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Review article

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COVID-19: FROM THE STRUCTURE AND REPLICATION CYCLE OF SARS-COV-2 TO ITS DISEASE SYMPTOMS AND TREATMENT

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In December 2019, a small number of cases of pneumonia of unknown origin were recognized in the city of Wuhan, China. Soon, the disease, whose etiological factor was recognized as a coronavirus SARS-CoV-2, had spread across the world. The resulting CoV-associated diseases were classified by the WHO as *COVID-19*, and a pandemic was declared in March 2020. By 25 November 2021, there have been nearly 256.8 million of confirmed cases of COVID-19 around the world, including 5.17 million deaths. This review focuses on basal characteristics of the SARS-CoV-2 virus - its structure, replication cycle, variants and course of infection. It also briefly characterizes the currently recommended drugs and vaccines. Coronaviruses (CoVs) are a group of RNA viruses with a characteristic solar corona image observable on electron micrographs. SARS-CoV-2 possesses high affinity to human angiotensin converting enzyme 2 (ACE2) which serves as a cellular entry receptor. Its replication in human cells is accompanied by a high mutation rate. Six variants of SARS-CoV-2 have been found to be associated with essential changes of global public health significance; they are referred to as 'variants of concern' (VOC). The main route of transmission is through respiratory droplets. Although COVID-19 presents primarily as a respiratory disease, it can affect various other organs and systems that present the ACE2 protein to which the virus binds, including the heart, kidneys, intestines, liver, muscular and nervous system. COVID-19 infection can result in uncontrolled systemic hyperinflammation caused by release of a large amount of pro-inflammatory cytokines (a 'cytokine storm'), which can lead to multi-organ failure, rapid clinical deterioration and even death. Around 30% of those infected with SARS-CoV-2 remain asymptomatic, with the majority of patients demonstrating only mild or moderate symptoms; however, about 20% develop severe or critical disease. Three main groups of medications are currently recommended for therapy of COVID-19: monoclonal antibodies against the S protein of SARS-CoV-2, antiviral drugs and immunosuppressants which inhibit the cytokine storm. At present, the safest and most cost-effective way to prevent COVID-19 illness is a preventative vaccination.

Key words: *coronaviruses, SARS-CoV-2, COVID-19, multiorgan failure, inflammation, clinical symptoms, angiotensin converting enzyme 2, pro-inflammatory cytokines anti-COVID-19 medicines, vaccines*

INTRODUCTION

The first cases of 'pneumonia of unknown origin' were reported in the city of Wuhan, Hubei Province, China, in December 2019 (1). A month later, the causative agent was identified as a member of the *Coronaviridae* family, and termed by the World Health Organization (WHO) as '2019-novel coronavirus (2019-nCoV)'. Later on, the virus was designated as 'SARS-CoV-2' by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (2), and novel coronaviral pneumonia and CoV-associated diseases were classified by the WHO as 'COVID-19'. On March 11, 2020, the outbreak was declared a pandemic by the WHO. Globally, as of 25 November 2021, there have been 256,830,438 confirmed cases of COVID-19, including 5,174,646 deaths, reported to the WHO (3). This devastating pandemic has badly disrupted normal social activities and economic growth worldwide.

CORONAVIRUSES: GENERAL INFORMATION

Coronaviruses (CoVs) are a highly-diverse group of enveloped, positive-sense, single-stranded RNA (+ssRNA) viruses with a characteristic solar corona image on electron micrographs; they have been classified into the *Coronaviridae* family, suborder *Cornidovirineae*, order *Nidovirales*, and realm *Riboviria* (2). They possess the largest genomes (26.4 – 31.7 kb) among all known RNA viruses, with G + C contents varying from 32% to 43%. Coronaviruses infect humans, other mammals and avian species. Human CoVs (HCoVs) are genotypically and serologically categorized by the International Committee for

Taxonomy of Viruses into four major genera: *Alphacoronaviruses* (AlphaCoV), *Betacoronaviruses* (BetaCoV), *Gammacoronaviruses* (GammaCoV) and *Deltacoronaviruses* (DeltaCoV). Whereas AlphaCoV and BetaCoV exclusively infect mammalian species, GammaCoV and DeltaCoV are specific to birds, but occasionally can also infect mammals. Human and animal coronavirus infections mainly result in respiratory and enteric diseases. Seven human coronaviruses (HCoVs) have been identified so far: HCoV-HKU1, HCoV-NL63, HCoV-OC43, HCoV-229E, SARS-CoV, MERS-CoV and SARS-CoV-2. HCoV-229E and HCoV-NL63 are placed under AlphaCoV, whilst HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV and SARS-CoV-2 are classified as BetaCoV. The widely-dispersed HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU are responsible for around one-third of seasonal and usually mild respiratory tract infections associated with symptoms of the 'common cold'. In severe cases, however, they can cause bronchiolitis and life-threatening pneumonia in immunocompromised adults and children. Additionally, these HCoVs have been found to be associated with enteric and neurological diseases (4).

