UDC [578.834.1+616-036.21]-053.2-02-092+616-036.22
DOI: 10.56871/CmN-W.2024.86.55.002

CORONAVIRUS INFECTION AND COVID-19 IN CHILDREN. PART 1. EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS

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For citation: Kosenkova TV, Timchenko VN, Bannova SL, Chernova TM, Shakmaeva MA, Bulina OV, Egorova IA. Coronavirus infection and COVID-19 in children. Part 1. Epidemiology, etiology, pathogenesis. Children's Medicine of the North-West. 2024;12(4):21–38. DOI: https://doi.org/10.56871/CmN-W.2024.86.55.002

Received: 04.09.2024 **Revised: 17.10.2024** **Accepted: 16.12.2024**

ABSTRACT. The lecture presents data on the epidemiology of coronaviruses as causative agents of seasonal respiratory viral infections in children, as well as the SARS-CoV-2 virus, which caused the COVID-19 pandemic. The classification, morphology and structure of seasonal coronaviruses are given. The source and transmission routes of the pathogen in a new coronavirus infection are shown, attention is paid to the role of COVID-19 as an infection associated with healthcare. The structural features of SARS-CoV-2, its antigenic determinants that ensure penetration of the virus into target cells, as well as the main and alternative mechanisms of virus penetration into cells are described. Target cells that highly express entry receptors for SARS-CoV-2 are indicated. The pathogenesis of the new coronavirus infection, as well as pathomorphological changes in organs and tissues in COVID-19 in children, are presented in detail

KEYWORDS: *COVID-19, children, etiology, epidemiology, pathogenesis*

КОРОНАВИРУСНАЯ ИНФЕКЦИЯ И COVID-19 У ДЕТЕЙ. ЧАСТЬ 1. ЭПИДЕМИОЛОГИЯ, ЭТИОЛОГИЯ, ПАТОГЕНЕЗ

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Для цитирования: Косенкова Т.В., Тимченко В.Н., Баннова С.Л., Чернова Т.М., Шакмаева М.А., Булина О.В., Егорова И.А. Коронавирусная инфекция и COVID-19 у детей. Часть 1. Эпидемиология, этиология, патогенез. Children's Medicine of the North-West. 2024. Т. 12. № 4. С. 21–38. DOI: https://doi.org/10.56871/CmN-W.2024.86.55.002

Поступила: 04.09.2024 **Одобрена: 17.10.2024** **Принята к печати: 16.12.2024**

РЕЗЮМЕ. В лекции представлены данные об эпидемиологии коронавирусов как возбудителей сезонных респираторных вирусных инфекций у детей, а также о вирусе SARS-CoV-2, который вызвал пандемию COVID-19. Приведена классификация, морфология и структура сезонных коронавирусов. Показаны источник, пути передачи возбудителя при новой коронавирусной инфекции, уделено внимание роли COVID-19 как инфекции, связанной с оказанием медицинской помощи. Описаны особенности строения SARS-CoV-2, его антигенные детерминанты, обеспечивающие проникновение вируса в клетки-мишени, а также основные и альтернативные механизмы проникновения вируса в клетки. Указаны клетки-мишени, которые высоко экспрессируют рецепторы входа для SARS-CoV-2. Подробно представлен патогенез новой коронавирусной инфекции, а также патоморфологические изменения в органах и тканях при COVID-19 у детей.

КЛЮЧЕВЫЕ СЛОВА: *COVID-19, дети, этиология, эпидемиология, патогенез*

EPIDEMIOLOGY

Coronaviruses (causative agents of seasonal viral infections in children) are a group of viruses that causes zoonotic infections transmitted between animals (mammals, birds, amphibians and, presumably, reptiles) and humans; they belong to the genus *Alphacoronavirus* and *Betacoronavirus*, order *Nidovirales*, family *Coronaviridae*, subfamily *Coronaviridae* [1]. The viruses can cause epidemic and even pandemic processes, and the disease proceeds with multisystemic damage of varying severity [2]. Currently, more than 40 types of coronaviruses are known, the list of which is constantly expanding due to spontaneous mutations, so all types of coronaviruses can potentially be dangerous to humans. There are four subfamilies of coronaviruses: *Alphacoronavirus*, *Betacoronavirus*, Gammacoronavirus and *Deltacoronavirus*. The ***Alphacoronavirus*** subfamily includes 2 subgenera, each of which includes one species of coronaviruses of medical significance (the subgenus *Davinalovirus* includes the species *HCoV 229E* and the subgenus *Setracovirus* includes the species *HCoV NL63*). The ***Betacoronavirus*** subfamily includes 5 species of coronaviruses of medical significance, which are divided into 3 subgenera: *Embecovirus* (two species— *HCoV HKU1*, *HCoV OC43*), subgenus *Merbecoronavirus* (species *MERS-CoV*) and subgenus *Sarbecovirus* (species *SARS-CoV* and *SARS-CoV-2*), ***Gammacoronavirus*** *and* ***Deltacoronavirus*** [1, 3]. Nowadays, *Alphacoronavirus* and *Betacoronavirus* pose a danger to people.

