease in adults and occurs in few children around the world. To date, just over 600 cases have been described. The mortality rate is about 1 – 2%. This includes three hundred patients in the United States, mainly 5 – 14 years old, several deaths, and about 100 cases in the UK and other European countries. This syndrome is usually reported in children approximately 2 months after the onset of the outbreak in the country. In May, we wrote in our review on the website of the Union of Pediatricians of Russia (*www.pediatr-russia.ru*), that there will be such cases in the Russian Federation in the coming days/weeks. And so it happened. Over the past weeks, about 25 patients with systemic inflammatory syndrome have been admitted to hospitals in Moscow and other regions. The overwhelming majority of these patients were discharged home in 2 – 3 weeks, some of them with coronary vasodilation/aneurysm.

An interesting calculation was presented by *F.P.Wilson* from Yale University [45]. Knowing that the incidence of COVID-19 in the pediatric population is incredibly low, he made the following calculation: approximately 5% (5,000) of 100,000 children who can become infected with SARS-CoV-2, will require hospitalization, in theory. Among them, there may be 733 cases of multisystem inflammatory syndrome (Kawasaki-like syndrome), including 20 deaths (that is, the mortality rate in children with COVID-19 was estimated at 0.02%). This forecast was surprisingly accurate and was confirmed fully over the next months. This syndrome, in contrast to the true Kawasaki syndrome, is not associated with "raspberry" tongue and bilateral conjunctival injection. Also, rashes are less common, and the patients are about 2 times older. Unfortunately, the clinicians still use the wrong diagnosis in some regions of the Russian Federation. They call this condition "Kawasaki syndrome" or "Kawasaki disease" instead of "multisystem inflammatory syndrome in children" (or "Kawasaki-**LIKE** syndrome") and therefore use the irrelevant protocols for the children with true Kawasaki syndrome.

The routes of transmission of the pathogen in the child population are airborne, contact-household, and fecal-oral – the same as in adults.

The virus persists in aerosol form for about 2 hours, it survives on plastic/metal surfaces for up to 6 – 8 hours [46, 47], on hair for up to 3 days [48], in the room where the patient was staying for several days [49]. Although some scientists doubt these numbers and continue their research [50].

The virus transmission begins 1 – 2 days before the onset of clinical symptoms. The viral RNA can be detected in nasopharyngeal swabs of children for up to 6 – 22 days of illness and even longer (!), in feces – from 5 to 28 days and longer [51–57, 20], although not always in active form. The main question is whether the detection of a virus in a biological locus should be defined as a carrier status or considered a disease? On the one hand, it is obvious that the presence of a virus without clinical symptoms is just a coexistence of a microorganism and a macroorganism. On the other hand, how do we distinguish a disease that is caused by another pathogen in the presence of the novel coronavirus and the disease caused by this coronavirus, if the child has any relevant symptoms? Differential diagnosis should be mandatory for every pediatric case of COVID-19 because a child is surrounded by many potentially dangerous pathogens to which he has not developed the immunity yet.

The research also suggests that masks have advantages over other methods to prevent the spread of SARS-CoV-2 [58]. An aerosol that is released during a conversation, including particles with coronavirus, "hangs" in the air for 14 minutes and can be easily inhaled by other people during this time [59]. Another group of researchers found that SARS-CoV-2 continues to replicate in the small intestine but is inactivated in the colon. Most likely, it is inactive in feces [60]. That is, the fecal-oral route is hardly the main one, but it should not be dismissed so far. For example, American scientists also write that the fecal-oral route of transmission was confirmed in the US [61].

The viral load and duration of viral shedding does not correlate with the severity of COVID-19 [53, 54], although it was initially thought that patients with the severe disease shed the virus longer. The recent works confirm that viral shedding is directly related to the disease severity.

Vertical transmission of the virus has not been confirmed yet. Not a single case has been published worldwide that describes isolation of the viral RNA from a newborn, from the amniotic fluid, or placental tissues. The 2 published cases of neonates with SARS-CoV-2 IgM should be interpreted with caution [62–64].

There is no evidence that the virus is transferred through human milk [22, 65].

There is another important aspect. **Young people (!) rather than children** are the biggest "distributors" of the infection. It has been shown [66] that young people aged 15 – 34 years (first of all, people of 20 – 24 years old) make the greatest contribution to the spread of the virus in comparison with people of 35 – 49 years old and younger adolescents of 10 – 14 years old. Therefore, the preventative measures should be different for these age groups.

The incubation period in children is 4 – 6 days as in the adult population (with a range from 1 to 14 days or more). Although some studies show that the average incubation period in children is equal to 3 days with a range from 0 to 24 days [67].

The data on the actual incidence of COVID-19 in children is scarce. The Chinese Center for Disease Control and Prevention reported that 2.2% of the patients with the confirmed diagnosis were under 19 years old since the beginning of the epidemic of the novel coronavirus disease COVID-19 in China. Among this subpopulation, the disease was confirmed more often in the patients over 10 years old [68]. These numbers are a bit higher that the numbers in the first reports from China (0.25% for children aged 0 – 18 years) [16] but are still quite insignificant in comparison with adults. Currently, about 20 million cases and about 750,000 (3.75%) deaths have been reported worldwide. Children are still rarely mentioned among the sick and dead [69].