The first HCoV pandemic was caused by SARS-CoV, initiated in November 2002 in Foshan, Guangdong Province, China, and lasted until 2014. It affected 28 countries around the world with 8096 cases and 774 deaths, giving a fatal rate of 10% (5). The second HCoV pandemic was caused by MERS-CoV, originated in June 2012 at Jeddah, Saudi Arabia (6). At the end of June 2021, 2574 cases of MERS-CoV had been reported in 27 countries, resulting in 886 fatalities, with a case-fatality ratio of 34.4% (7). While SARS-CoV-2 is less deadly than SARS-CoV, it is transmitted much more easily (8), and the long incubation period and non-existent to moderate symptoms make its identification, tracing and elimination very difficult.

Human CoVs are zoonotic pathogenic viruses derived from animal CoVs (9). The recent SARS-CoV-2 outbreak highlights the hidden wild zoonotic reservoir of highly-virulent and deadly viruses, and the possible threat of spillover zoonoses (10). Although the direct origin of SARS-CoV-2 remains unknown, most HCoVs have been found in bats. SARS-CoV-2 has high overall genetic similarity to bat coronaviruses belonging to the subgenus *Sarbecovirus* (genus *Betacoronavirus*): RaTG3 (96%) and RmYN02 (93%). On the other hand, SARS-CoV-2 is 79-80% identical to SARS-CoV, and only 50-51.8% identity is observed between SARS-CoV-2 and MERS-CoV (11). There is a strong suspicion that SARS-CoV and MERS-CoV may have been transmitted to humans through exposure to immediate animal hosts: Himalayan palm civet cats (*Paguma larvata*) for the former and dromedary camels (*Camelus dromedarius*) for the latter. Recent studies point to pangolins (*Manis javanica*) as a potential intermediate host for SARS-CoV-2, as the coronavirus isolated from this species shares 99% nucleotide sequence homology with the virus that infects humans (for an excellent review see (12)).

Coronaviruses infect numerous animal and human hosts and are characterized by a remarkable frequency of recombination, which, together with the high rate of mutation, encourage their adaptation to new hosts. This raises an important question on susceptibility to SARS-CoV-2 of various animal species (wild-living animals, pets and livestock). However, at present knowledge on this subject remains limited. A detailed analysis of studies on various animal species infected with SARS-CoV-2, experimentally or naturally, revealed that *Rousettus aegyptiacus* (fruit bats), pangolins, felines, minks, ferrets and rabbits are all susceptible to SARS-CoV-2, while dogs are weakly susceptible, and pigs, poultry and tree shrews appear to be immune (13).

SARS-COV-2: FROM STRUCTURE TO REPLICATION CYCLE

The genome sequence of SARS-CoV-2 was released in GenBank on January 11, 2020 (accession no. *MN908947.3*) (14). The SARS-CoV-2 genome forms a linear, positive-sense, single-stranded RNA (+ssRNA) comprising 29 891 nucleotides coding for 9860 amino acids. The positive-strand genome can act as a messenger RNA and therefore can be translated directly into viral proteins by ribosomes of the host cells. The 5'UTR region of the genome consists of 265 nucleotides and the 3'UTR region of 358 nucleotides (15).

The SARS-CoV-2 genome encodes the synthesis of four major structural proteins, 16 nonstructural proteins (Nsps) and several accessory proteins.