The coronavirus was first isolated by A.F. Schalk, M.C. Hawn (1931) and described as an infectious bronchitis virus in chickens [4]. The first publications on respiratory diseases caused by coronaviruses in human date back to 1965, when a description of acute respiratory infection (ARI) appeared in a British child with the isolation of the pathogen *α-coronavirus* group 1, initially described as isolate B814, then defined as HCoV-229E human coronavirus, causing *human coronavirus disease 229E*, and in 1967 K. Mcintosh discovered coronavirus in a tracheal cell culture [5–8]. In 1968, coronaviruses were grouped into the *Coronavirus* group [7], which appeared in the catalogues of the International Committee on Taxonomy of Viruses (ICTV) in 1971. In 1976, the taxonomic rank was raised from genus to family [2]. In 1996, at the 10th International Virology Congress, a taxonomic group was proposed — an order called *Nidovirales* (from Latin *nidos* — nest). In 1967–1972, a number of cases of ARI in adults were recorded, the causative agent of which was β-coronavirus (*HCoV-OC43 from group 2 of lineage A, human coronavirus OC43*). In 2004, coronaviruses HCoV-HKU1 of lineage A of group 2 *β-coronaviruses* and HCoV-NL-63 were isolated, and in 2005, HcoV HKU1 was found [2].

Until 2004, the existence of four representatives of the *Coronavirinae* family, subfamily *Orthocoronavirinae (HCoV 229E, HCoV NL63, HCoV HKU1, HCoV OC43)* was known, which, circulating year-round, caused from 15 to 30% of annual cases of ARI, which, as a rule, occurred with damage to the upper respiratory tract of mild or moderate severity; no fatal outcomes were established [9–11]. However, in 2003–2004, an outbreak of atypical pneumonia of coronavirus etiology was noted in China, which was named severe acute respiratory syndrome (SARS), and the *β-coronavirus SARS-CoV* of group 2 lineage B (reservoir — bats) was isolated. Eight years later, in 2012, in the city of Jeddah, Saudi Arabia, during a study of nasopharyngeal swabs taken from a man with ARI, the *β-coronavirus SARS-CoV* of group 2 lineage C — *MERS-CoV* (middle east respiratory syndrome coronavirus) was isolated. Its reservoir is dromedary camels. The virus caused the Middle East respiratory syndrome (MERS). Both viruses had the ability to spread in epidemics, and outbreaks of coronavirus infection were registered in the world, while the mortality rate of patients, including those under 18 years of age, during the first outbreak was about 10%. The cause of death of 774 people in 37 countries was confirmed. During the second episode, the mortality rate reached 40%. By 2020, 866 deaths from MERS were registered, which forever secured the status of *life-threatening for the coronavirus infection*. Since 2004, no new cases of atypical pneumonia caused by SARS-CoV have been registered, but MERS-CoV continues to circulate and cause new cases of the disease [2, 8, 12].

PANDEMIC OF THE NEW CORONAVIRUS INFECTION

The new coronavirus that entered human circulation at the end of 2019 is a highly homologous copy of SARS-CoV (79%) and MERS-CoV (50%). On February

11, 2020, the International Committee on Taxonomy of Viruses assigned the official name SARS-CoV-2 (*Betacoronavirus*, assigned to pathogenicity group II) to this virus [13–15]. The virus had a lower severity of the diseases it caused and lower mortality rates, and determined the ***pandemic of a new coronavirus infection*** that began on December 8, 2019, in Hubei Province (Wuhan City) of the People's Republic of China. It was there that the first case of a human disease caused by an unknown pathogen was officially registered, and on January 7, 2020, a new virus belonging to the *Coronaviridae* family was identified, temporarily named *2019-nCoV* (from English novel coronavirus 2019). On January 10, 2020, Genbank published the complete genome of the 2019-nCoV virus strain (*Wuhan-Hu-1* under number MN908947, RefCeq NC_045512) for the first time. On January 30, 2020, with a large number of infections and deaths, the World Health Organization (WHO) declared the ongoing outbreak caused by the 2019-nCoV virus a public health emergency of international concern. WHO has renamed the 2019-nCoV virus to *SARS-CoV-2* (severe acute respiratory syndrome 2 — SARS coronavirus 2). On February 1, 2020, WHO assigned the official name of the infection caused by *SARS-CoV-2* to be COVID-19 (Coronavirus disease — 2019). On March 11, 2020, a pandemic was declared [16, 17].

