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EPIDEMIOLOGICAL AND CLINICAL AND LABORATORY FEATURES OF COVID-19 IN PEDIATRIC PATIENTS

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The article presents up-to-date data on the main pathogenetic mechanisms and features of the new coronavirus infection caused by the SARS-CoV-2 virus. The review highlights the main epidemiological features of infection with SARS-CoV-2 in children at various age periods, features of the immune response and variants of the course of the disease with lung damage, as well as other organs and systems. The clinical and laboratory features of the course of a new coronavirus infection in children are highlighted. It was found that children are less likely to develop severe COVID-19 than adults. More than 95% of all cases of the disease range from asymptomatic course to clinical manifestations of mild and moderate severity. About 2% of children's patients need hospitalization, including in the intensive care unit and ventilator. However, extrapulmonary manifestations are registered in children more often than in adults, especially from the gastrointestinal tract and circulatory organs. According to numerous authors, the features of the clinical and laboratory course of COVID-19 in pediatric patients are probably associated with a number of factors, among which age-related features of the immune response, the functioning of angiotensin-converting enzyme-2 (ACE-2) used by coronaviruses as a cellular receptor are indicated. Understanding the role of the child population in the dynamics of transmission of infection is important, since children significantly affect the rate of infection spread.

Keywords: coronavirus infection; acute respiratory distress syndrome; pathogenesis; immune response; children.

ЭПИДЕМИОЛОГИЧЕСКИЕ И КЛИНИКО-ЛАБОРАТОРНЫЕ ОСОБЕННОСТИ COVID-19 У ПАЦИЕНТОВ ДЕТСКОГО ВОЗРАСТА

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В статье представлены современные данные об основных патогенетических механизмах и особенностях новой коронавирусной инфекции, обусловленной вирусом SARS-CoV-2. В обзоре выделены основные эпидемиологические особенности инфицирования SARS-CoV-2 детей в различные возрастные периоды, особенности иммунного ответа и варианты течения заболевания с поражением легких, а также других органов и систем. Освещены клинико-лабораторные особенности течения новой коронавирусной инфекции у детей. Установлено, что у детей реже, чем у взрослых, развивается тяжелое течение COVID-19. Более 95 % всех случаев заболевания варьируют от бессимптомного течения до клинических проявлений легкой и средней степени тяжести. Около 2 % пациентов детского возраста нуждаются в госпитализации, в том числе в отделение интенсивной терапии, и проведении искусственной вентиляции легких. Однако у детей чаще, чем у взрослых, регистрируются внелегочные проявления, особенно со стороны желудочно-кишечного тракта и органов кровообращения. По данным многочисленных авторов, особенности клинико-лабораторного течения COVID-19 у пациентов детского возраста, вероятно, связаны с целым рядом факторов, среди которых указаны возрастные особенности иммунного ответа, функционирования ангиотензин-превращающего фермента-2 (ACE-2), используемого коронавирусами в качестве клеточного рецептора. Важно понимание роли детской популяции в динамике передачи инфекции, поскольку дети значимо влияют на темпы ее распространения.

Ключевые слова: коронавирусная инфекция; острый респираторный дистресс-синдром; патогенез; иммунный ответ; дети.

Over the past 20 years, humanity has faced three epidemics caused by coronaviruses, namely, severe acute respiratory syndrome (SARS-2003), Middle East respiratory syndrome (MERS, 2012), and a new coronavirus infection (nCoV) [33]. In early January 2020, a new type of coronavirus (CoV) was detected in a bronchoalveolar lavage sample from a patient with pneumonia of unknown origin in China, which was provisionally named novel coronavirus (2019-nCoV) to distinguish it from SARS-CoV and MERS-CoV which caused previous outbreaks. Subsequently, the International Committee on Taxonomy of Viruses identified it as SARS-CoV 2, and the disease associated with it was named coronavirus disease 2019 (COVID-19) [11].

SARS-CoV-2 spread quickly worldwide; therefore, on January 30, 2020, the World Health Organization declared an outbreak of a disease caused by a new coronavirus as a public health emergency of international concern [50].

The first confirmed case of SARS-CoV-2 infection in children was reported in Shenzhen (a province in southern China) on January 20, 2020 [10]. As early as February 10, 2020, 398 cases of COVID-19 in children were reported in China, except the Hubei province where initially children were very rarely tested for SARS-CoV-2. In an analysis of 44,672 laboratory-confirmed cases of COVID-19 from all over China, as of February 11, 2020, 0.9% of the patients were children aged <10 years, and 1.2% of these patients were aged 10–20 years [37]. To date, we know that children get sick much less often with the clinical forms of this infection, especially with its severe course, compared with adults. However, data on the epidemiological characteristics and clinical aspects of the course of COVID-19 in children are still scarce. A Chinese Center for Disease Control and Prevention (CDC) report of 72,314 cases indicates that approximately 2% of all patients were patients aged <19 years [51]. In Italy, one of the first countries affected by the COVID-19 pandemic, 1.2% of all patients were children [29]. In the USA, as of October 22, 2020, there were 7,207,186 cases of COVID-19, and 11% of them occurred in children (1,053 cases per 100,000 pediatric population). Moreover, 0.6%–6.9% of patients with identified cases of infection requiring hospitalization, which accounted for 1%–3.6% of all patients hospitalized. The rate of lethal outcomes among hospitalized children was 0.23% [6, 15].

In China, 94% of children had asymptomatic or mild/moderate disease, approximately 5% of the pediatric patients had a severe course, and 1% had an extremely severe disease [36]. Most often, COVID-19 was detected in the group aged up to 5 years and older than 10 years; however, severe COVID-19 was more common in children aged 5–10 years. Boys were sick slightly more often than girls (52% versus 48%). The majority of confirmed cases (68.6%) had contact with family members with COVID-19. More than 90% of the patients had an asymptomatic, mild, or moderate course. A severe course was recorded in 10.6% of children aged <1 year, 7.3% of children aged 1–5 years, 4.2% of children aged 6–10 years, 4.1% of children aged 11–15 years, and 3.0% of children aged ≥16 years [17].

According to the Russian Federal State Agency for Health and Consumer Rights, more than 3,159 million cases of COVID-19 were detected in 85 regions of the Russian Federation in 2020. The incidence rate was 2152.63 per 100 thousand populations. Changes in the number of COVID-19 cases in Russia in 2020 were characterized by two increases in incidence. Among all COVID-19 cases, 5.1% were recorded in schoolchildren and 1.8% in students, and 3.3% in preschool children. Severe forms of COVID-19 were mostly registered in the group aged >55 years (77.6%) [2].