Here are some of the epidemiological data that were provided by researchers in different parts of the world:

- Switzerland: The morbidity rate in children under 10 years old is 0.4%, 10 – 9 years old – 2.6% of all patients with COVID-19.
- Sweden: Up to 10 years – 0.5%, 10 – 19 years – 1.3% of all cases [70].
- Spain: Children (under 18) – 0.8% of all cases [71].
- India: Children (under 10 years old) – 2.5%, 10 – 19 years old – 5% [72].
- Iceland: The population screening did not reveal any cases of children under 10 years old and confirmed 0.8% among older children [73].

Most children are infected in their families [9, 23–25, 52, 53, 56, 57].

On May 20, 2020, the Reuters news agency drew attention to the latest data from British scientists [74], who revealed 2 new facts:

- Children are less likely to develop symptoms than adults (about 20%).
- The acquired immunity to the novel coronavirus infection does not last long [75].

To date, all researchers and doctors admit that the disease is usually asymptomatic or mild in children, in contrast to adults [76–90].

As mentioned above, there are very few scientific publications on COVID-19 in children, but in general they all agree with the information above. These data were confirmed by a study [91] on the epidemiological characteristics of 2,143 pediatric patients with COVID-19. The cases were reported to the China CDC from January 16 to February 8, 2020. More than 94% children had asymptomatic, mild, or moderate disease. An important aspect is the number of patients with the severe/critical disease and deaths. The number of severely ill children among the 2,143 cases was 3 times less than among adults (18.5%). 5.9% of the children were in critical condition, and one child died (at the end of February). The disease was more severe among infants and children under 5 years of age with chronic conditions. However, the Chinese researchers emphasize that most of the described severe and critical cases did not have a positive laboratory test for coronavirus and could be caused by other pathogens (influenza, RSV, RV, etc.) in association with the underlying disease. In addition, there is no data on whether anosmia appeared in sick children as often as in adult patients. It is still unknown whether the patten of anosmia was different in children as compared to adults. Is there a difference in the course of COVID-19 in children and adults?

Thus, children accounted for a very insignificant part of the cases. The fatal outcomes were not registered in China until mid-February. The children had mild symptoms or were asymptomatic carriers [82, 90, 92, 93].

The patterns of the "children's epidemic of coronavirus" in China is repeated in other countries. An analysis of COVID-19 incidence in children in the United States from February 12 to April 02, 2020 was published [94]. During this time, more than 890,000 cases of the disease and more than 45,000 deaths were recorded worldwide, including over 239,000 cases and almost 5,500 deaths in the United States, and it was important for American clinicians to analyze the pediatric situation. Children of 0 – 17 years old currently make up 22% of the population in the United States. If children got sick as often as adults, the morbidity rate would be the same.

However, only 2,572 cases were described among children under 18 years of age (1.7%) out of 149,760 laboratory-confirmed cases of coronavirus disease from February 02 to April 04. Only ¾ of these patients had any symptoms, such as fever, cough, or difficulty breathing (almost all adults of 18 – 64 years old, 93%, had symptoms) and only 5.7% required hospitalization (this number was 2 times higher, 10%, among adults). 3 lethal outcomes were reported.

According to the Federal Children's Resuscitation and Advisory Center of the Russian Federation (operational data of the Ministry of Health of the Russian Federation), about 50,000 children in our country were diagnosed with COVID-19 by the end of June 2020. This equals to about a half of the patients with the U code (the rest were cases of pneumonia, the J code). These patients account for 6.6%

cases with both codes, 4.5% with the U code out of more than 450,000 infected Russians. About 50 children with a clinically or laboratory confirmed diagnosis of COVID-19 were treated in intensive care units. In June, the number of children in the intensive care units increased slightly (on average, up to 60 children were treated in intensive care throughout the country, some of whom were on mechanical ventilation). In July–August, the number of children in intensive care decreased to 50 – 40, then to 30. 42 deaths were reported in total (children make up 0.35% of the 12,000 deaths!).

Thus, the important distinctive features of the course of COVID-19 in the pediatric population are:

- the vast majority of pediatric cases are mild or moderate;
- children can be asymptomatic carriers significantly more often than adults (or COVID-19 is often not associated with such symptoms as fever, cough, and difficulty breathing in children);
- even though most children have a mild illness, there are those who still need hospitalization, including patients with obesity, diabetes, and other comorbidities associated with overproduction of coagulation factors, but not with allergies and asthma;
- in addition, children can still develop a systemic inflammatory response with a "cytokine storm" (fortunately, this is completely different from the classic "cytokine storm" in patients with rheumatic diseases) very rarely after COVID-19. As we predicted in May 2020, the systemic inflammatory syndrome was reported in Russian children in the end of May and during the first two summer months.

The detailed description of the clinical picture of COVID-19 in children also differs clearly from adults. In the first months of the pandemic (from January to April 2020), only a few articles were published in the world describing cases of COVID-19 in the pediatric population, mainly from China. Therefore, the patients of this country will also be mentioned in this review [83–90, 95].

According to the Chinese epidemiological data, the incubation period in children was 5 – 7 days. All patients in China had close contacts or were from clusters, including family ones. A small part of the patients had fever, unproductive cough, and signs of "general intoxication". The other patients were asymptomatic. An exceedingly small number of sick children had the upper respiratory tract symptoms (nasal congestion, rhinorrhea) or gastrointestinal disorders (nausea, vomiting, abdominal pain or discomfort, or diarrhea). Single patients had symptoms of lower respiratory tract damage (mostly bronchitis and a few cases of viral pneumonia).