The main variants of SARS-CoV-2 have evolved during the pandemic from pre-alpha, alpha and delta to omicron, the highly transmissible variants of which have led to an increase in the incidence and hospitalization of children in many countries around the world, including Russia [18, 19]. Children became the main source of the spread of the virus, since its release into the environment occurs not only during the incubation period, but also within 7–14 days after the complete resolution of the clinical picture of the disease. As variants of the dominant virus strains changed, the severity of disease in children changed significantly, and by 2021, most patients had mild symptoms (58%) or no symptoms (36%), and hospitalization rates dropped from 10% to 0.2%. By early May 2023, the COVID-19 epidemic situation was assessed by WHO as favorable, which made it possible to lift the international emergency regime and declare the end of the pandemic on May 5, 2023.

MORPHOLOGY AND STRUCTURE OF CORONAVIRUSES AND SARS-COV-2 VIRUS

Analysis of the SARS-CoV-2 genome has shown thatit is very similar to the genome of bat coronaviruses, and the receptor-binding domain of the spike

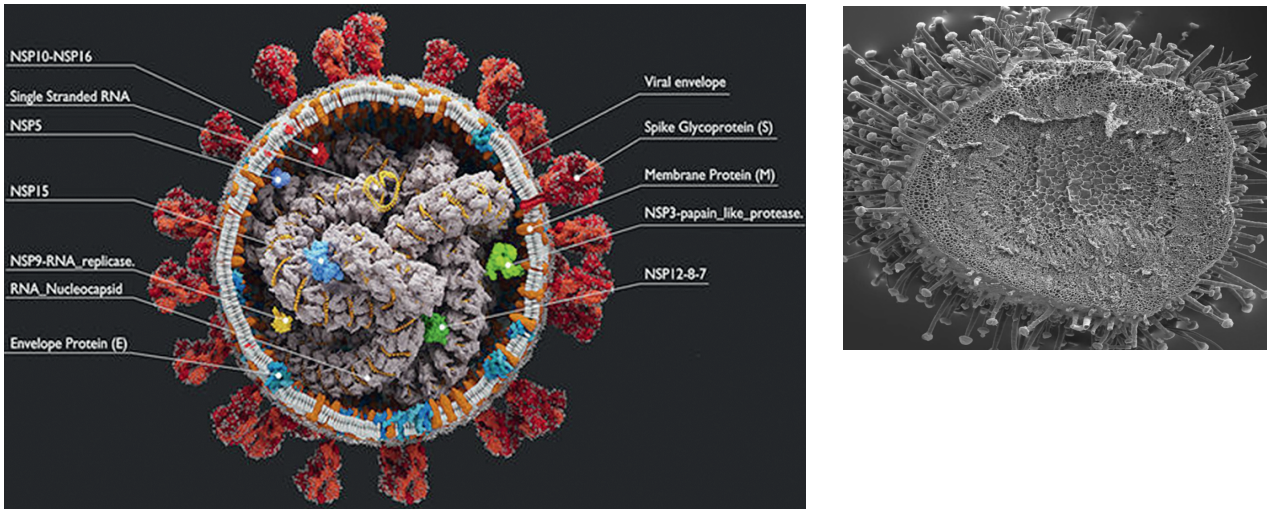


Fig. 1. The structure of coronaviruses (Source: https://img-new.cgtrader.com/items/2534580/8fe84e53e0/large/corona-virus-scientifically-accurate-3d-model-3d-model-obj-fbx-blend-abc-gltf-usdz.jpg)

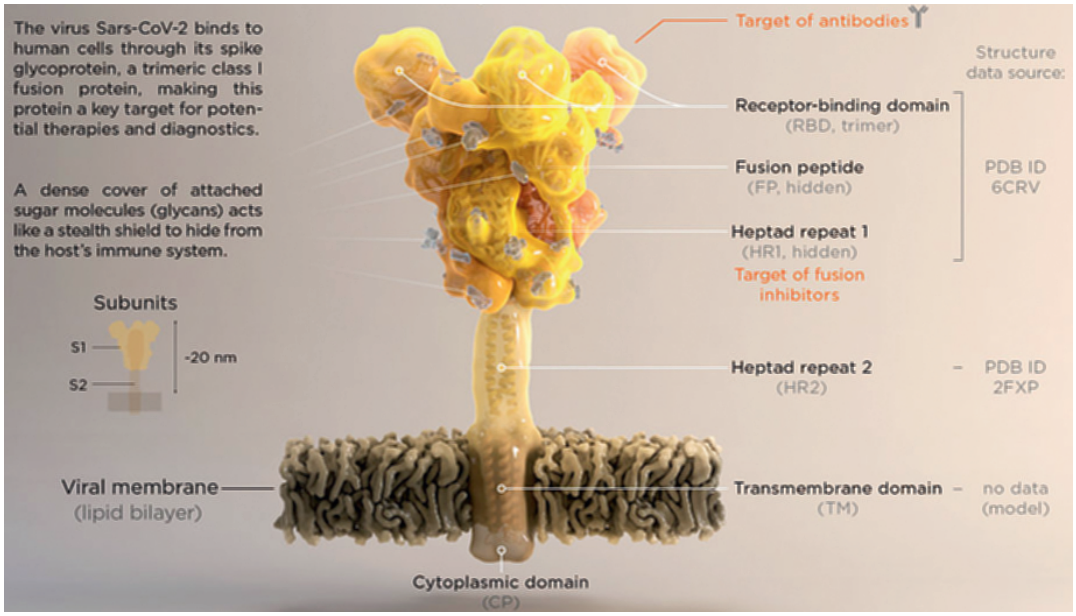
Рис. 1. Строение коронавирусов (Источник: https://img-new.cgtrader.com/items/2534580/8fe84e53e0/large/corona-virus-scientifically-accurate-3d-model-3d-model-obj-fbx-blend-abc-gltf-usdz.jpg)