The pathogenesis of COVID-19 has already been sufficiently studied to date. A phylogenetic analysis revealed that the genetic code of SARS-CoV-2 is 70% similar to SARS-CoV; accordingly, the virus can use the same receptor to enter the cell. However, the affinity of the S-peptide for human angiotensin-converting enzyme 2 (ACE2) in SARS-CoV-2 is 10–20 times higher than that of the SARS-CoV spike, which facilitates its transmission from person to person [56]. Coronavirus susceptibility is associated with the presence of dipeptidyl peptidase 4 and ACE2 receptors in the lower respiratory tract, which are the main receptors for the SARS-CoV S-peptide [33]. Evidence shows that ACE2 expres-

sion is the highest in children, adolescents, and young women and lowest in older men. ACE2 is a part of the ACE2/angiotensin-(1–7)/MAS system that counteracts the pro-inflammatory effects of the ACE/angiotensin II axis. It catalyzes the conversion of angiotensin II to angiotensin I, 3–7, which modulates vasoconstriction, leukocyte migration, inflammatory cytokine expression, and fibrinogen activation [26]. That is, a high expression of ACE2 may be beneficial, as virions compete for receptor binding to angiotensin II. Children can maintain sufficiently high levels of angiotensin I, 3–7, to counterbalance the pro-inflammatory effects of angiotensin II. Thus, variable expression of ACE2 across age groups may explain why most children and young adults shake off SARS-CoV-2 infection without developing severe symptoms or complications and disprove the hypothesis that children are not the source of infection because they have no severe disease symptoms.

Several immune defense mechanisms are capable of eliminating viruses from the host organism. Antigen-presenting cells, such as dendritic cells and macrophages, phagocytize antigens and cleave them into fragments using lysosomes. These fragments are loaded onto major class I or class II histocompatibility complex molecules and transported to the cell surface for antigen presentation. Toll-like receptors (TLRs) on T cells, together with co-receptors, bind to the presented antigen. Helper T cells secrete cytokines that activate cytotoxic T cells (T_Cs) and B cells. T_Cs destroy infected cells through cell-mediated immunity, and antibody-secreting B cells mediate humoral immunity. According to Li et al. [26], the human innate immune system detects viral pathogen-associated molecular patterns using pattern-recognition receptors represented by TLR, RIG-I-like (RLR), NOD-like (NLR), cytoplasmic, and type C lectin-like receptors (CLmin). Moreover, TLRs, having recognized the S-protein of SARS-CoV-2, activate the production of numerous pro-inflammatory cytokines by epithelial cells and macrophages. The release of active mature interleukin 1, beta (IL-1β) recruits neutrophils to the lung tissue, increases heat production, and activates the production of type I interferon (IFN-I). Airway epithelial cells also secrete various cytokines, chemokines, antimicrobial peptides, and other factors in response to viral infection [26, 54].

COVID-19 is accompanied by an extremely high production of pro-inflammatory cytokines (IFN-α, IFN-γ, IL 1β, IL-6, IL-12, IL-18, IL-33, tumor necrosis factor [TNF]-α, granulocyte-macrophage colony-stimulating factor, etc.) and chemokines; therefore, the cytokine reaction in patients with infection was called cytokine storm syndrome (CSS). These cytokines and chemokines recruit effector immunocytes, causing the development of local inflammatory response. CSS underlies the development of acute respiratory distress syndrome (ARDS) and multiple organ failure, which are fatal in severe cases [54]. The lethality of COVID-19 is associated precisely with a high level of IL-6 and a decrease in IL-10 in the blood serum [39]. SARS-CoV-2 is highly sensitive to the action of IFN but encodes proteins that counteract innate immune defenses, including suppressing the activity of IFN-I production (immune evasion mechanism). The absence of IFN-I leads to a defect in antibody production [46].

The development of COVID-19 is accompanied by excessive activation of cellular immunity, as evidenced by a sharp increase in the representativeness of cells expressing human leukocyte antigen-DR and CD38, associated with a significant decrease in the population of $CD4^+$ and NK cells in the peripheral blood. Cytotoxic $CD8^+$ T cells in COVID-19 produce large amounts of granzymes A and B and perforin. Patients have a high level of pro-inflammatory $CCR6^+$-Th17 cells. Excessive Th17 cell activation and extremely high levels of $CD8^+$ T cell cytotoxicity are believed to underlie the severity of immune damage to the lung tissue. With COVID-19, depletion of the pool of regulatory T cells (Treg cells) is also registered, which predetermines the unlimited activation of inflammation mechanisms and delays the process of resolving the inflammatory process [54]. The activation of virus-specific B cells leads to their differentiation into the plasma cells, which sequentially produce specific antibodies of the IgM and IgG classes. Antibody-producing cells with COVID-19 appear in the peripheral bloodstream on day 7. A gradual increase in the concentration of antibodies of the IgM and IgG class in the blood serum is noted from day 7 to

day 20 of the disease. Specific IgM disappears at the end of week 12 from disease onset, and IgG persists for a long period, indicating the level of protection against re-infection [1, 54].

In the early phase of the disease, which generally is mild, the main role is played by nonspecific defense mechanisms and specific adaptive immune response that allows the elimination of coronavirus from the body [1]. However, if the immune response is ineffective, a late phase develops, which is based on the SARS-CoV-2 super-replication and CSS. Large-scale viral replication is accompanied by the generation of numerous virions, which leads to massive damage to target body tissues, including the lungs. Damaged ACE2-expressing cells produce pro-inflammatory cytokines that recruit effector cells (i.e., macrophages and neutrophils), release even more pro-inflammatory cytokines, and induce CSS development. If the immune function of patients in the acute phase is effective, there are no comorbid diseases, and optimal treatment is performed, the virus can be eliminated with the transition to the recovery phase [46].

Lung damage in COVID-19 is the main cause of severe disease and lethal outcomes [54]. After the penetration of SARS-CoV-2 into the body, the production of the ACE2 protein is inhibited, which leads to a decrease in the level of its representativeness, especially in lung tissues, increase in the concentration of angiotensin II, increase in capillary permeability, development of pulmonary edema, activation of apoptosis, and development of an inflammatory response in the lung tissue. A decrease in ACE2 concentration also leads to the activation of signaling pathways associated with the inducible B1 receptor Des-Arg9 bradykinin, which further increases inflammation and contributes to lung tissue damage. At the first stage of lung damage, alveolar macrophages, having recognized SARS-CoV-2, begin to produce pro-inflammatory ILs and chemokines that recruit effector T-lymphocytes. In the late period, an extremely high production level of IL-6, IL-1β, TNF-α, and other pro-inflammatory cytokines causes an influx of numerous monocytes and neutrophils, which enhance inflammation and contribute to the development of pulmonary edema. IL-1β and TNF-α induce hyaluronan synthase 2 activity in endothelial cells, lung alveolar epithelial cells, and fibroblasts, resulting in excess hyaluronic acid production and fluid accumulation in the alveolar space [23, 24].