The group of structural proteins include:

- Phosphorylated nucleocapsid (N) protein (419 aa), which is responsible for packaging the viral genome into a ribonucleocapsid. It participates in the modification of cellular processes and viral replication. The RNA genome is wrapped by the N protein, which thus forms a coiled tubular structure. This helical nucleocapsid is surrounded by the viral E protein, which is associated with other structural proteins, such as the M and S proteins. This is a highly immunogenic protein, produced in large amounts during infection.
- Membrane protein (M) - the main protein of the viral matrix composed of 222 aa. The M protein interacts homotypically and heterotypically with other structural proteins. These interactions play a key role in membrane budding. The M protein interacts with the S protein to trap the virus in the endoplasmic reticulum - Golgi complex, where new virions are assembled and then released by secretory vesicles. Any accumulation of large amounts of viral proteins during SARS-CoV-2 infection can overload the endoplasmic reticulum, thus activating a cascade of complex biochemical processes leading to cell death.
- Envelope protein (E) - the smallest (75 aa) of the structural proteins responsible for *inter alia* the formation of virions and the induction of pro-inflammatory factors release. This protein modifies the host cell membrane by creating pores through which the virion can escape from infected cell. Its absence significantly reduces the viral load, and its presence is primarily linked with the virulence of SARS-CoV-2.
- Spike-shaped monotrimeric surface protein (S). The S protein (1273 aa) belongs to the I class of transmembrane glycoproteins. Its presence has been demonstrated in all types of human coronaviruses, as well as in HIV, influenza, Ebola and paramoviruses. The S proteins are arranged radially on the surface of the virus, giving the virus a characteristic solar corona appearance on the electron microscope image. The S protein has two major subunits, S1 and S2. The distal S1 subunit has two well-defined structural domains: the receptor binding domain (RBD) and the *N*-terminal galectin like domain (S-NTD). It plays a crucial role in receptor recognition and binding. A region upstream of the RBD is involved in adhesion to sialic acid-containing oligosaccharides and regulation of viral infection. The S2 subunit contains five functional domains: a fusion peptide (FP), heptad repeat *N*- and *C*-terminal regions (HR-N and HR-C), a transmembrane domain (TM), and a cytoplasmic domain. The S2 subunit facilitates the viral fusion process *via* interaction with a transmembrane serine protease 2 (TMPRSS2) on the host cell surface. This subunit mediates fusion of the viral and the host cell membranes.

The M, E and S proteins are glycoproteins and form the viral envelope. Glycosylation of the S protein protects specific epitopes on the viral surface from attack by host antibodies (16).

After infection, the life cycle of SARS-CoV-2 follows five steps: attachment, penetration, biosynthesis, maturation, and

release. The initial steps of infection involve the specific binding of the coronavirus S protein to the cellular entry receptor - angiotensin converting enzyme 2 (ACE2). In addition to receptor binding, successful fusion requires a proteolytic cleavage of the S protein to S1 and S2 subunits by host cell-derived proteases, primarily TMPRSS2, but also TMPRSS4, furin, cathepsin, trypsin, or a trypsin-like protease of the human respiratory tract. The S1 subunit is responsible for viral attachment to an extracellular part of ACE2, and S2 for fusion with the host cell membrane. RBD of S1 continuously transforms between a pre-fusing upright ('open') position that binds to the receptor, and a post-fusing down ('closed') configuration, the latter playing a key role in neutralizing antibodies. The S2 subunit, on the other hand, contains FP. Following disruption of the cell lipid membrane by FP, the lipids of the viral envelope fuse with those of the cell membrane. Once inside the cell, the envelope fuses with the endosomal membrane and releases the viral genome into the cytoplasm, where the replication and assembly of new viral particles occur (17, 18).

A peculiar feature of the SARS-CoV-2 S protein is an acquisition of a polybasic cleavage site (PRRAR) at the S1 – S2 boundary, which permits an efficient protein cleavage by furin. It is suggested that this cleavage contributes to increased transmissibility of the virus. Importantly, such cleavage sites have not been identified in other members of the *Sarbecovirus* subgenus (19).