glycoprotein is similar to the Malayan pangolin coronavirus. Therefore, SARS-CoV-2 likely originated from a bat-derived CoV and was transmitted to humans via an unknown mammalian intermediate host, possibly the Malayan pangolin. In addition, the SARS-CoV-2 S1/S2 spike protein cleavage site has acquired a furin site that is absent in bats and pangolins, which may indicate natural selection either in the host animal before zoonotic transfer or in humans after zoonotic transfer [20].

All coronaviruses have the same morphological properties and structure, although some species have differences (Fig. 1) [2].

HCoV virions are spherical in shape with diameters ranging from 80 to 229 nm and are the largest among RNA viruses.

The RNA of coronaviruses has helical symmetry and is located inside the ***nucleoprotein***, which forms the ***nucleocapsid*** covered by the ***supercapsid membrane*** consisting of a lipid bilayer. **Structural proteins** are located underneath. The ***spike protein*** (150–220 kDa) is located on the surface of the lipid bilayer of the virus in the form of club-like processes, which gives the virus a crown shape. It is a glycoprotein that creates trimers in the form of peplomers, which form the "teeth of the crown" and ensure the penetration of the virus into the



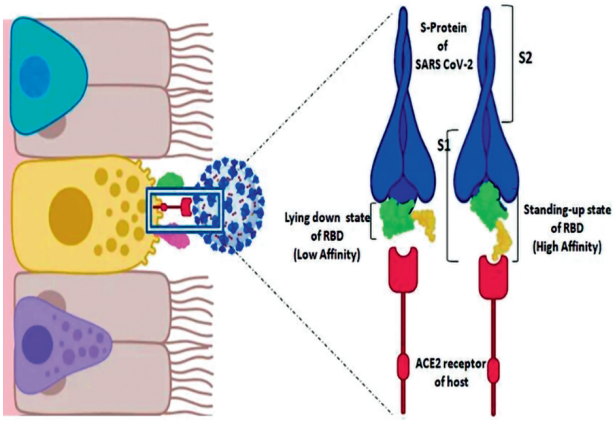


Fig. 2. Structure of the spike protein (SP) of the SARS-CoV-2 virus (Source: https://svrobo.org/where-are-the-robots-when-you-need-them/)

Рис. 2. Строение спайк-протеина (SP) вируса SARS-CoV-2 (Источник: https://svrobo.org/where-are-the-robots-when-you-need-them/)

cell. ***M-protein*** (23–25 kDa) is a transmembrane glycoprotein that provides the shape of the virion and controls particle size and assembly efficiency and is located deeper than the SP. The ***N-protein*** (50–60 kDa) is a phosphorylated protein by chemical structure and protects the viral RNA, keeping it in a stable state within the viral envelope. The ***E-protein*** (9–12 kDa) is enveloped, adjacent to the nucleocapsid, and is found only among viruses of the *Orthocoronavirinae* subfamily. Its pentamers form ion channels and are an important pathogenicity factor. The protein can bind to gene-regulating proteins, alter the pattern of human gene activation, and participate in virion assembly and virion release outside the cell. In some coronaviruses (*HCoV-OC43* and *HCoV-HKU1*), an additional surface protein is detected. It is called ***hemagglutinin esterase*** (HE protein, 9–12 kDa), which is a glycoprotein [2, 4, 8, 9, 20]. Viruses that have the HE protein have hemagglutinating and esterase activities, which they use as a mechanism for penetrating target cells. ***There no HE protein in all particularly dangerous viruses (SARS-CoV, MERS-CoV, SARS-CoV-2)*** [2].

SARS-CoV-2 has four conserved structural proteins (SP, E, M, and N) [21] and accessory proteins (3a, 6, 7a, 7b, 8b, 9b) that may influence the infectivity and pathogenicity (e.g., 3a and 7a activate ion channels, increase NF-κB activity, and enhance the induction of host target cell apoptosis) of the virus [22]. SARS-CoV-2 SP is a trimeric glycoprotein (6–8 million Da) with three domains: an *ectodomain* (subdomains S1, the receptor-binding subunit, and S2, the membrane-bound subunit), a *transmembrane region*, and an *intracellular domain* that has a short intracellular tail [23]. S1 SP contains the N (N-terminal domain — NTD) and C (C-domain — CTD) domains [22] (Fig. 2).