With COVID-19, other organs and systems are also affected. SARS-CoV-2 infection, by suppressing ACE2 expression, can lead to excessive accumulation of angiotensin II, which causes the development of fulminant myocarditis and ARDS. Two-thirds of patients who died from COVID-19 had a history of arterial hypertension, cardiovascular disease, or diabetes mellitus [1, 20]. It is assumed that the COVID-19 course associated with cardiovascular diseases is predetermined by the state of the renin–angiotensin system. The mechanism of acute myocardial injury caused by SARS-CoV-2 is perhaps associated with increased expression of the ACE2 protein, CSS, and hypoxemia [55]. Two competing hypotheses are put forward: First, the blockade of the renin–angiotensin system reduces the pro-inflammatory activity of angiotensin II, reducing the risk of ARDS, myocarditis, or mortality. Second, the blockade of the renin-angiotensin system increases the expression of ACE2, contributing to the internalization of SARS-CoV-2 into lung and heart cells, which leads to ARDS, myocarditis, and death [20].

The kidneys also become a specific target for SARS-CoV-2, since ACE2 is actively expressed in the epithelial cells of the proximal tubules [52]. With COVID-19, pro-inflammatory macrophages are recruited into the tubulointerstitium, and a pronounced deposition of complement C5b-9 in the renal tubules occurs, which can cause acute renal failure. In addition, 78%–88% of patients with severe COVID-19 have signs of damage to the central nervous system, such as impaired consciousness, cerebrovascular disorders, reduced taste (hypogeusia), and olfactory sensitivity (hyposmia) [31]. It is assumed that SARS-CoV-2, like other coronaviruses, initially infects peripheral nerve endings and then, using the mechanism of transsynaptic transfer, penetrates the tissue of the central nervous system, mainly affecting the cells of the thalamus and brainstem [27].

In children, the disease is usually mild/moderate, and only in rare cases, CSS occurs. There are

suggestions on various factors contributing to these aspects, as children travel less, which reduces the risk of communication, and this may have played a role in the beginning of the pandemic; in adults, especially in risk groups (elderly patients), the clearance of the pathogen may be reduced [1]. Children have a lower burden of comorbid pathology. Some authors also indicated the characteristics of the immune response in children compared with adults, including the presence of strong innate and weaker adaptive immune responses. These aspects contribute to a more effective containment of the virus and/or reduction of lymphocyte-mediated secondary inflammation. The role of the local microbiome and presence of concomitant viral infections (including joint sanitation), which contribute to a milder COVID-19 course in children, has been discussed [15, 17].

The protective role of routine vaccination against bacterial and viral infections in the formation of resistance against SARS-CoV-2 is also considered. Live-attenuated vaccines (e.g., against measles or Calmette–Guerin bacillus (BCG)) provide protection beyond the intended target antigen. This heterologous immune response is probably mediated by changes in innate immune mechanisms. Thus, according to some data, in individuals who received the BCG vaccine, the production of IL-1β and TNF-α increases in response to the invasion of *Staphylococcus aureus* or *Candida spp*. In addition, a decrease in mortality from sepsis is registered among children vaccinated with BCG [13]. Thus, recent vaccinations in children may protect against COVID-19, and immune aging and associated decline in T cell clonality in the elderly predispose to severe disease. Given the structural similarities between coronaviruses and SARS-CoV-2 (e.g., common viral S proteins), an adaptive immune response against coronaviruses may also provide protection against SARS-CoV-2 [19]. That is, the high recurrence rate of respiratory tract infections in children, combined with the nonspecific effects of mandatory vaccinations, may also protect against SARS-CoV-2.

Other possible protective mechanisms are differences in endothelial damage due to age-related changes in protein concentration in the blood coagulation system. In addition, quantitative and almost certainly qualitative differences occur in the hemostasis system with age. Finally, children, especially younger children, have healthier airways than older people and are not affected by cigarette smoke and pollution, which may reduce the risk of severe COVID-19. The question of whether the geographical location of the regions affects the incidence rate remains debatable, as there are many other factors including migration, population density, etc.

The role of children in infection transmission at home and in organized settings is still at the center of debates. Possible explanations for conflicting reports on the incidence and prevalence of SARS-CoV-2 infection among children and adolescents are caused by the use of various testing methods (polymerase chain reaction (PCR) and serology). According to Stringhini et al. [43], home contact with patients with SARS-CoV-2 infection results in seroconversion in 17.9% of children, which is comparable with adults, and lower seropositivity rates are detected in young children (0.8%) and elderly (4.1%), with the highest seroconversion rates in middle-aged people (9.9%).

The routes of SARS-CoV-2 transmission in the pediatric population are similar to those in adults, namely, airborne droplets, airborne aerosols, fecal–oral, and household contact. The virus can persist in aerosol form for up to 2 h and 6–8 hours on plastic/metal surfaces, 3 days on hair, and several days in the room where the patient stayed [3].

According to different authors, 7.5%–86.4% of children with COVID-19 had close contact with patients in intrafamilial foci [16]. The most common source of infection for children and adolescents was a parent or a sibling, followed by contact with a person outside the family or an unknown person. Posfay-Barbe et al. [34] reported that in 40 children with COVID-19, the onset of the disease clinical presentation occurs after or simultaneously with the disease of adult family members and suggested that children were probably not the source of infection. Moreover, adult patients remain PCR-positive for a longer time than children [42]. Close contact (e.g., sleeping in the same room with the patient) or even casual contact (eating in the same room with the patient) increases the risk of transmission.

The shedding of the virus may precede the onset of symptoms, which facilitates the spread of the infection. Given that not all family members coughed, most of the viruses were possibly transmitted via the saliva, as SARS-CoV-2 was also found in saliva [45]. To date, repeated cases of diagnosing the disease in children have been described, which preceded the onset of symptoms in parents on days 6–8 [7, 57]. This raises the question, is the incubation period in children shorter than that in adults? Did the parents develop an infection following contact with the child? A German study reported that the viral load in children aged <6 years did not differ significantly from that in adults [38]. This means that even if children exhibit fewer symptoms, they can still infect others, just like adults.

Children with COVID-19 usually have typical symptoms of acute respiratory infections, such as fever (95%), headache (60.3%), and asthenia (57.8%). Cough, tachypnea, hypoxia, and diarrhea were registered in 39%, 41.7%, 34.2%, and 34.7% of cases, respectively, whereas rhinorrhea and sore throat were detected in 18.3% of cases [21]. The severity of clinical symptoms in children with COVID-19 depended on the age of the child and the presence of risk factors, such as unfavorable premorbid background, comorbid pathology (lung and cardiovascular diseases, neuromuscular pathology, anemia, and type 1 diabetes mellitus), immunodeficiency states of various origins, and co-infection with respiratory syncytial and other viruses at the time of infection or in presence of infection with SARS-CoV-2 [30].