In general, the coronavirus infection was mild in children, and they recovered within 1 – 2 weeks. It is noteworthy that not a single newborn from mothers with established COVID-19 infection had a positive test for the pathogen (this fact refuted the theory of transplacental transmission of SARS-CoV-2), and no newborn cases were reported until the end of February 2020. By the beginning of April, one of the first articles on this topic presented the results of treatment of 55 pregnant women infected with COVID-19, and 46 newborns with no clear signs of vertical transmission [96]. Later, publications appeared on a positive test for the RNA of the pathogen in a newborn 36 hours after the delivery [97]. But the authors of the article themselves are not inclined to consider this an evidence of intrauterine infection (the time interval was too much, and the tissues of the placenta and umbilical cord did not contain the viral RNA). The same interpretation was given by the authors who described 10 other newborns with positive tests for SARS-CoV-2 [98] and by the authors of the newspaper article [99] and in later publications. Moreover, WHO published a position statement saying that mothers with confirmed COVID-19 should continue breastfeeding (provided, of course, that all hygiene rules are observed!), because the virus was not excreted with milk in any of the women with coronavirus infection [100]. Cases of 33 newborns from mothers with COVID-19 clinic signs were published on April 07, 2020. 3 (9%) of these children also had a clinical diagnosis of coronavirus infection [101]. All three were born by cesarean section, had low APGAR scores (3/4/5) at 1, 5, and 10 minutes, the radiographic findings of pneumonia resolved by the 14th day of antibiotic therapy, and test for SARS-CoV-2 in nasopharyngeal and anal swabs were positive on the 2nd and 4th day of life and were negative on the 7th. According to the authors, the children were infected intrapartum, but vertical transmission cannot be ruled out completely. Later publications, including those in May and June, described the situation in the same manner.

Of course, the clinical picture of a new infection in the pediatric population should be closely monitored, and the clinicians should be able to respond quickly to new facts. It is noteworthy that child deaths were reported more often in previous epidemics of coronavirus infection (SARS and MERS), while the mortality rate of patients of all ages was significantly higher than the current epidemic (approximately 30 – 40% for MERS and 8.5 – 12% for SARS versus 3.5 – 5% for COVID-19 at the moment).

Thus, some clinical symptoms of COVID-19 in children are much less common and some are much more common than in adults. Some symptoms have been described in adults, but not described in children, and vice versa.

1. The common clinical symptoms in children include:
   - asymptomatic course;
   - fever (only in 40 – 56% of the cases);
   - cough (about every second child);
   - sore throat/pharyngitis (in 40% of the cases);
   - mild diarrhea;
   - co-infections (influenza A and B, *M. pneumoniae*, RSV, RV, etc.).
2. Clinical symptoms that are rarely seen in children:
   - rhinorrhea;
   - wheezing;
   - fatigue/headache/myalgia.
3. Symptoms that are common in adults and occur with an unknown frequency in children: anosmia/hyposmia (is considered a pathognomonic symptom in adults);
   - conjunctivitis (RT-PCR+);
   - acute kidney damage that requires renal replacement therapy is reported in 36.6% of hospitalized adults and in 90% of ventilated adults.

4. Manifestations that are common in children, but have not been reported in adults yet:
   - **"COVID fingers"** in the absence of other symptoms of the disease (fingers or phalanges with signs of cutaneous vasculitis, painful, like frostbite, were described in children in Spain, USA). New publications about this symptom appeared in Italy and Spain after the May 20. Also, the data from other countries (including US) say that this symptom can be used as pathognomonic to diagnose COVID-19 in children even without the laboratory confirmation.

Later, papulovesicular rash (as in chickenpox) in patients of all ages in Italy [102, 103] and neurological complications (*Guillain–Barré* syndrome, strokes, polyneuropathies, including transient ones), and also psychiatric complications (delirium followed by depression, increased anxiety, insomnia, and long-term consequences of post-traumatic stress) were described. A high burden of COVID-19 on mental health has been noted for Latin Americans, primarily those with language difficulties in the United States [104].

The number of publications on the neurological symptoms of the new coronavirus infection has increased in the last 2 – 2.5 months. The correlation of these symptoms with the severe symptoms of anosmia/hyposmia and ageusia/dysgeusia, as well as with the previously proven effect of SARS and MERS on the central and peripheral nervous systems was explored.

Italian scientists [105] described the neurotropic effects of SARS-CoV-2 using a clinical example of a 25-year-old woman who worked with patients in one of the hospital departments. The patient had a dry cough for 1 day, as well as loss of smell and taste, fever, and other symptoms of COVID-19. Her CT-scan and nasal endoscopy showed no changes in lungs and sinuses, respectively. However, MRI of the head 3 days after the onset of symptoms showed distinct changes in the form of hyperintense signals in the area of the right gyrus rectus and olfactory bulba, which disappeared after 28 days. Based on this, it has been suggested that the virus enters the central nervous system directly through the eye/optic nerve. This means that glasses or screens provide additional protection from the virus.

The fact that IgM antibodies to SARS-CoV-2 (but not the viral RNA) are detected in the cerebrospinal fluid may indicate that the pathogen stays in the central nervous system at the time of illness, which means that COVID-19 can indeed take the form of an acute encephalitis/encephalomyelitis [106]. Animal studies have confirmed that the virus can enter the brain (after the injection into the nasal fibers). The authors describe 3 cases (all African Americans), including 2 patients with encephalitis who recovered and were discharged and a woman with encephalomyelitis and concomitant sickle cell anemia who died.