In this case, S1-CTD acts as a receptor-binding domain (RBD) that interacts with ACE-2 (zinc-dependent peptidase of the renin-angiotensin system) entry receptor for SP. The RBD SP determines viral tropism and infectivity, and is responsible for viral attachment to the target cell membrane and cell entry. Therefore, any RBD mutation may have a significant impact on SARS-CoV-2 receptor binding [22]. The S2 domain is the membrane fusion subunit and contains the fusion peptide (FP), heptad repeat 1 (HR1), central helix (CH), connector domain (CD), heptad repeat 2 (HR2), and transmembrane domain (TM). S2 has two cleavage sites, one at the S1/S2 border (R685) and the other at S2 (R815). HRs trimerize to form a helical structure and pull the viral envelope and host cell membrane bilayer into close proximity, facilitating their fusion [22]. At the junction of the S1 and S2 subunits of SP there is a "*furin site*" that is cleaved by furin, a host cell protease contained in lysosomes, which greatly simplifies the interaction of SP with TMPRSS2 (transmembrane serine protease 2) and increases the rate of viral entry into the cell.

The CTD domain is the receptor-binding domain for SARS-CoV-2, which recognizes **ACE2** [24, 25] — *a zinc-dependent peptidase of the renin-angiotensin system* — a type I transmembrane glycoprotein [12], as an entry receptor. It functions as a monocarboxypeptidase, catalyzing the cleavage of angiotensin II (Ang II), which is responsible for systemic vasoconstriction and aldosterone release and also has prooxidant and proinflammatory effects. During the process, the heptapeptide angiotensin 1–7 (Ang 1–7) is formed, which counteracts the action of the Ang II peptide, causing vasodilating, antiproliferative and antifibrotic effects) [12].

For effective penetration of the virus into the cell, activation of the TMPRSS2 SP [26], its cleavage and attachment to the active zones of ACE2 are required. TMPRSS2 has three functional domains and mediates the first cleavage of the SP at the S1–S2 boundary (R685) and the second at the S2' regions (R815) [27]. The virus's entry into the cell is aided by its receptor-binding domain (RBD), which SARS-CoV-2 releases when capturing the cell and which more effectively "latches" to ACE2, allowing the virus to enter the cell 4 times faster than SARS-CoV [28].

Note. The "Omicron" variant and its varieties ("Centaur", "Ninja", etc.) are characterized by reduced binding of SP to TMPRSS2 and the presence of multiple mutations in SP (17 in RBD; 8 in NCD). Moreover, both domains are immunodominant targets for neutralizing antibodies produced by COVID-19 vaccines and antibodies in those who have recovered; 10 mutations in the SP region that contacts the ACE2 receptor, combined with its 2.4-fold decrease in the ability to bind to soluble sACE2 and be cleaved by furin; high stability of SP, difficulty in cleaving S1; mutations in S2, etc. This makes the strain the most transmissible among all SARS-CoV-2 variants, which leads to a decrease in its virulence, facilitates easy and rapid invasion into target cells, and also increases the resistance of the virus to vaccines with neutralizing antibodies [29–31].

PATHOGENESIS OF COVID-19

The source of infection is a sick person and/or human in the incubation period, as well as an asymptomatic carrier. The greatest danger to others is posed by a sick person in the last two days of the incubation period and the first days of the disease. **The pathogen is transmitted** mainly by ***airborne droplets*** (when coughing, sneezing, talking) at a close distance (less than 2 meters) [32]; ***airborne dust***, less often by ***contact*** (when shaking hands and other types of direct contact with an infected person), as well as through food products, surfaces and objects contaminated with the virus [1, 33].

The vast majority of infections occur through contact with clinically manifested cases in family clusters (75–85%); transmission of infection from asymptomatic children to adults is possible [34]. Also possible: **fecal-oral** route, because SARS-CoV-2 RNA was detected in fecal samples from 8 out of 10 pediatric patients examined for several weeks after recovery and normalization of nasopharyngeal swabs [35]. **Sexual** transmission is possible: the virus was detected in the semen of 15.8% of those infected, 26.7% of them had an acute infection, and 8.7% were considered recovered [36]. The **transplacental** route is also possible, and the basis of vertical transmission of the virus from mother to fetus is placental vasculopathy (maternal viremia, placental infection lead to inflammation of the placenta and neonatal viremia) [37–39]. The possibility of vertical transmission is 5.3%, the incidence of COVID-19-positive newborns is 8% [40]. RNA of the virus or antibodies to SARS-CoV-2 are detected in vaginal fluid (4.6%), umbilical cord blood (6%), umbilical cord (6%), placental tissue (12%), amniotic fluid (5.6%), and breast milk (5%) [41]. The presence of PCR-positive throat swabs in newborns born to mothers with COVID-19 immediately after birth, as well as SARS-CoV-2 virus-specific IgM and IgG antibodies in blood serum, confirms the possibility of vertical transmission of infection [42, 43]. However, IgM antibodies are not able to penetrate the placenta, which may indicate intrauterine infection of the child. The incidence of infected newborns was almost 2 times higher in cesarean sections (5.3%) than in vaginal deliveries (2.7%) [44].