Following the entry, the viral RNA genome is released into the cell cytoplasm. The RNA (+) strand is first replicated to an RNA (-) strand, which is used either for replication to another RNA (+) strand for new virion assembly, or for transcription of sub-genomic mRNA which can be translated into variety of viral proteins. Two-thirds of the SARS-CoV-2 genome is occupied by two large open reading frames, ORF1a and ORF1b, located at the 5' end. The translation of ORF1a and ORF1b from the genomic RNA produces two polyproteins: replicase polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab). The resulting polyproteins are cleaved by two cysteine proteases: papain-like protease (PL^{pro}) and chymotrypsin-like protease (3LCpro; Mpro), located respectively within Nsp3 and Nsp5, to 16 nonstructural proteins (Nsp1-16). Nsp1 is involved in degradation of the host mRNA, and translation inhibition. Nsp2–16 compose the viral replication-transcription complex (RTC). Nsp2–11 are involved in modulation of intracellular membranes, host immune evasion and provide cofactors for replication, whereas Nsp12–16 contain the core enzymatic functions involved in RNA synthesis, RNA proofreading and RNA modification. In particular, RNA synthesis is performed by Nsp12, a RNA-dependent RNA polymerase (RdRP), and its two cofactors: Nsp7 and Nsp8. Nsp14 has an 3' – 5' exonuclease activity that assists RNA synthesis with a unique RNA proofreading function. The coronavirus capping machinery is composed of Nsp10, which functions as a cofactor, Nsp13, which provides the RNA 5'-triphosphatase activity, and Nsp14 and Nsp16, which perform functions of *N*7-methyltransferase and 2'-*O*-methyltransferase, respectively (16).

The remaining one-third of the genome, at the 3' end, contains overlapping ORFs encoding four major structural proteins which act as the components of the mature virus, *viz*. spike (S), membrane (M), envelope (E) and nucleocapsid (N), as well as various accessory proteins, including ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF9 and ORF10. Accessory proteins are principally thought to contribute to modulating host responses to infection and are determinants of viral pathogenicity. Notably, Orf3a belongs to a viroporin family, which forms ion channels in the host cell membrane. This protein also contains a tumor necrosis factor receptor-associated factor (TRAF) binding domain, which activates NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and the NLRP3 inflammasome. Furthermore, Orf3a stimulates the extrinsic apoptotic pathway initiated by the cleavage of caspase-8. Active caspase-8 cleaves the BID protein (a pro-apoptotic member of the Bcl-2 family), leading to release of cytochrome C from mitochondria, apoptosome formation and caspase-9 activation of apoptosis (16).

The translation of RNA encoding the N protein takes place in the cytoplasm, while mature forms of the M, E and S proteins are formed in the rough endoplasmic reticulum (ER). The N protein surrounds the newly-synthesized RNA (+) strand, forming the nucleocapsid. Viral structures and nucleocapsid subsequently assemble in the ER-to-Golgi intermediate compartment (ERGIC). New virions packed in Golgi vesicles fuse with the plasma membrane and are released from the infected cell *via* exocytosis (16).

SARS-COV-2 VARIANTS

Due to the lack of a mismatch repair mechanism, the replication process of SARS-CoV-2 virus is accompanied by a high mutation rate. The vast majority of mutations occur in only a single variant, suggesting that they result from a genetic drift. Since the pandemic began in China in December 2019, thousands of variants of SARS-CoV-2 have emerged. The SARS-CoV-2 variant of concern (VOC) or variant of interest (VOI) is defined as the variant which has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- "increase in transmissibility or detrimental change in COVID-19 epidemiology; or
- increase in virulence or change in clinical disease presentation; or
- decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics" (20, 21).

The following mutation variants have prevailed, disseminate rapidly, and are classified as VOC/VOI: alfa (20I/501Y.V1, lineage B.1.1.7), beta (20H/501Y.V2, lineage B.1.351), gamma (20J/501Y.V3, lineage P.1; also called B.1.1.28), delta (lineage B.1.617.2), kappa (lineage B.1.617.1), lambda (lineage C.37) and mu (lineage B.1.621) (20, 22).

The first highly-transmissible variant of SARS-CoV-2, alpha, was isolated and identified in September 2020 in Kent and Greater London, the United Kingdom. This variant became the dominant strain in England in November/December 2020, and has been detected in 94 countries since December 2020 (23). The variant carries 17 mutations in the viral genome. Of these, eight mutations (Δ69-70, Δ144, N501Y, A570D, P681H, T716I, S982A, D1118H) are in the spike protein; four mutations on the ORF1ab protein, three mutations on the ORF8 protein and two mutations on the N protein. One mutation, N501Y, located in the receptor binding motif (RBM), part of the receptor binding domain (RBD) of the S protein, could strengthen the binding of the virion to the ACE2 receptor (23, 24). This variant has shown increased transmissibility (56%) within the population compared to a wild-type virus. At present B.1.1.7 is classified as a de-escalated variant (22) as its circulation has been drastically reduced following the emergence of the dominating B.1.617.2 (delta) variant (3).