Chinese researchers [107] retrospectively studied the case histories of 214 patients who received treatment in 3 specialized centers in Wuhan from January 16 to February 19, 2020 and described neurological changes in every third patient (36.4%). These neurological changes included cerebrovascular disorders, altered consciousness, skeletal muscle damage that was more pronounced with more severe symptoms of COVID-19 in older people with comorbidities (hypertension).

A review in *JAMA* dated May 29, 2020 draws attention to the fact that the virus can potentially enter the central nervous system by different routes (transsynaptic transfer directly through the infected neurons, penetration through the optic nerve or vascular endothelial cells, migration with leukocytes across the blood-brain barrier). And the most frequently described neurological symptoms are anosmia/hyposmia, ageusia/dysgeusia, headache, as well as stroke, impaired consciousness, seizures, encephalopathy, etc. [108].

We would also like to cite the publication of American researchers from the University of Maryland, published on July 31, 2020 in *JAMA Psychiatry* [109]. The authors emphasize that both the impact of the disease itself (the SARS-CoV-2 virus) and the measures that were taken to reduce the number of new cases (separation of people, quarantine, when families sometimes stayed in very cramped conditions for a long time, other restrictions in the everyday life, a significant drop in the economic indicators in all countries) led to a sharp increase in both the number of acute psychiatric conditions (delirium, primarily) and delayed psychiatric conditions (in the form of depression, increased anxiety, post-traumatic stress syndrome). The cognitive impairments caused by the direct effect of the new coronavirus on the central nervous system and by the indirect psychological mechanisms are even more subtle, but especially relevant for children. These impairments include, for example, disruption of the usual world order, fear of death, fear of "fantastic creatures in spacesuits" for hospitalized children, and others. In this regard, the author once again emphasizes the idea that any active or passive immunomodulatory treatment (vaccination, administration of passive antibodies, steroids, biological agents, and so on) that reduce the degree of immune inflammation caused by the virus will significantly improve the mental health of patients.

The researchers reported from the very beginning of the pandemic that laboratory diagnosis of COVID-19 in children is similar to that in adults. However, more recent publications indicate that leukopenia, lymphopenia, and thrombocytopenia are uncommon [52, 53, 80], and the levels of CRP and PCT are normal or moderately elevated in children in general. At the same time, adults with severe lung damage have lymphopenia (due to the decreased levels of NK cells and CD8 lymphocytes), an increase in the level of IL-6 and LDH, CRP > 200, PCT > 0.5, ferritin > 2,500, D-dimer > 2,500 [110, 111]. As mentioned above, similar changes are detected in children mainly in association with multi-inflammatory syndrome.

On May 19, the *Lancet* published the results of a new study (the largest one in the United States). It was a prospective follow-up of 1,150 patients from 2 Presveterian hospitals in New York [112]. The study showed that markers of inflammation and thrombosis are predictors of possible deaths in critical COVID-19 patients who require intensive care (257 (22%) patients of the study cohort). ⅔ of

them needed mechanical ventilation and ⅓ needed a renal replacement therapy. A 10% risk of death was noted for every 10% increase in IL-6 and D-dimer levels. These data confirm the pathogenetic significance of systemic inflammation that damages vascular endothelium and determine the prospects for future research of drugs with immunomodulatory and anticoagulant effects. The gender, racial and ethnic differences were also found. Among the critically ill patients (67% of them were men), 62% were Hispanic/Latino, 19% were African Americans, 3% were Asians, and only 12% were Caucasian. 82% of the patients (mean age 62 years) had at least one comorbidity, most often – hypertension (63%) and diabetes (36%). 41% of the critically ill patients were on mechanical ventilation and 39% died. The previously published data from the UK (a cohort of almost 11,300 patients) confirm the high mortality rates of patients on mechanical ventilation. In that cohort, 50% died within a month from the initiation of intensive care. Many researchers also emphasize that mortality is high in patients with both types of diabetes. The other risk factors include older age, obesity, and uncontrolled blood glucose levels (A1c).

Instrumental (radiation) diagnostics of COVID-19 in children is similar to that in adult patients. All patients with suspected or established diagnosis of coronavirus infection need chest CT as early as possible. The typical CT-scans show mono- or bilateral, mono- or multifocal, peripheral, more often subpleural characteristic changes in lung tissue in the form of "ground glass" or "watch glasses". The scans show no signs of pleural effusion and intrathoracic lymphadenopathy, which indicates that the lung tissue damage in non-infectious. The chest X-ray is rather uninformative [53, 87, 113].

The diagnosis of coronavirus infection in children is established with a positive epidemiological history (children who have traveled or live in the site of coronavirus infection within 14 days preceding the onset of the disease; children who have been in contact with people with high fever or respiratory symptoms from the site of infection; children from families or other sites of the new viral disease; newborns from mothers infected with the novel coronavirus infection). The children should also have any 2 of the clinical symptoms with laboratory confirmation:

- Fever (although many pediatric patients have subfebrile or normal body temperature), nonproductive cough, sore throat, diarrhea, papulovesicular rash, "COVID-fingers".
- Typical changes in the lung CT-scan.
- Normal blood counts at the onset of the disease (leukopenia and/or lymphopenia are also possible).
- Other pathogens that can cause similar clinical symptoms cannot be identified.

The diagnosis is confirmed by positive RT-PCR for SARS-CoV-2 in the samples from the upper respiratory tract (nasopharyngeal or oropharyngeal swabs) or blood or tissues of the lower respiratory tract (the urine is not tested!). RT-PCR for SARS-CoV-2 in samples from the lower respiratory tract obtained by bronchoscopy is more informative than nasopharyngeal swabs, especially in critically ill patients [97], but these samples are very rarely collected in children.