Note. **The role of COVID-19 as a healthcare-associated infection has been established.** Healthcare workers are at the highest risk of infection because they have prolonged aerosol contact while performing their professional duties. The risk of airborne, dust and contact-household transmission of the pathogen increases in conditions of non-compliance with the requirements of the sanitary and anti-epidemic regime, epidemiological safety rules, including the use of personal protective equipment. There is also a risk of the formation of epidemic foci of COVID-19 in organized groups and groups of closed-type organizations if infection prevention measures are not followed.

It is known that at room temperature, SARS-CoV-2 can remain viable in various environmental objects for several hours to 3 days, while in dried form — up to 3 days, in a liquid medium — up to 7 days. The virus remains stable over a wide range of pH values (up to 6 days at pH 5 to 9 and up to 2 days at pH 4 and pH 11). At a temperature of +4 °C, the virus remains stable for more than 14 days. When heated to 37 °C, the virus is completely inactivated within 1 day, at 56 °C — within 45 minutes, at 70 °C — within 5 minutes. The virus is sensitive to ultraviolet radiation and the action of various disinfectants in working concentrations [16].

The virus penetrates target cells that have ACE2 receptors, which are highly expressed in the epithelial cells of the mucous membrane of the nose, mouth, tongue, and salivary glands, which explains the loss of smell and impaired taste perception during the development of clinical symptoms of COVID-19 [12]. It also penetrates the conjunctiva of the eyes [16], as well as the epithelium of the bronchi and lungs, but in alveolocytes, the expression of ACE2 is significantly higher than in the bronchi, while type II alveolocytes, which produce surfactant, express ACE2 in 83% of cases in relation to type I alveolocytes [45]. The virus is tropic to the epithelial cells of the stomach, duodenum, ileum and rectum, which explains the occurrence of abdominal and dyspeptic syndromes in patients [46, 47] and in the proximal tubules of the kidneys, bladder [12, 47–49]. Also the virus penetrates cardiomyocytes, the membrane of pericytes, which regulate the permeability of the blood-brain barrier and the lumen of blood vessels [12, 46]. The virus penetrates the syncytiotrophoblast (STB), villous cytotrophoblast (VTB),

extravillous trophoblast (EVTB), endothelium, vascular smooth muscle cells and decidual cells of the placenta [50], in umbilical cord cells [51], in the epithelium and stroma of the endometrium in the secretory phase compared to the proliferation phase [52], in vagina, and also in the tissues of the mammary glands, which does not exclude the possibility of infection of breast milk [53, 54].

Note. Endothelial cells, fibroblasts, perivascular macrophages do **not express ACE2**, but synthesize the VWF factor (von Willebrand factor, a plasma glycoprotein that attaches platelets to the damaged area of the vessel). Pericytes, which normally do not come into contact with whole blood, when infected with the SARS-CoV-2 virus, create the opportunity to influence the functions of the vascular endothelium, which significantly changes the thrombogenetic function of the blood [55]. ACE2 is not expressed in the liver, hepatocytes, Kupffer cells, but is found in cholangiocytes [46].

Most frequently, SARS-CoV-2 interacts with goblet cells of the nasal epithelium, type II alveolocytes and enterocytes. At the same time, glutamyl aminopeptidase may be the second probable receptor for the virus [10]. ACE2, TMPRSS2 and FURIN are co-expressed in human lung tissue, so SARS-CoV-2 replication is significantly higher in the lungs. When the virus is inoculated into the respiratory tract, *mucociliary clearance activity* is suppressed by inhibiting the motility of epithelial cilia, which leads to the death of epithelial cells. The *surfactant system*, its production and function are *destroyed*, which leads to the collapse of the alveoli, and as a result of a sharp disruption of gas exchange, acute respiratory distress syndrome (ARDS) develops. *The permeability of cell membranes increases and there is an increased transport of albumin-rich fluid into the interstitial tissue of the lung and the lumen of the alveoli* [3]. In intestinal epithelial cells, two serine proteases (TMPRSS2 and TMPRSS4) are expressed at once, and their co-expression also contributes to the most pronounced aggression from SARS-CoV-2 [56, 87]. This may explain the very frequent manifestation of COVID-19, especially in children, with intestinal manifestations.