The second major variant of concern was beta. It emerged from the first wave of the South African COVID-19 epidemic in the Eastern Cape province in early 2020. By the end of November 2020, it become the predominant virus lineage in the Eastern and Western Cape province (25). The variant has been detected in 48 countries worldwide by March 2021 and has a similar mechanism of action to alpha (24, 25). This new variant

carries 21 mutations, among which nine (L18F, D80A, D215G, R246I, Δ242-244, K417N, E484K, N501Y, A701V) have been identified in the S protein region. Three of these (K417N, E484K, and N501Y) are located in the RBD and increase the binding affinity for the ACE2 receptors (25).

The third variant, similar to beta, was first reported by the National Institute of Infectious Diseases in Japan on 6 January 2021 in four travelers from Brazil, and named as gamma (P.1). The gamma variant outbreak was mainly found in Manaus (Brasil), which experienced widespread infections in May 2020 (23, 26). It has been detected in 25 countries (24). Compared with alfa and beta, the P.1 variant emerged with more changes in the S protein (L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, H655Y, and T1027I), including three in the RBD (K417T, E484K, and N501Y) associated with increased binding to the human ACE2 (26). Based on the WHO epidemiological update on 30 March 2021, this variant has spread to 45 countries. Importantly, this variant may have reduced neutralization by monoclonal antibody therapies, convalescent sera, and post-vaccination sera. Based on genomic and mortality data, it is estimated that gamma may be 1.7- to 2.4-fold more transmissible and pathogenic than previous variants of SARS-CoV-2 (26).

The fifth variant, B.1.617 (so-called the 'double mutant'), identified in India in October 2020, is responsible for the spread of fatal COVID-19 cases in the western state of Maharashtra, India, and is vastly spreading in various locations including the United Kingdom, the United States, and other locations. It carries two prominent mutations: E484Q and L452R. Three distinct lineages have been identified within B.1.617: B.617.1, B.617.2 (variant delta) and B.617.3. Variant delta is defined by T19R, Δ156-157, R158G, L452R, T478K, D614G, P681R, D950N mutations in the S protein. The incidence of infection by B.1.617.2 is increasing rapidly in the United Kingdom and has also been detected in several other countries worldwide (21, 22).

Another variant found to be spreading in Bengal (India), B.1.618 (also known as 'triple mutant'), is suspected to have evolved from B.1.617, and has a V382L mutation in addition to E484Q. The structural analysis of RBD mutations L452R and E484Q along with P681R in the furin cleavage site, revealed that these may demonstrate increased transmissibility *via* increased ACE2 binding and a higher rate of S1-S2 cleavage. The same two RBD mutations demonstrated a lower level of neutralization by a convalescent plasma and decreased binding to select monoclonal antibodies (mAbs), which may affect their neutralization potential (27). The latest SARS-CoV-2 VOC is omicron (B.1.1.529). This variant was first reported to WHO from South Africa on 24 November 2021 (28). At the time of the writing no details of mutations and transmissibility of this variant have been published.

The lambda variant, first detected in Peru in December 2020, carries three spice mutations of interest: L452Q, F490S, D614G. The mu variant, first detected in Colombia in January 2021, has five spice mutations of interest: R346K, E484K, N501Y, D614G, P681H. Recently European Centre for Disease Prevention and Control (ECDPC) has added an AY.4.2 variant (known also as delta plus) to its list of VOI. This variant was first detected in the United Kingdon in June 2021. It harbors six spike mutations of interest: L452R, T478K, D614G, P681R, A222V, Y145H (22). In addition, ECDPC has classified ten new mutation variants of SARS-CoV-2, first detected between December 2020 and September 2021, as variants under monitoring (22).

THE COURSE OF SARS-COV-2 INFECTION

The transmission of SARS-CoV-2 virus mainly occurs from both symptomatic and asymptomatic persons to others through respiratory droplets and, to a lesser extent, *via* aerosols generated during talking, coughing or sneezing. In an early stage of the pandemic, a direct contact with contaminated fomites (inanimate surfaces or objects) and subsequent contact with the respiratory or ocular mucosa were also implicated in the virus transmission. Shedding of the virus is the highest in the nose and throat within the first three days from the onset of symptoms. The mean time between exposure to the virus and the symptoms onset, i.e. the incubation or presymptomatic period, is around five to seven days, but can be up to 14 days. During this period, for one to

Table 1. Categories of COVID-19 severity according to the United States National Institute of Health (30).