It should be noted that since about May 2020, more and more articles on the topic of "clinical intuition" began to appear, when the absence of laboratory confirmation of the diagnosis of COVID-19 (American clinicians report 2 – 30% of such patients) should not mislead the doctor. At the same time, it is necessary to continue to follow the treatment protocols. By the way, the US FDA monitors closely the diagnostics used to test the population and regularly recalls test systems from even highly respected manufacturers due to their frequent false negative or false positive results.

The course of COVID-19 can be different **in children**.

- The infection can be asymptomatic (that is often seen in patients of all ages), i.e. children with a positive test for SARS-CoV-2 and no symptoms.
- COVID-19 in the form of **acute viral infection of the upper respiratory tract** (often found in children and healthy adults) manifests with fever, cough, sore throat, nasal congestion, headache, fatigue, myalgia, discomfort, etc., but no radiographic signs of pneumonia or symptoms of a sepsis.
- Children with **mild pneumonia** (often asymptomatic, or mild to moderate pneumonia) might have fever, have respiratory symptoms (cough, etc.), radiological signs of pneumonia, but no signs of severe pneumonia.
- **Severe pneumonia caused by SARS-CoV-2 and requiring mechanical ventilation is very rare in children (isolated cases) and is associated with:**
  - increasing shortness of breath ⩾ 70 per minute for children in the first year of life, ⩾ 50 per minute for children over a year old when they are not crying and do not have their peak body temperature;
  - decrease in saturation < 92%;
  - hypoxia: need for respiratory support (nasal cannulas, etc.), cyanosis, intermittent breathing with episodes of apnea;
  - impaired consciousness.
- **The critical condition**, including patients with the systemic multi-inflammatory syndrome (all patients with a respiratory disorder who need mechanical ventilation, have shock or damage to other organs and systems should be transferred to the ICU).

Fatal outcomes in SARS-CoV-2 positive infants and children have been described, but the main causes of death have not been found. The first child death was reported in Germany on April 09, 2020. The rates of hospitalizations, transfers to ICUs, and deaths for infants are published more often. The data from China, Spain, USA, and Germany were published. The latest publication in *Pediatrics* confirms this suggestion [114]. The authors analyzed data on 177 pediatric patients who were treated in the Washington National Children's Hospital (33 hospitalized and 144 outpatients), the authors concluded that the smallest (infants in the first year of life) and the oldest (adolescents over 15 years old) children are hospitalized more often than the others. These two age groups accounted for 64% (32% each) of all hospitalized children. 9 children were in critical condition. About 25% of child deaths in the Russian Federation is accounted for by newborns, mainly premature. Their clinical course of the disease is still unknown.

Interesting data have emerged recently regarding some special groups of pediatric patients and pregnant women. Turns out, the fears of the relatively high potential mortality of these patients from SARS-CoV-2 are greatly exaggerated.

Children with IDS of different etiology and immunocompromised patients:

- **PID (Primary Immunodeficiency Disorders)**: The COVID-19 cases are rare and no fatal outcomes have been reported.
- **Oncological patients**: Several cases of the disease were described in China, Italy, Spain, and Switzerland. The results were predictable, no deaths were reported.
- **Patients after organ and tissue transplantation**: No severe cases in solid organ recipients have been reported from Italy [115].
- **Autoimmune diseases**: A benign course of the disease has been described in 8 patients with IBD receiving immunomodulatory therapy and biological agents.
- **Patients with asthma** (with a controlled course of the disease) rarely become infected and do not develop the severe disease [116]. It is recommended to continue inhalation therapy with inhaled glucocorticoids (but not through nebulizers!) and to replace it with metered-dose inhalers, including those with spacers. If the patient is receiving systemic steroid therapy, it is recommended to continue this therapy. Oral steroids should be used in a short course, if short-acting $beta_2$-agonists (salbutamol) are unavailable.

Patients with rheumatic diseases who receive TNF-α inhibitors have significantly lower risks (60%) of severe course and hospitalization with SARS-CoV-2 infection, as was shown by the Global Rheumatology Alliance COVID-19 Registry [117]. At the same time, the patients who received 10 mg or more of prednisolone per day, had 2 times higher (105%) risk of hospitalization compared with those who did not receive steroids. The registry was launched on March 24, 2020 and contained data on more than 1,300 patients, collected by 300 rheumatologists from 40 countries by the May 12. The analysis of data from the first 600 patients in the registry showed that 46% were hospitalized and 9% died. The risk factors for the severe course and hospitalization were the same as in the rest of the population and included age and comorbidities (diabetes, obesity, arterial hypertension, diseases of the cardiovascular system, kidneys, and lungs).The use of hydroxychloroquine (or other antimalarial drugs) did not affect the hospitalization rate. Notably, patients with systemic lupus erythematosus (SLE) had a higher risk of hospitalization (80%), in contrast to patients with rheumatoid arthritis (RA).

Analysis of data from 17 million UK residents, including 885,000 patients with RA, SLE, and psoriasis showed a 23% higher hospitalization rate in patients with existing comorbidity [118].