The consequence of the binding of the SARS-CoV-2 NTD SP to mACE2 is the proteolytic activation of the spike proteins by host cell proteases and the penetration of the SARS-CoV-2/ACE2 complex into the cell via the mechanisms of fusion of the virion membrane with the host cell membrane or by endocytosis [57]. Following the initial interaction between the S1 domain and ACE2, the S2 segment mediates the fusion of the host cell membrane and the viral membrane. This allows the SARS-CoV-2 RNA genome to enter the host cells. This is followed by viral RNA replication, assembly of new virions, and their exit from the cell. New viral particles are released into the extracellular space via exocytosis. The ACE2 receptor is internalized by the infected cell, resulting in its downregulation [57].

Note. **Alternative mechanisms of virus penetration into target cells are described:** the use of cathepsin L (CTSL), which ensures the penetration of the virus into the cell through the formation of endosomes; with the participation of furin, elastase, factor X or trypsin, which prepare SP by cleaving it into smaller fragments [58]; via the protease ADAM17, it cleaves ACE2; using the co-receptors neuropilin-1 (NRP1), heparin sulfate (HS), which promote binding between SP and ACE2 [59]; by binding to C-type immune cell lectins (DC-SIGN, Langerin, MGL, MR, Dectin-1 and Mincle), which are expressed by dendritic cells and macrophages, which leads to suppression of their function, causing the release of proinflammatory cytokines and induction of T-lymphocyte apoptosis, which may result in an immune response in the form of a cytokine storm [60]. One of mechanisms is interacting with polysaccharides of pulmonary microbiome bacteria [61, 62], which can cause respiratory tract infections; by binding to the target cell membrane antigen, the CD147 protein (basigin), which promotes the penetration of the virus into cells by endocytosis, its expression increases susceptibility to SARS-CoV-2 infection [63, 64]. Although CD147 does not bind to ACE2, CD147 silencing reduces ACE2 levels through an as yet unknown mechanism [61, 65, 66]) and performs a large number of physiological functions in the body, including the activation of extracellular matrix metalloproteinases, which ensure the restructuring of the intercellular substance in tissues [66]. Glucose-related protein 78 (GRP78) promotes viral entry by acting as a receptor or stabilizing the binding between SP and ACE2 [67, 68]. Both CD147 and GRP78 are tumor markers [69], which explains why cancer patients have a higher risk of severe COVID-19. Another mechanism is carried out through the interaction of the coronavirus protein Orf9b with the human mitochondrial chaperone protein (TOM70), which affects the synthesis of type I IFN and increases the replication of the SARS-CoV-2 virus [70]. This variant of protein interaction is common

to all three epidemically significant coronaviruses (SARS-CoV-1, MERS-CoV and SARS-CoV-2), which allows us to consider this type of binding (Orf9b-TOM70) pathogenetically important and causing not only the insufficiency, but also the perversion of the innate immune response and interferonogenesis in the first day of COVID-19. The consequence of this is uncontrolled replication, accumulation of viral particles and increased viral load with the subsequent development of a hyperinflammatory immune response by the 7th-10th day of COVID-19 disease. All factors that regulate the expression of the ACE2 gene contribute to more efficient penetration of the virus into cells. SARS-CoV-2 can also invade target cells through mechanisms of hemoglobin (β-1 chain) blocking, porphyrin binding and inhibition of heme synthesis, which affects the nature of the immune response [71]. All alternative mechanisms of SARS-CoV-2 virus invasion not only significantly increase its interaction with target cells, but can also determine the possibility of vertical transmission of infection from mother to fetus.

SARS-CoV-2 can downregulate ACE2 expression by directly binding to the receptor on endothelial cells, resulting in overactivation of the ACE2/Ang II/AT1 axis and inhibition of the ACE2/Ang-(1-7)/MasR axis. This results in the development of vascular pathological changes such as increased permeability, inflammatory response and oxidative stress. This leads to disruption of endothelial function and degradation of endothelial junction proteins, including disruption of the blood-brain barrier, which contributes to fluid extravasation and the development of vasogenic edema [72]. The possibility of specific damage to lymphocytes by the virus with their apoptosis and pyroptosis has also been proven, which underlies prognostically unfavorable lymphopenia, macrophage activation syndrome and hemophagocytic syndrome, and deficiency of neutrophils as one of the causes of ARD syndrome.

Dissemination of SARS-CoV-2 from the systemic bloodstream or through the ethmoid plate leads to brain damage. Changes in the sense of smell (anosmia) in patients at an early stage of the disease may indicate both CNS damage by the virus, which penetrates primarily through the olfactory nerve, and damage to the cells of the nasal mucosa.

The critical form of COVID-19 is a type of cytokine storm, and its manifestations are similar to the course of primary and secondary hemophagocytic syndrome (macrophage activation syndrome). Moreover, the cytokine storm is a predictor of mortality in patients with COVID-19 [74].