NIH category	Signs and symptoms
Asymptomatic or presymptomatic infection	• Positive test for SARS-CoV-2 • No symptoms consistent with COVID-19
Mild illness	• Signs and symptoms of COVID-19 (e.g. fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, ageusia) • No shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	• Evidence of lower respiratory tract disease during clinical assessment or imaging • Oxygen saturation (SpO_2) ≥ 94% on room air
Severe illness	• SpO_2 < 94% on room air • Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg • Respiratory frequency > 30 breaths/min, or lung infiltrates > 50%
Critical illness	• Respiratory failure, septic shock, and/or multiple organ dysfunction

three days before the symptoms onset, some infected persons can be contagious. The proportion of persons who become infected with SARS-CoV-2 and remain asymptomatic is roughly estimated to be around 30% (29).

The course of COVID-19 is very variable. Most patients demonstrate only mild (40%) or moderate (40%) symptoms; however, approximately 15% develop severe illness that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury (29). The United States National Institute of Health (NIH) classified COVID-19 into five categories of severity (*Table 1*) (30).

Studies indicate that the rapid clinical deterioration and high mortality risk associated with severe COVID-19 could be related to an accompanying so-called cytokine storm. The cytokine storm is a condition of uncontrolled systemic hyperinflammation caused by the release of a large amount of pro-inflammatory cytokines, among them IL-1, IL-6, IL-18, IFN-γ and TNF-α, leading to multi-organ failure and even death (31-33).

Clinical manifestations of COVID-19 are more severe in older patients and in those with comorbidities, with a higher mortality rate being observed in these groups (34, 35). The major comorbid conditions leading to severe COVID-19 include hypertension (7 – 39%), diabetes (6 – 25%), cardiovascular diseases (1 – 10%), respiratory diseases (1 – 8%), malignancy (1 – 6%), obesity (8%) and chronic renal diseases (7%). Critical COVID-19 is more common in patients with hypertension (15 – 64%), diabetes (14 – 60%), cardiovascular diseases (9 – 40%), respiratory diseases (5 – 10%), malignancy (1.5 – 10%), obesity (31%) and chronic renal diseases (19%) (29, 36). The mortality rate in SARS-CoV-2 infections is lower than in infections caused by SARS (10%) and MERS (34.4%) (7, 37). Sex does not seem to influence susceptibility to SARS-CoV-2 infection; however, men demonstrate a mortality rate 2.4 times higher than women due to differences in immunological, genetic, endocrinological, social and behavioral factors (38, 39). Multivariable analyses have confirmed that older age, higher sequential organ failure assessment (SOFA) score and D-dimers > 1 μg/L on admission were associated with higher mortality. In most severely-ill COVID-19 patients, the major contributor to the high mortality rate is the cytokine storm. Among patients with critical illness, the mortality rate increased to 50% at the beginning of the epidemic and then progressively dropped to approximately 35 – 45% (29).

TISSUE/CELL DISTRIBUTION OF ACE2, THE MAIN SARS-COV-2 ENTRY RECEPTOR

Although COVID-19 presents primarily as a respiratory disease, emerging evidence has highlighted its impact on other organ systems. The ubiquitous distribution of ACE2, the main viral entry receptor, may explain how SARS-CoV-2 is able to cause widespread disease characterized by the systemic organ involvement including, among others, the heart, kidneys, liver, intestines, the muscular and nervous system. In the lung, expression of the enzyme is primarily restricted to type II pneumocytes. ACE2 is also found in type I pneumocytes, alveolar macrophages and blood vessels in the lungs. It is suggested that the large total surface area of the alveoli, consisting of pneumocytes, could explain the particular susceptibility of the respiratory system to SARS-CoV-2 infection. ACE2 has also been found in 1) blood vessels (both arteries and veins, endothelial cells and smooth muscles); 2) the heart - in cardiofibroblasts, cardiomyocytes, pericytes and epicardial adipose tissue; 3) the kidneys - mainly in the proximal tubules, and to a lesser extent in the glomeruli, Henle's loop, distal and collecting tubules; 4) the digestive tract - the small intestine, esophagus, stomach, pancreas (especially in the islets of Langerhans), and the colon; 5) cholangiocytes and hepatocytes of the liver, and in the gallbladder; 6) the eyes; 7) thrombocytes and macrophages; 8) the testicles - in Leydig and Sertoli cells; 9) the skin - in the basal layer of the epidermis, smooth muscles surrounding the sebaceous glands; 10) the adipose tissue; 11) the thyroid gland; 12) the nervous system - both in neurons and glial cells (40-42).