The new publication describes 347 patients with **multiple sclerosis (MS)** [119] from the Francophone registry who had COVID-19 from March 01, to May 21, 2020. Only 248 patients received disease-modifying therapy (DMT) for MS. Some of the patients (21%) suffered from a moderate disease (were hospitalized, but without mechanical ventilation) or severe disease, 12 (3.5%) patients died. The proportion of patients, who did not receive DMT, had the worst scores on the EDSS scale, were older, and had obesity, was significantly higher among the moderate to severe cases and the fatal cases.

Pregnant women

Most published cases describe **pregnant women** in the third trimester without any complications that would have been typical only for pregnant women [120].

According to the recent publications, the severity of COVID-19 is significantly lower than that of H1N1 flu. Follow-up of 86,293 pregnant women from March 1 to April 15, 2020 showed that the hospitalization rate due to severe COVID-19 disease was 4.9 per 1,000 pregnant women (2 times more pregnant women are hospitalized with flu, 8 per 1,000). Only 427 (0.5%) women were hospitalized due to the severity COVID-19.

The vertical transmission of the virus has not been documented yet [121–125].

Newborns

An asymptomatic course of infection (with a normal CT scan of the lungs) has also been described in newborns [113, 124, 126].

3 cases described newborns with early but rapidly terminated viral shedding.

Complications in the perinatal and postnatal period in uninfected infants from mothers with COVID-19 have been described [125].

Once again: COVID-19 viral infection (including pneumonia) in children is usually mild. Sometimes the disease causes the typical changes in the lung CT-scans that should be monitored over time. As children rarely have a positive PCR test for coronavirus RNA (for various reasons), the changes in the lung CT-scan should be the reason for managing the child as having COVID-19 infection and early initiation of adequate therapy. On the other hand, the decision-making based on the CT data alone can lead to overdiagnosis of COVID-19, especially if there is a co-infection or the disease has a similar clinical picture, but a different etiology.

As noted above, the COVID-19-like symptoms in children should be differentiated from the following infections:

- Influenza;
- Parainfluenza;
- Adenovirus infection;
- RSV infection;
- RV infection;
- Human metapneumovirus infection;
- SARS coronavirus infection;
- Other viral infections;
- Infections caused by *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*;
- Bacterial pneumonia.

At the end of May and the beginning of June, 2 important documents were published that described the princi-

ples of diagnosis, treatment, and rehabilitation of patients with a new coronavirus infection, both in adults and children. WHO published a document on May 27, 2020 (available through a link on the WHO website *https://www.who.int/publications/i/item/clinical-management-of-covid-19*), and CDC published a protocol on June 11 (*https://www.covid19treatmentguidelines.nih.gov*) [127].

The WHO document introduced a "traffic light" system for the guidelines that helps visually comprehend what is proven and therefore should be applied in clinical practice (**"green checkmarks"**), what should be avoided (**"red crosses"**), and what can be used only in specific circumstances (**"yellow exclamation marks"**). In addition, the WHO guideline covered the principles of screening and triage, laboratory diagnostics, therapy of patients with mild, moderate, and severe pneumonia, acute distress syndrome, septic shock, principles of prevention of severe complications of mechanical ventilation, the use of drugs with antiviral, immunomodulatory, and antibacterial effects, steroids, treatment of acute and chronic infections in patients with COVID-19, management of patients with neurological and mental problems, chronic noncommunicable diseases, rehabilitation of those who have recovered, as well as separate management of women during pregnancy and after childbirth, care and feeding of newborns and babies from mothers with coronavirus infection, caring for elderly patients, palliative care, ethical issues of the optimal organization of care during the pandemic and clinical trials, and the guidelines for reporting deaths.

It was emphasized that drugs such as chloroquine/hydroxychloroquine (with or without azithromycin), antivirals (lopinavir/ritonavir, remdesivir, umifenovir, favipiravir), immunomodulatory agents (tocilizumab, interferon-β-1a), and convalescent plasma should be avoided in the prevention and treatment of COVID-19 (outside of clinical trials!).

It is not recommended to use glucocorticoids for the routine treatment of viral pneumonia. They should be reserved for special cases (septic shock, antenatal prevention of miscarriage, etc.).

Antibiotics are **strictly not recommended** for the prevention and treatment of mild or moderate disease (only for severe cases of COVID-19) when therapy must be started within the first hour after the blood sampling for the initiation of antibacterial therapy.

It was emphasized that individualized rehabilitation of patients should begin in the in-patient settings (including in intensive care) and that **psychological rehabilitation** should be considered a priority, especially in patients with signs of disadaptation (sleep disturbance, etc.).

The mode of delivery should not be chosen based on the pregnant woman's COVID-19 status but should be solely determined by the state of the mother and her child. At the same time, pregnant women or women who have given birth and are feeling normal should not be hospitalized but must be monitored at home and admitted to a specialized hospital if necessary. All women with suspected or confirmed positive status for COVID-19 are recommended to initiate or continue breastfeeding of their babies.

A randomized, placebo-controlled clinical trial involving 821 patients shown that administration of hydroxychloroquine within 4 days after contact with an infected patient had no preventative effect [128]. In addition, several studies have re-emphasized the potential dangers of hydroxychloroquine (especially in combination with azithromycin) in patients with preexisting prolongation of the *QT* interval.

There were 3 important updates in the CDC manual: a special section dedicated to children was added, new data on the antiviral therapy were added, and information on kidney damage in COVID-19, laboratory diagnosis of the disease, oxygen therapy and mechanical ventilation, and the use of IL-1 and IL-6 inhibitors were updated.