In the USA, the incidence of severe COVID-19 in children has been low. An analysis of the medical records of 177 children and adolescents with COVID-19 treated between March 15 and April 30, 2020, at a medical center in Washington, D.C., reported that 25% of the patients were hospitalized among those who fell ill, and 20.5% of them required emergency care (89% of patients required respiratory support, and one child developed Kawasaki-like syndrome) [14]. Among children admitted to the New York City Children's Hospital, 80% had fever, 64% had respiratory symptoms, and 6% had only gastrointestinal symptoms. The most common comorbidity was obesity (22%). Moreover, the authors note that obesity was associated with the need for artificial lung ventilation in children aged >2 years. Patients with severe COVID-19 had significantly higher levels of C-reactive protein, procalcitonin, IL-6, ferritin, and D-dimer. Lymphopenia was usually noted at admission, but the indicators did not depend on the severity of the disease course. A long-term positive PCR test result (maximum 27 days) was registered in 8% of the patients [55].

In Egypt, 25.9% of 398 children hospitalized with COVID-19 had a severe disease course. Furthermore, 41.7% of children with severe disease required mechanical lung ventilation, and 20.4% of these patients died. Atypical manifestations were registered in 3.5% of children, including acute pancreatitis, deep-vein thrombosis, and multisystem inflammatory syndrome in children (MIS-C) [40]. The authors stated that COVID-19 was significantly severe in patients with high D-dimer levels, hypoxia, shock, and mechanical lung ventilation.

Approximately from day 7 to day 14 of infection, COVID-19 begins to affect the lungs, heart, and gastrointestinal tract with typical clinical symptoms and increased levels of inflammatory mediators and cytokines [26]. At this disease stage, hematological changes develop particularly significant lymphopenia. This can be due to several mechanisms: (a) exposure to SARS-CoV-2 causing lysis of lymphocytes, since lymphocytes have ACE2 receptors on their surface; (b) apoptosis of lymphocytes caused by a systemic inflammatory process with subsequent production of cytokines; and (c) atrophy of lymphoid organs, such as the spleen, which impairs the circulation of lymphocytes [35].

In 28.9% of pediatric patients with COVID-19, hematological changes occurred, such as leukopenia/lymphopenia [16, 22] and increased levels of C-reactive protein [40], erythrocyte sedimentation rate, and D-dimer in children with severe disease [35, 44]. Moreover, the erythrocyte sedimentation rate and D-dimer levels correlated directly with the severity of the patient's condition [35].

Chest computed tomography (CT) changes in children with COVID-19 are recorded with varying frequency depending on the severity of the

lesion. Children with severe disease with lung involvement had ground-glass changes in CT (68%) and crazy paving (ground-glass combinations with thickened interlobular septa, and crazy paving patterns) (16.5%) [40]. In asymptomatic COVID-19, no changes on CT scan were noted in more than 1/3 of children; in 50% of children with moderate or severe COVID-19, bilateral multilobular diffuse ground-glass opacities, crazy paving patterns, and lung tissue induration were noted (consolidation, a symptom of halo). Lung consolidation results from the combination of numerous desquamated and exudate cells and proteins that fill lung tissues to form hyaline membranes in the alveoli. A systematic review study of 674 children with COVID-19 demonstrated abnormalities in 50% of the patients. Among 605 children who underwent chest CT, 29% had ground-glass opacities, 27% had nonspecific unilateral lesions, and 23% of had bilateral lesions [59].

Unlike adults, children more often have extrarespiratory symptoms, with diarrhea (9.4%) and vomiting (7.3%) as the most frequently reported, usually preceding the onset of typical respiratory symptoms [59]. Previous studies have demonstrated the presence of the virus in intestinal and stool biopsy samples of recovered patients, indicating a possible tropism of SARS-CoV for gastrointestinal tract cell receptors [25]. This partly explains the extrarespiratory symptoms and persistent fecal viral shedding [54]. At present, increasing evidence reveals that this isolation mechanism may be characteristic of SARS-CoV-2. In 10 children with COVID-19, SARS-CoV-2 was detected in rectal swabs after a negative nasopharyngeal PCR test [32, 53].

Some researchers have noted abdominal pain and loss of appetite in children with COVID-19. Cases of necrotizing pancreatitis have been reported, including in a 7-year-old girl, when, in addition to respiratory symptoms, the child had anorexia, abdominal pain, fever, and high serum lipase levels (1,672 U/L) [4]. This was probably due to the pathophysiology of the SARS-CoV-2 pancreatic lesion as a result of ACE2 expression in both islet and exocrine cells. Pancreatic injury in COVID-19 is secondary to an immune-mediated process.

While most children and young people have mild or asymptomatic COVID-19, more recently, severe cases have also been reported. In the literature, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV2 (PIMS-TS) and MIS-C are used to describe the phenotypes of hyperinflammatory diseases associated with SARS-CoV-2 infections in children [12]. Manifestations of PIMS-TS/MIS-C vary considerably and include clinical and laboratory evidence of systemic inflammation. A wide range of symptoms vary from fever and systemic inflammation to myocardial lesion, leading to tissue damage and shock and, in some patients, to the development of coronary artery dilatation/aneurysm [32]. However, it is still unclear whether excessive inflammatory manifestations in children are directly related to active SARS-CoV-2 infection or whether they result from immune activation to the presence of the virus. Some authors support the hypothesis that PIMS-TS/MIS-C is caused not by the pathogen itself but by host immune mechanisms in the context of infection control [38]. Arguments in favor of this hypothesis include the finding that PIMS-TS/MIS-C first appears several weeks after the first peak of COVID-19 in adults and that the majority of patients with PIMS-TS/MIS-C have negative PCR tests when testing nasopharyngeal and/or fecal samples. A significant proportion of children and young adults with PIMS-TS/MIS-C have gastrointestinal symptoms. IgG antibodies against SARS-CoV-2 are found in a significant proportion of patients with PIMS-TS/MIS-C at the time of diagnosis. Since seroconversion usually occurs approximately 14 days after infection, this is indicative of a para-/post-infection immune activation underlying PIMS-TS/MIS-C [18]. Another possible explanation for the development of PIMS-TS/MIS-C is closely related to the presence of laboratory signs of CSS. Unhindered viral replication in the early stages of the disease, for example, in the respiratory epithelium, leads to cell death and the release of the virus and intracellular components into the extracellular space. This activates the complement system and leads to the mobilization of immune cells to the infection site, their activation, local inflammation, tissue damage, and finally systemic inflammatory

reactions. Variable T cell activation and response contribute to various disease outcomes [38]. The temporal–spatial composition of immune responses is likely to play a key role in determining the disease progression and outcomes [31]. The hyperinflammatory syndrome in children is possibly due to uncontrolled viral replication in the presence of an impaired antiviral response (PIMS-TS/MIS-C), for example, as a result of a decrease in INF-I production, which may contribute to the development of CSS. Most likely, the mechanisms that play a key role in determining disease susceptibility and severity, including an increased risk of adverse outcomes, are not yet recognized.