ACE2 functions as an important regulator of the renin - angiotensin - aldosterone system (RAAS), mainly by converting angiotensin (Ang) I and Ang II to Ang(1–9) and Ang(1–7), respectively. Ang(1–7) has vasodilatory, anti-inflammatory, anti-proliferative, anti-fibrotic properties, thereby countering effects of Ang II. Noteworthy, upon SARS-CoV-2 infection, ACE2 activity is reduced either by downregulation or by shedding. This results in several pathophysiological events, including, among others, dysregulation of RAAS with the functional predominance of the ACE-Ang II-AT1 receptor arm (17, 43).

Several papers have addressed the issue of using angiotensin-converting enzyme inhibitors (ACEIs) and AT1 receptor blockers (ARBs) for treatment of hypertension in COVID-19 patients. While we wait for more clinical data, at present discontinuation of using these drugs in COVID-10 patients is not recommended (43, 44).

CLINICAL SYMPTOMS OF COVID-19

Respiratory tract

SARS-CoV-2 predominantly targets the respiratory system. The virus mainly enters the host organism through the respiratory tract, but it can also gain entry through the mucous membranes of the mouth, nose and eyes. Some of the first targets of viral entry are the epithelial cells in the airway and the alveoli, as well as alveolar macrophages and vascular endothelial cells (45, 46).

Infection with SARS-CoV-2 triggers a broad spectrum of the respiratory tract symptoms, from mild upper airway symptoms (sore throat, rhinorrhea, sneezing) to life-threatening pneumonia, acute respiratory distress syndrome (ARDS) and death. Accumulating data indicates that SARS-CoV-2 replicates abundantly not only in the lower respiratory tract but also in the epithelium of the upper respiratory tract. Initial symptoms from the upper respiratory tract are often prodromal or mild, although viral RNA was detected in oro- or naso-pharyngeal swab specimens taken during the first days of infection. In severe COVID-19 cases, the virus reaches the lower respiratory tract and infects type II pneumocytes, leading to their apoptosis and loss of surfactant. The influx of macrophages and neutrophils induces the cytokine storm, and the capillary leakage results in alveolar edema. All of these pathological changes result in alveolar damage and collapse, impairing gas exchange (45, 47-49).

Most COVID-19 patients demonstrate bilateral pneumonia. The condition most frequently develops around day six or seven of infection, and is associated with shortness of breath and severe fatigue. In an early stage of pneumonia, before the emergence of neutralizing antibodies, tissue damage probably results from the rapid replication of SARS-CoV-2 and the virus cytotoxicity. During first weeks, an acute inflammation is observed, characterized by edema, pneumocyte hyperplasia, infiltrates and fibrinous exudate. This early phase is followed by a second, late phase, during which the immune response is triggered by infected cells. In this phase, T lymphocytes, monocytes, and neutrophiles release multiple cytokines which can cause both local and systemic inflammatory response if they enter the circulation (50-53).

Biopsy and autopsy examinations of the lungs of patients who died due to ARDS reveal diffuse alveolar damage, the formation

of hyaline membranes, diffuse thickening of the alveolar wall, interalveolar fibrin deposits, pneumocyte necrosis or apoptosis and the infiltration of air spaces by mononuclear cells and macrophages. The bronchi and bronchioles were blocked by mucus plugs, and the bronchial epithelium was damaged. Thrombi in large blood vessels, microthrombi, capillary congestion and endothelial cell damage were also reported. It is suggested that SARS-CoV-2 infection could cause loss of pericytes; this leads to proliferation of endothelial cells and induces intussusceptive angiogenesis. The occupation of the essential space within the alveolar walls by newly-formed blood vessels could also potently worsen the lung function (51, 52, 54-56).

While no changes may be apparent in X-ray images during early stages of the disease, more advanced stages can be associated with bilateral multifocal alveolar opacities that can demonstrate complete opacity of the lungs. In COVID-19 patients, these opacities frequently have a peripheral distribution. Lung opacities may progress into a consolidative pattern within one to three weeks of the symptoms onset. Pleural effusion has also been observed (51, 57).