The pediatric section focuses on the multisystem inflammatory syndrome. There are still no officially recommended treatment regimens for this condition. Most American centers propose to treat the syndrome with intravenous immunoglobulin and steroids, anticoagulants and antiaggregants, and other immunomodulatory agents (inhibitors of IL-1 and IL-6).

The guidelines on the use of remdesivir vary. It is recommended for hospitalized severe patients with COVID-19 with saturation less than 94% and non-compulsory oxygen support (AI) for 5 days (AI), on mechanical ventilation or ECMO (BI). If no improvement is seen within 5 days, the therapy can be extended to 10 days (CIII). This drug should not be used to treat mild or moderate disease. Chloroquine/hydroxychloroquine (also in combination with azithromycin) should **not be used** to prevent or treat COVID-19 (AI – AIII).

Lopinavir/ritonavir and other HIV/AIDS medications are **not recommended** for the treatment of COVID-19 (AI, AIII).

General principles for treatment of children with COVID-19

Bed rest, sufficient nutrition and adequate hydration, control of electrolyte balance and homeostasis, monitoring of vital functions and oxygen saturation, monitoring of the patency of the respiratory tract, and oxygen therapy (mostly non-invasive), if indicated, monitoring of blood and urine tests (CRP, electrolytes, liver and myocardial enzymes, renal parameters, and coagulogram) are recommended. Blood gases test and repeated X-ray of the lungs should be performed if indicated. **To date, there are no clinical studies on the efficacy and safety of individual drugs in children with COVID-19!**

Symptomatic treatment

Physical methods of cooling and paracetamol at age-appropriate dosages should be used in patients with the body temperature > 38.5 that causes discomfort. The recommendations to avoid NSAIDs (ibuprofen, etc.) are not supported by the EMA, WHO, and the expert community [129]. Anticonvulsants should be used in severe patients

(do not confuse with muscle twitching as a symptom of the disease!).

Oxygen therapy

Start oxygen therapy through a nasal tube or mask immediately in case of signs of hypoxia. High-flow oxygen therapy, non-invasive or invasive mechanical ventilation, and, if indicated, forced ventilation should be used in exceptional cases.

Antiviral therapy

At the moment, 3 drugs have a **proven *in vitro*** antiviral activity against SARS-CoV-2: remdesivir [130], a combination of **lopinavir/ritonavir** [131] and **hydroxychloroquine** [132]. But these drugs have also been excluded from the guidelines.

The results of one clinical trial of **remdesivir** in severe patients (without a control group) are available. The respiratory function improved by 68% [133]. The clinical trials of remdesivir are ongoing.

The clinical trials of **lopinavir/ritonavir** have shown **its inefficacy** [132].

At the beginning of the epidemic, studies appeared on the high efficacy of hydroxychloroquine (with or without azithromycin) in patients with COVID-19 [134, 135], as well as the reviews of its potential use that took into account its *in vitro* and *in vivo* antiviral activity [136]. An increasing number of publications in the last weeks showed **absence of positive results** in the treatment of COVID-19 with hydroxychloroquine. Moreover, the number of severe patients and patients with **heart failure is reported to be growing**, especially among those receiving hydroxychloroquine in combination with azithromycin. Therefore, hydroxychloroquine was excluded from the latest guidelines (WHO, CDC).

Oseltamivir and other anti-influenza drugs are recommended only for the treatment of influenza. Oseltamivir and other influenza drugs should only be used in patients with the influenza virus. Influenza A or B viruses were most often detected in Chinese children with COVID-19 (an exceedingly small percentage of the Chinese population, including children, is vaccinated against influenza).

Umifenovir and interferon preparations have been used in Chinese patients with COVID-19, but there is no evidence of their effectiveness and safety in specially organized clinical trials.

Antibiotics

Unjustified use of antibiotics, especially broad-spectrum ones, should be avoided. Children with a co-infection, signs of a bacterial or fungal infection should be monitored. When the pathogen is identified, antibacterial or antifungal therapy is prescribed. Azithromycin prolonged the *QT* interval in patients with COVID-19, so it is used only in hospital and with caution.

Glucocorticoids

The decision to start glucocorticoids (GCs) is based on the severity of the systemic inflammatory response, the degree of dyspnea (with or without signs of respiratory distress syndrome), changes in the X-ray picture of the lungs. GCs are prescribed for a short course of 3 – 5 days. The dosage of methylprednisolone should not exceed 1 – 2 mg/kg/day.

GCs were included in the guidelines at the very beginning of the pandemic because many patients had high blood levels of pro-inflammatory cytokines (IL-6, TNF-α, etc.).

The idea of using biological agents, for example, tocilizumab, was based on the same fact. Over the past months, biological agents were proven to be effective against COVID-19 (they arrest the "cytokine storm") and reduce the risk of hospitalization and severe disease for patients with various inflammatory diseases (rheumatic diseases, IBD, etc.). Many children with systemic inflammatory syndrome recovered without the biological agents in the Russian Federation.

Another option is zinc pyrithione, which has been proven to inhibit the activity of coronavirus *in vitro* [137]. The data on the use of vitamin D show that it reduces the likelihood of severe disease and hospitalization in the risk groups. Vitamin D was included in many clinical guidelines for adult patients.

Heparin

Heparin is indicated for all patients with blood coagulation disorders and with a family history of tendency to thrombosis or thrombosis. This drug should be used with coagulogram monitoring.

Immunoglobulins

These agents were used in severe patients at the beginning of the pandemic. Their effectiveness was not proved, and they were excluded from the latest guidelines. A new interest has emerged in recent weeks in connection with the systemic inflammatory syndrome in children.