Extensive venous thrombosis and severe venous outflow obstruction with COVID-19-associated limb gangrene were described in a 12-year-old girl [47], although it was previously believed that venous thromboembolism occurs only in adults with COVID-19 [48].

In Bergamo, the province of Italy most affected by the epidemic, from February 18 to April 20, 2020, 10 children with Kawasaki-like syndrome were admitted to the intensive care unit of the city hospital. Moreover, five children had the classic form of Kawasaki disease, and five had MIS-C with non-exudative bulbar conjunctivitis, changes in the lips and/or oral cavity, polymorphic rash, and electrocardiogram changes [47]. In the UK, during the COVID-19 outbreak, eight children with hyperinflammatory shock were admitted to the clinic within 10 days alone, although the usual hospitalization rate for such patients is 1–2 people per week. Among the patients, boys predominated (5 of 8), 7 of 8 children were overweight, but none of the children had lung lesions. In addition, in all patients, the primary PCR test for SARS-CoV-2 was negative, the repeated test was positive in 2 of 8 cases, but a week later, antibodies to SARS-CoV-2 were detected in all patients. One Afro-Caribbean patient aged 15 years who was obese died of acute heart failure despite therapy [47].

In India, among children admitted to the intensive care unit, 7 (36.8%) patients were in a critical condition, 4 (21%) required mechanical lung ventilation with a mean duration of 14.1 days, and 1 had a lethal outcome [5]. The authors note that older children, African Americans or Hispanics, as well as boys are at risk for severe COVID-19, and signs such as hypoxia, thrombocytopenia, and elevated C-reactive protein levels may be useful markers for predicting a severe disease course.

To date, the role of intrauterine infection of the fetus in pregnant women with COVID-19 is still discussed. A study of nine infants born to women with laboratory-confirmed COVID-19 by cesarean section revealed that all newborns later had negative PCR results for COVID-19 [41]. However, the authors suggested that newborns born through vaginal delivery from infected mothers may still be at risk of infection because of close contact during childbirth. SARS-CoV-2 test results on amniotic fluid, cord blood, nasopharynx swabs from newborns, and colostrum samples from infected mothers were negative. According to some researchers, SARS-CoV-2 can be transmitted vertically from an infected mother to her infant, although very rarely. However, this issue remains debatable, since IgM antibodies are found in newborns born to mothers with COVID-19 [9]. Of 91 newborns born to mothers with SARS-CoV-2 infection, 3 had elevated serum IgM levels at birth. A systematic review of 65 articles suggests that the clinical presentation in newborns may be somewhat different from that in older children, with 12% experiencing severe COVID-19 [28]. To minimize infection during the neonatal period, in China, all children are separated from mothers with SARS-CoV-2 infection for at least 14 days [37, 49]. However, the CDC in the USA recommends that the issue of temporary separation of an infected mother from her child should be resolved in each case [8].

Thus, nowadays, a severe COVID-19 course is known to develop in children less often than in adults, and 95% of all cases vary from asymptomatic to clinical manifestations of mild-to-moderate severity. By contrast, approximately 2% of pediatric patients require hospitalization in the resuscitation and intensive care unit or mechanical lung ventilation. Understanding the role of the pediatric population in the rate of infection transmission is important, as children influence significantly the spread of infection. The reaction of the innate immune system in patients remains insufficiently

studied. Therefore, more extensive epidemiological and clinical cohort studies are required to understand better the course and possible consequences of COVID-19 in children.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with the ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article and have read and approved the final version before its publication.

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REFERENCES

1. Abaturov AE, Agafonova EA, Krivusha EL, et al. Pathogenesis of COVID-19. *Zdorov'e rebenka*. 2020;15(2):133–144. (In Russ.). DOI: 10.22141/2224-0551.15.2.2020.200598
2. O sostoyanii sanitarno-ehpidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2020 godu: Gosudarstvennyi doklad. Moscow: Federal'naya sluzhba po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka; 2021. 256 p. (In Russ.) Available from: https://www.rospotrebnadzor.ru/documents/details.php? ELEMENT_ID=18266
3. Rekomendatsii VOZ dlya naseleniya v svyazi c rasprostraneniem novogo koronavirusa (2019-nCoV): mify i lozhnye predstavleniya. (In Russ.) Available from: https://www.who.int/ru/emergencies/diseases/ novel-coronavirus-2019/advice-for-public/myth-busters
4. Alloway BC, Yaeger SK, Mazzaccaro RJ, et al. Suspected case of COVID-19-associated pancreatitis in a child. *Radiol Case Rep*. 2020;15(8):1309–1312. DOI: 10.1016/j.radcr.2020.06.009
5. Bhumbra S, Malin S, Kirkpatrick L, et al. Clinical features of critical coronavirus disease 2019 in children. *Pediatr Crit Care Med*. 2020;21(10):e948–e953. DOI: 10.1097/PCC.0000000000002511
6. Bialek S, Gierke R, Hughes M, et al. Coronavirus disease 2019 in children United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):422–426. DOI: 10.15585/mmwr.mm6914e4
7. Cai JH, Wang XS, Ge YL, et al. First case of 2019 novel coronavirus infection in children in Shanghai. *Zhonghua Er Ke Za Zhi*. 2020;58(2):86–87. DOI: 10.3760/cma.j.issn.0578-1310.2020.02.002
8. CDC (2020) Coronavirus Disease 2019 (COVID-19). In: Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html
9. Simões e Silva AC, Leal CR. Is SARS-CoV-2 vertically transmitted? *Front Pediatr*. 2020;8:276. DOI: 10.3389/fped.2020.00276
10. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395(10223):514–523. DOI: 10.1016/S0140-6736(20)30154-9
11. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (2020). The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 2019;5:536–544. DOI: 10.1038/s41564-020-0695-z
12. Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health*. 2020;4(9):669–677. DOI: 10.1016/S2352-4642(20)30215-72020/07/13
13. de Bree LCJ, Koeken V, Joosten LAB, et al. Non-specific effects of vaccines: Current evidence and potential implications. *Semin. Immunol*. 2018;39:35–43. DOI: 10.1016/j.smim.2018.06.002
14. DeBiasi RL, Song X, Delaney M, et al. Severe Coronavirus Disease-2019 in children and young adults in the Washington, DC, Metropolitan Region. *J Pediatr*. 2020;223:199–203E1. DOI: 10.1016/j.jpeds.2020.05.007
15. Desai A, Mills A, Delozier S, et al. Pediatric patients with SARS-CoV-2 infection: clinical characteristics in the US from a large Global Health Research Network. *Cureus*. 2020;12(9): E10413. DOI: 10.7759/cureus.10413
16. Ding Y, Yan H, Wenbin GW. Clinical characteristics of children with COVID19: a meta-analysis. *Front Pediatr*. 2020;8:431. DOI: 10.3389/fped.2020.00431
17. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6): e20200702. DOI: 10.1542/peds.2020-0702
18. Felsenstein S, Herbert JA, McNamara PS, et al. COVID-19: immunology and treatment options. *Clin Immunol*. 2020;215:108448. DOI: 10.1016/j.clim.2020.108448
19. Grifoni A, Sidney J, Zhang Y, et al. A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARS-CoV-2. *Cell Host Microbe*. 2020;27(4):671–680.E2. DOI: 10.1016/j.chom.2020.03.002
20. Hanff TC, Harhay MO, Brown TS, et al. Is There an Association Between COVID-19 Mortality and the