Note. In the critical course of COVID-19, pathological activation of innate and adaptive (Th1 and Th17 types) immunity, dysregulation of the synthesis of proinflammatory, immunoregulatory, anti-inflammatory cytokines and chemokines (IL-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-18, granulocyte colony-stimulating factor (GKSF), granulocyte-macrophage colony-stimulating factor (GMKSF), tumor necrotizing factor alpha (TNF-α), IFN-α and IFN-β and others, as well as inflammation markers (CRP, ferritin) develop. Patients with severe COVID-19-infection develop vascular endothelial dysfunction, coagulopathy, thrombosis with the presence of antibodies to phospholipids, with a clinical picture resembling catastrophic antiphospholipid syndrome. Cytokine storm in COVID-19, as a rule, leads to the development of acute respiratory distress syndrome (ARDS), multiple organ failure and can be fatal [16, 75–77].

The severity of the inflammatory response in COVID-19 depends, on the one hand, on the virulence of the pathogen, and on the other, on the immune resistance of the host organism. In low-virulence strains of SARS-CoV-2, the primary site of virus fixation is the ciliated epithelial cells of the upper respiratory tract, which leads to the development of mild, sometimes asymptomatic infections [78]. The highly virulent SARS-CoV-2 strain infects type II alveolar cells and triggers the secretion of a large number of proinflammatory cytokines and chemokines (IL-2, IL-7, IL-10, G-CSF, TNF-α, etc.), to a lesser extent activates the secretion of TNF-α and IL-6, and very minimally - IFNα / β [79, 80]. As a result, severe pulmonary dysfunction occurs due to inflammation and edema caused by viral proliferation in the lung tissue, which ultimately disrupts alveolar gas exchange. Such changes lead to hypoxia, including cerebrovascular type [81].

An intermediate product of SARS-CoV-2 replication is the formation of ssRNA, which triggers the activation of the antiviral program in the cell. This results in the induction of expression of more than 300 IFN I-related genes (ISG), which together determine the antiviral status of the cell through the synthesis of a huge number of antiviral proteins, cyto- and chemokines, as well as interferon-related enzymes, which leads to inhibition of the spread of the virus. Moreover, SP SARS-CoV-2 is a key inhibitor of IFN I synthesis activation, blocking

the induction of IFN synthesis, which prevents the initiation of the innate antiviral immune response and makes the patient with COVID-19 defenseless against infection [21].

PATHOMORPHOLOGY OF COVID-19

Pathological examination of lung tissue did not reveal any specific macroscopic signs of COVID-19, although the morphological picture can be considered characteristic [16]. *Lung damage in COVID-19 is characterized by pronounced plethora of capillaries of the interalveolar septa, as well as branches of the pulmonary arteries and veins, with a slowdown in blood flow, erythrocyte sludge, fresh fibrin and organizing thrombi; intrabronchial, intrabronchiolar and intraalveolar hemorrhages, which are a substrate for hemoptysis, as well as perivascular hemorrhages.*

Patients with critical COVID-19 develop vascular endothelial dysfunction, coagulopathy, thrombosis with the presence of antibodies to phospholipids, with a clinical picture resembling catastrophic antiphospholipid syndrome. Clinical and pathological changes are difficult to differentiate from multiorgan thrombosis developing with ARDS and thrombotic microangiopathy (TMA).

The SARS-CoV-2 virus is detected in ciliated cells of the bronchi, bronchiole epithelium, alveolocytes and macrophages, as well as in the vascular endothelium.

Specific viral and cytokine storm-induced, and at a later stage, possibly autoimmune, damage to the endothelium, called *SARS-CoV-2-associated endothelial dysfunction* and even endotheliitis, and hypercoagulation syndrome are the basis of the thrombotic microangiopathy characteristic of COVID-19, mainly in the lungs, less often in other organs (myocardium, brain, kidneys, etc.), and thrombosis of large arteries and veins (often with thromboembolism). The possibility of platelet activation by antibodies to SARS-CoV-2 as an important cause of the development of hypercoagulation syndrome is not excluded.

Changes have also been identified in other organs that can presumably be associated with the generalization of coronavirus infection or immune disorders. Changes may occur in the *intestines* (catarrhal and hemorrhagic gastroenterocolitis, ischemic lesions), *brain and pia mater* (encephalitis, meningitis, hypoxic and ischemic lesions), heart (myocarditis, acute coronary syndrome), *pancreas, kidneys, spleen, testicles*.

Skin manifestations typical of COVID-19 are described (from hemorrhagic syndrome to various types of rashes). The pathogenesis is unclear. There is evidence that SARS-CoV-2 is capable of activating previous chronic infectious processes.

The second part of the lecture will describe the clinical picture, diagnosis and treatment of coronavirus infection.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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