Respiratory support

Non-invasive ventilation is preferred. Invasive ventilation should be used in life-threatening cases, and ECMO is indicated when the invasive mechanical ventilation is ineffective. Many studies show that fatal outcomes are reported more often in the patients who were mechanically ventilated. Fatal outcomes in ventilated children were reported in the Russian Federation.

Support of blood circulation

Monitor the volume of injected fluids, improve microcirculation, use vasoactive drugs, and hemodynamic moni-

toring, if needed. There is evidence that state of many patients worsened after the administration of unnecessarily large volumes of fluids (!).

Psychotherapy

Counseling is essential for a speedy recovery. Active psychological support and treatment is indicated for older pediatric patients, especially with sings of phobias, anxiety, and psychological disorders. In general, about 30% of children and adolescents show a decrease in cognitive functions. Primarily these are patients with pre-existing problems. That is why the psychological rehabilitation is necessary for all children after COVID-19, including mild and asymptomatic disease. The rehabilitation is described in detail in the guidelines of the Ministry of Health of the Russian Federation [15].

Prophylaxis

Do not stop the routine vaccination! On the contrary, it is necessary to continue the routine primary vaccination of infants to prevent the outbreaks and epidemics of such diseases as measles and poliomyelitis (WHO). Vaccination is described in detail in the corresponding section of the guidelines by Healthcare Ministry of Russian Federation and on the website of the Union of Pediatricians of Russia. For example, the United States CDC recommended strict adherence to the routine immunization schedule for children, especially the first 24 months of life, on March 24, 2020. On May 8, the CDC published a report [138] on the current situation with vaccination of children, that included an analysis of the number of vaccines ordered by doctors to immunize children from early January to late April 2020 (compared to the same period in 2019). The report assessed all vaccines recommended for children (except for influenza vaccines, which are seasonal), including a separate data on vaccines against measles-rubella-mumps (the use of which is calculated separately for children under 2 years of age and for children from 2 to 18 years old). The decrease in the number of ordered vaccines for the specified period amounted to hundreds of thousands and millions: more than 3 million children less were vaccinated in 2020 as compared to 2019, including 400,000 less against measles-rubella-mumps, primarily at the expense of children aged 2 – 18 years. Data from India indicate a 69% decline in measles-rubella-mumps vaccination among children [139].

Additional disappointing facts that indicate a significant decrease in the vaccination rate in 2020 as compared to 2019 were reported in different US states. The average decrease was 33%. The decrease by 60.5% was noted in people aged 19 – 49-years and by 83.1%, in those who are 65 and older [140]. The summer months should be used to restore the wide vaccination coverage. Priority should be given to vaccination of pregnant women against diphtheria-pertussis-tetanus (T_{dap}) with acellular vaccines, immunization against measles-rubella-mumps in adults, seasonal flu vaccination in late summer 2020, as well as against pneumococcus and *Haemophilus influenzae* type b.

Of course, immunization should be carried out in conditions that prevent the spread of coronavirus infection.

The primary immunization regimens in infancy, predominantly using combination vaccines, in strict accordance with the national immunization schedule and with standard guidelines should be a priority in the pediatric population. For people over 18 years old, it is important to vaccinate the susceptible individuals and patients from risk groups against pneumococcal infection, hemophilic infection type b, and seasonal flu before the autumn rise in the respiratory morbidity.

Supporting the immunity

A balanced diet, adequate physical activity, regular visits to the attending doctor, and avoidance of excessive physical exercise, as well as emotional stability and mental activity prevent the infection effectively. Recent works [141] put forward a hypothesis that "fermented vegetables" (sauerkraut, for example) and other fermentation products (homemade curdled yogurts, kefir, and kvass produced with homemade cultures, etc.) help reduce the morbidity and mortality from COVID-19. Vaccination is an effective way to prevent infection. The vaccines are being developed.

Information sources and the people's knowledge

Professor *J.Bousquet et al.* from Montpellier processed big data on queries in the Google search engine about the SARS-CoV-2 virus and such symptoms of COVID-19 as anosmia/hyposmia and ageusia/dysgeusia. They then superimposed these curves on the plots of new cases of coronavirus disease in different regions of the world. The researchers came to the surprising conclusion that the wave of inquiries anticipated the wave of cases by several days (unpublished data). Thus, Internet resources can kind of predict an "infectious tsunami", which, of course, is COVID-19 today. A bit more about the mass media. Indian researchers [142] surveyed 1,246 respondents (744 medical workers and 502 non-medical citizens). More than 94% of the respondents were ethnic Hindus. 80% of the doctors and 82% of the citizens were afraid of getting the novel coronavirus infection, and more than 90% of both groups took appropriate measures to protect themselves from the virus. 98% of the medical workers and 97% of the citizens considered "difficulty breathing" the main symptom of COVID-19. 28.9% of the healthcare practitioners and 26.5% of the citizens knew that there is no targeted antiviral therapy available. But the respondents drew the information from completely different sources: doctors, from official medical websites (WHO, CDC, NIH, NEJM, etc.); other people, from the media (from TV and from social networks such as WhatsApp, Instagram, Telegram, and TikTok).

This raises the relevant question of sources of reliable information on COVID-19, both in adults and children, for our citizens.

Conclusion

This review covers the latest views on the course, clinical manifestations, treatment, outcomes, and prevention of the new coronavirus infection in children and other groups of patients. However, the emerging further information about this disease should be carefully monitored and analyzed while the pandemic is ongoing.

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