Renin-Angiotensin System-a Call for Epidemiologic Investigations. *Clin Infect Dis*. 2020;71(15):870–874. DOI: 10.1093/cid/ciaa329
21. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: a systematic review. *J eClin Med*. 2020;100433. DOI: 10.1016/j.eclinm.2020.100433;24:100433
22. Kosmeri C, Koumpis E, Tsabouri S, et al. Hematological manifestations of SARS-CoV-2 in children. *Pediatr Blood Cancer*. 2020;67(12): e28745. DOI: 10.1002/pbc.28745
23. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875–879. DOI: 10.1038/nm1267
24. Kuster GM, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J*. 2020;41(19): 1801–1803. DOI: 10.1093/eurheartj/ehaa235
25. Leung WK, To K-F, Chan PKS, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology*. 2003;125(4): 1011–1017. DOI: 10.1016/s0016-5085(03)01215-0
26. Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. *J Med Virol*. 2020;92(4):424–432. DOI: 10.1002/ jmv.25685
27. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552–555. DOI: 10.1002/jmv.25728
28. Liguoro I, Pilotto C, Bonanni M, et al. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr*. 2020;179:1029–1046. DOI: 10.1007/s00431-020-03684-7
29. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA*. 2020;323(14):1335. DOI: 10.1001/jama.2020.4344
30. Mantovani A, Rinaldi E, Zusi C, et al. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis: International Pediatric Research Foundation, Inc; 2020. *Pediatr Res*. 2021;89:733–737. DOI: 10.1038/s41390-020-1015-2
31. Mao L, Wang M, Chen S, et al. Neurologic Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China. Retrospective Case Series Study. *Jama Neurology*. 2020;77(6):683–690. DOI: 10.1001/jamaneurol.2020.1127
32. Pain CE, Felsenstein S, Cleary G, et al. Novel paediatric presentation of COVID-19 with ARDS and cytokine storm syndrome without respiratory symptoms. *Lancet Rheumatol*. 2020;2(7): E376–E379. DOI: 10.1016/S2665-9913(20)30137-5
33. Pandit K, Gupta S, Sharma AG. Clinico-pathogenesis of COVID-19 in children. *Indian J Biochem Biophys*. 2020;57(3):264–269.
34. Posfay-Barbe KM, Wagner N, Gauthey M, et al. COVID-19 in children and the dynamics of infection in families. *Pediatrics*. 2020;146(2):e20201576. DOI: 10.1542/peds.2020-1576
35. Razavi A, Davoodi L, Shojaei L, et al. COVID-19 in children: a narrative review. *Open Access Maced J Med Sci*. 2020;8(T1):23–31. DOI: 10.3889/oamjms.2020.4714
36. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill*. 2020;25(4):2000058. DOI: 10.2807/1560-7917.ES.2020.25.4.2000058
37. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607–1608. DOI: 10.1016/S0140-6736(20)31094-1
38. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol*. 2020;20(8):453–454. DOI: 10.1038/s41577-020-0367-52020/06/18
39. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846–848. DOI: 10.1007/s00134-020-05991-x
40. Saleh NY, Aboelghar HM, Salem SS, et al. The severity and atypical presentations of COVID-19 infection in pediatrics. *BMC Pediatrics*. 2021;21:144. DOI: 10.1186/s12887-021-02614-2
41. Simões e Silva AC, Leal CR. Is SARS-CoV-2 vertically transmitted? *Front Pediatr*. 2020;8:276. DOI: 10.3389/fped.2020.00276
42. Song R, Han B, Song M, et al. Clinical and epidemiological features of COVID-19 family clusters in Beijing, China. *J Infect*. 2020;81(2):E26–E30. DOI: 10.1016/j.jinf.2020.04.018
43. Stringhini S, Wisniak A, Piumatti G, et al., Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet*. 2020;396(10247):313–319. DOI: 10.1016/S0140-6736(20)31304-02020/06/15
44. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834–847. DOI: 10.1002/ajh.25829
45. To KKW, Tsang OTY, et al. Consistent detection of 2019 novel coronavirus in saliva. *Clinical Infectious Diseases*. 2020;71(15):841–843. DOI: 10.1093/cid/ciaa149
46. Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism

of interferon. *Curr Opin Virol*. 2012;2(3):264–275. DOI: 10.1016/j.coviro.2012.04.004
47. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771–1778. DOI: 10.1016/S0140-6736(20)31103-X
48. Visveswaran GK, Morparia K, Narang S, et al. Severe acute respiratory syndrome coronavirus 2 infection and thrombosis: phlegmasiaceruleadolenspresenting with venous gangrene in a child. *J Pediatr*. 2020;226: 281–284. DOI: 10.1016/j.jpeds.2020.07.032
49. Wang L, Shi Y, Xiao T, et al. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (first edition). *Ann Transl Med*. 2020;8(3):47. DOI: 10.21037/atm.2020.02.20
50. WHO Director-General's opening remarks at the media briefing on COVID-19. 11 March, 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19 %2D%2D-11-march-2020
51. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13): 1239–1242. DOI: 10.1001/jama.2020.2648
52. Wysocki J, Schulze A, Batlle D. Novel Variants of Angiotensin Converting Enzyme-2 of Shorter Molecular Size to Target the Kidney Renin Angiotensin System. *Biomolecules*. 2019;9(12):886. DOI: 10.3390/biom9120886
53. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med*. 2020;26: 502–505. DOI: 10.1038/s41591-020-0817-4
54. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420–422. DOI: 10.1016/S2213-2600(20)30076-X
55. Zachariah Ph, Johnson CL, Halabi KC, et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City. *JAMA Pediatr*. 2020;174(10)e202430. DOI: 10.1001/jamapediatrics
56. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. 2020;9(1): 386–389. DOI: 10.1080/22221751.2020.1729071
57. Zhang YP. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Chin J Epidemiol*. 2020;41(2):145–151. DOI: 10.3760/cma.j.issn.0254-6450.2020.02.003
58. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17: 259–260. DOI: 10.1038/s41569-020-0360-5
59. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis. Treatment and Prevention Options in Children. *Pediatr Infectious Disease Journal*. 2020;39(5): 355–368. DOI: 10.1097/INF.0000000000002660

СПИСОК ЛИТЕРАТУРЫ

1. Абатуров А.Е., Агафонова Е.А., Кривуша Е.Л., и др. Патогенез COVID-19 // Здоровье ребенка. 2020. Т. 15, № 2. С. 133–144. DOI: 10.22141/2224-0551.15.2.2020.200598
2. О состоянии санитарно-эпидемиологического благополучия населения в Российской Федерации в 2020 году: Государственный доклад. Москва: Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека. 2021. 256 с. Режим доступа: https://www.rospotrebnadzor.ru/documents/details.php? ELEMENT_ID=18266. Дата обращения: 02.10.2021.
3. Рекомендации ВОЗ для населения в связи с распространением нового коронавируса (2019-nCoV): мифы и ложные представления. Режим доступа: https://www.who.int/ru/emergencies/diseases/novel-coronavirus-2019. Дата обращения: 02.10.2021.
4. Alloway B.C., Yaeger S.K., Mazzaccaro R.J., et al. Suspected case of COVID-19-associated pancreatitis in a child // Radiol Case Rep. 2020. Vol. 15, No. 8. P. 1309–1312. DOI: 10.1016/j.radcr.2020.06.009
5. Bhumbra S., Malin S., Kirkpatrick L., et al. Clinical features of critical coronavirus disease 2019 in children // PediatrCrit Care Med. 2020. Vol. 21, No. 10. P. e948–e953. DOI: 10.1097/ PCC.0000000000002511
6. Bialek S., Gierke R., Hughes M., et al. Coronavirus disease 2019 in children United States, 2020 // MMWR Morb Mortal Wkly Rep. 2020. Vol. 69, No. 14. P. 422–426. DOI: 10.15585/mmwr.mm6914e4
7. Cai J.H., Wang X.S., Ge Y.L., et al. First case of 2019 novel coronavirus infection in children in Shanghai // Zhonghua Er Ke Za Zhi. 2020. Vol. 58, No. 2. P. 86–87. DOI: 10.3760/cma.j.issn.0578-1310.2020.02.002
8. CDC (2020) Coronavirus Disease 2019 (COVID-19). In: Centers for Disease Control and Prevention. Режим доступа: https://www.cdc.gov/coronavirus/2019-ncov/hc/inpatient-obstetric-healthcare-guidance.html. Дата обращения: 02.10.2021.
9. Simões e Silva A.C., Leal C.R. Is SARS-CoV-2 vertically transmitted? Front Pediatr. 2020. Vol. 8. P. 276. DOI: 10.3389/fped.2020.00276
10. Chan J.F., Yuan S., Kok K.H., et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus

indicating person-to-person transmission: a study of a family cluster // Lancet. 2020. Vol. 395, No. 10223. P. 514–523. DOI: 10.1016/S0140-6736(20)30154-9
11. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (2020). The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2 // Nat Microbiol. 2019. Vol. 5. P. 536–544. DOI: 10.1038/s41564-020-0695-z
12. Davies P., Evans C., Kanthimathinathan H.K., et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study // Lancet Child Adolesc Health. 2020. Vol. 4, No. 9. P. 669–677. DOI: 10.1016/S2352-4642(20)30215-72020/07/13
13. de Bree L.C.J., Koeken V., Joosten L.A.B., et al. Non-specific effects of vaccines: Current evidence and potential implications // Semin Immunol. 2018. Vol. 39. P. 35–43. DOI: 10.1016/j.smim.2018.06.002
14. DeBiasi R.L., Song X., Delaney M., et al. Severe Coronavirus Disease-2019 in children and young adults in the Washington, DC Metropolitan Region // J Pediatr. 2020. Vol. 223. P. 199–203.e1. DOI: 10.1016/j.jpeds.2020.05.007
15. Desai A., Mills A., Delozier S., et al. Pediatric patients with SARS-CoV-2 infection: clinical characteristics in the US from a large Global Health Research Network // Cureus. 2020. Vol. 12, No. 9. P. 210413. DOI: 10.7759/cureus.10413
16. Ding Y., Yan H., Wenbin G.W. Clinical characteristics of children with COVID19: a meta-analysis // Front Pediatr. 2020. Vol. 8. P. 431. DOI: 10.3389/fped.2020.00431
17. Dong Y., Mo X., Hu Y., et al. Epidemiology of COVID-19 among children in China // Pediatrics. 2020. Vol. 145, No. 6. P. e20200702. DOI: 10.1542/peds.2020-0702
18. Felsenstein S., Herbert J.A., McNamara P.S., et al. COVID-19: immunology and treatment options // Clin Immunol. 2020. Vol. 215. P. 108448. DOI: 10.1016/j.clim.2020.108448
19. Grifoni A., Sidney J., Zhang Y., et al. A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARS-CoV-2 // Cell Host Microbe. 2020. Vol. 27, No. 4. P. 671–680.E2. DOI: 10.1016/j.chom.2020.03.002
20. Hanff T.C., Harhay M.O., Brown T.S., et al. Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System? A Call for Epidemiologic Investigations // Clin Infect Dis. 2020;71(15):870–874. DOI: 10.1093/cid/ciaa329
21. Hoang A., Chorath K., Moreira A., et al. COVID-19 in 7780 pediatric patients: a systematic review // J E Clin Med. 2020. P. 100433. DOI: 10.1016/j.eclinm.2020.100433;24:100433
22. Kosmeri C., Koumpis E., Tsabouri S., et al. Hematological manifestations of SARS-CoV-2 in children // Pediatr Blood Cancer. 2020. Vol. 67, No. 12. P. e28745. DOI: 10.1002/pbc.28745
23. Kuba K., Imai Y., Rao S., et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury // Nat Med. 2005. Vol. 11. P. 875–879. DOI: 10.1038/nm1267
24. Kuster G.M., Pfister O., Burkard T., et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? // Eur Heart J. 2020. Vol. 41, No. 19. P. 1801–1803. DOI: 10.1093/eurheartj/ehaa235
25. Leung W.K., To K.-F., Chan P.K.S., et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection // Gastroenterology. 2003. Vol. 125, No. 4. P. 1011–1017. DOI: 10.1016/s0016-5085(03)01215-0
26. Li G., Fan Y., Lai Y., et al. Coronavirus infections and immune responses // J Med Virol. 2020. Vol. 92, No. 4. P. 424–432. DOI: 10.1002/jmv.25685
27. Li Y.C., Bai W.Z., Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients // J Med Virol. 2020. Vol. 92, No. 6. P. 552–555. DOI: 10.1002/jmv.25728
28. Liguoro I., Pilotto C., Bonanni M., et al. SARS-COV-2 infection in children and newborns: a systematic review // Eur J Pediatr. 2020. Vol. 179. P. 1029–1046. DOI: 10.1007/s00431-020-03684-7
29. Livingston E., Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy // JAMA. 2020. Vol. 323, No. 14. P. 1335. DOI: 10.1001/jama.2020.4344
30. Mantovani A., Rinaldi E., Zusi C., et al. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis: International Pediatric Research Foundation, Inc; 2020 // Pediatr Res. 2021. Vol. 89. P. 733–737. DOI: 10.1038/s41390-020-1015-2
31. Mao L., Wang M., Chen S., et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: A Retrospective Case Series Study // Jama Neurology. 2020. Vol. 77, No. 6. P. 683–690. DOI: 10.2139/ssrn.3544840
32. Pain C.E., Felsenstein S., Cleary G., et al. Novel paediatric presentation of COVID-19 with ARDS and cytokine storm syndrome without respiratory symptoms // Lancet Rheumatol. 2020. Vol. 2, No. 7. P. E376–E379. DOI: 10.1016/ S2665-9913(20)30137-5
33. Pandit K., Gupta S., Sharma A.G. Clinico-pathogenesis of COVID-19 in children. Indian J Biochem Biophys. 2020. Vol. 57, No. 3. P. 264–269.

34. Posfay-Barbe K.M., Wagner N., Gauthey M., et al. COVID-19 in children and the dynamics of infection in families // Pediatrics. 2020. Vol. 146, No. 2. P. e20201576. DOI: 10.1542/peds.2020-1576
35. Razavi A., Davoodi L., Shojaei L., et al. COVID-19 in children: a narrative review // Open Access Maced J Med Sci. 2020. Vol. 8, No. T1. P. 23–31. DOI: 10.3889/oamjms.2020.4714
36. Riou J., Althaus C.L. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020 // Euro Surveill. 2020. Vol. 25, No. 4. P. 2000058. DOI: 10.2807/1560-7917.ES.2020.25.4.2000058
37. Riphagen S., Gomez X., Gonzalez-Martinez C., et al. Hyperinflammatory shock in children during COVID-19 pandemic // Lancet. 2020. Vol. 395, No. 10237. P. 1607–1608. DOI: 10.1016/S0140-6736(20)31094-1
38. Rowley A.H. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children // Nat Rev Immunol. 2020. Vol. 20, No. 8. P. 453–454. DOI: 10.1038/s41577-020-0367-52020/06/18
39. Ruan Q., Yang K., Wang W., et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China // Intensive Care Med. 2020. Vol. 46. P. 846–848. DOI: 10.1007/s00134-020-05991-x.
40. Saleh N.Y., Aboelghar H.M., Salem S.S., et al. The severity and atypical presentations of COVID-19 infection in pediatrics // BMC Pediatrics. 2021. Vol. 21. P. 144. DOI: 10.1186/s12887-021-02614-2
41. Simões e Silva A.C., Leal C.R. Is SARS-CoV-2 vertically transmitted? // Front Pediatr. 2020. Vol. 8. P. 276. DOI: 10.3389/fped.2020.00276
42. Song R., Han B., Song M., et al. Clinical and epidemiological features of COVID-19 family clusters in Beijing, China // J Infect. 2020. Vol. 81, No. 2. P. E26–E30. DOI: 10.1016/j.jinf.2020.04.018
43. Stringhini S., Wisniak A., Piumatti G., et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study // Lancet. 2020. Vol. 396, No. 10247. P. 313–319. DOI: 10.1016/S0140-6736(20)31304-02020/06/15
44. Terpos E., Ntanasis-Stathopoulos I., Elalamy I., et al. Hematological findings and complications of COVID-19 // Am J Hematol. 2020. Vol. 95, No. 7. P. 834–847. DOI: 10.1002/ajh.25829
45. To K.K.W., Tsang O.T.Y., et al. Consistent detection of 2019 novel coronavirus in saliva // Clinical Infectious Diseases. 2020. Vol. 71, No. 15. P. 841–843. DOI: 10.1093/cid/ciaa149
46. Totura A.L., Baric R.S. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon // Curr Opin Virol. 2012. Vol. 2, No. 3. P. 264–275. DOI: 10.1016/j.coviro.2012.04.004
47. Verdoni L., Mazza A., Gervasoni A., et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study // Lancet. 2020. Vol. 395, No. 10239. P. 1771–1778. DOI: 10.1016/S0140-6736(20)31103-X
48. Visveswaran G.K., Morparia K., Narang S., et al. Severe acute respiratory syndrome coronavirus 2 infection and thrombosis: phlegmasiaceruleadolenspresenting with venous gangrene in a child // J Pediatr. 2020. Vol. 226. P. 281–284. DOI: 10.1016/j.jpeds.2020.07.032
49. Wang L., Shi Y., Xiao T., et al. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (first edition) // Ann Transl Med. 2020. Vol. 8, No. 3. P. 47. DOI: 10.21037/atm.2020.02.20
50. WHO Director-General's opening remarks at the media briefing on COVID-19. 11 March, 2020. Режим доступа: https://www.who.int/dg/ speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19 %2D%2D-11-march-2020. Дата обращения: 02.03.2022.
51. Wu Z., McGoogan J.M. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention // JAMA. 2020. Vol. 323, No. 13. P. 1239. DOI: 10.1001/jama.2020.2648
52. Wysocki J., Schulze A., Batlle D. Novel Variants of Angiotensin Converting Enzyme-2 of Shorter Molecular Size to Target the Kidney Renin Angiotensin System // Biomolecules. 2019. Vol. 9, No. 12. P. 886. DOI: 10.3390/biom9120886
53. Xu Y., Li X., Zhu B., et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding // Nat Med. 2020. Vol. 26. P. 1–4. DOI: 10.1038/s41591-020-0817-4
54. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome // Lancet Respir Med. 2020. Vol. 8, No. 4. P. 420–422. DOI: 10.1016/S2213-2600(20)30076-X
55. Zachariah Ph., Johnson C.L., Halabi K.C., et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City // JAMA Pediatr. 2020. Vol. 174, No. 10. P. e202430. DOI: 10.1001/ jamapediatrics.2020.2430
56. Zhang W., Du R.H., Li B., et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes // Emerg Microbes Infect. 2020. Vol. 9, No. 1. P. 386–389. DOI: 10.1080/22221751.2020.1729071

57. Zhang Y.P. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China // Chin J Epidemiol. 2020. Vol. 41, No. 2. P. 145–151. DOI: 10.3760/cma.j.issn.0254-6450.2020.02.003
58. Zheng Y.Y., Ma Y.T., Zhang J.Y., et al. COVID-19 and the cardiovascular system // Nat Rev Cardiol. 2020. Vol. 17. P. 259–260. DOI: 10.1038/s41569-020-0360-5
59. Zimmermann P., Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis. Treatment and Prevention Options in Children // Pediatr Infectious Disease Journal. 2020. Vol. 39, No. 5. P. 355–368. DOI: 10.1097/INF.0000000000002660

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