Due to its high sensitivity, the first-line imaging technique of choice in suspected cases of COVID-19 who present with moderate-severe clinical features is a chest computer tomography (CT). Lung alterations appear to reach a maximum at around day 10 – 12 after the onset of symptoms and then generally decrease progressively in size and attenuation value. The distribution of chest abnormalities is most often bilateral, peripheral, and lower zone predominant. The most common signs of COVID-19 are ground-glass opacities (GGOs), or areas of hazy increased lung opacity, less opaque than consolidation, without cancelation of bronchial and vascular contours. The reported incidence of GGOs in COVID-19 cases can be as high as 91%. GGOs tend to progress in extent and attenuation value over the course of infection, and evolve either towards crazy paving areas or linear and retractile consolidation areas. Discharged patients have demonstrated the extension of GGOs with decreased density, with an incidence of 32%. Crazy paving have been observed in up to 36% of cases and are characterized by thickened interlobular septa and intralobular lines superimposed on diffuse GGO changes. It is suggested that this may result from the alveolar edema and interstitial inflammation of the lung. These arrangements are frequently observed 10 – 14 days after the onset of initial symptoms. However, the presence of crazy paving at early stages might be an indicator of rapid progression of the disease with a poor prognosis (51, 58, 59).

Consolidations are reported with a variable frequency, from 5% to 63%, with increased frequency at two weeks after the symptoms onset. Consolidated tissue is more radio-opaque than normally aerated lung parenchyma, indicating that the alveoli are completely filled by inflammatory exudation, hemorrhage or pus. Later on, the consolidations become resolved, whereas the areas of opacity persist (51, 58, 59). In addition, the lungs of patients with COVID-19 can present a range of signs, such as dilation of the pulmonary vessels around or within the airspace opacities, air bubbles, subpleural linear opacities parallel to the pleural surface, halo and reverse halo signs, bronchial wall thickening, and mediastinal lymphadenopathies (56, 60-65).

Lymphatic and immune system

COVID-19 patients with poor outcome can demonstrate uncontrolled local and systemic production of pro-inflammatory cytokines, i.e. the cytokine storm, with increased levels of inflammation-related cytokines: IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10 and TNF-α. Levels of these cytokines correlate with the disease severity (31, 33).

Autopsies of COVID-19 victims shown atrophy, hemorrhages and necrosis in the spleen, together with a significant reduction in the number of lymphocytes and neutrophils. In addition, reduced numbers of both CD4+ and CD8+ lymphocytes have been reported in lymph nodes. Lymphopenia was also observed in the peripheral blood in severe cases of COVID-19. It is likely that peripheral lymphopenia results from the virus invasion of the lymphatic organs, lymphocyte destruction by the virus, and apoptosis of lymphocytes triggered by cytokines (32, 33, 51).

Cardiovascular system

In addition to the respiratory symptoms, several COVID-19 patients present signs of cardiovascular system dysfunction, including heart palpitations and chest tightness/pain at the initial stage of the disease, but also various levels of cardiac injury, such as asymptomatic elevation of cardiac troponins I and II, acute coronary syndrome (ACS), myocarditis, cardiac arrhythmias (bradycardia, atrial fibrillation, ventricular tachyarrhythmia), decreased ejection fraction and acute heart failure, hypotension and circulatory shock. In addition, there have been reports of right ventricular dilatation, and cases of severe heart failure and even cardiac arrest. Acute heart failure has also been reported in appr. 24% of patients at initial presentation of COVID-19. Among patients with heart failure, about half did not have any previous history of hypertension or cardiovascular diseases. It is not known if heart failure was *de novo* dysfunction of the heart or it resulted from exacerbation of a previously undiagnosed disease (67-71).

In patients with myocarditis and myocardial injury, ECG abnormalities include T wave inversion, PR segment and ST segment deviations (depression and elevation). In some cases, the electrocardiogram can mimic ACS. In such cases echocardiography can be performed to differentiate between myocarditis and ACS; focal wall motion abnormality is more likely in ACS, while COVID-19-related myocarditis most likely will not reveal wall motion defects or global wall motion dysfunction. In patients with COVID-19, ECG and echocardiographic abnormalities are markers of illness severity and are correlated with worse outcomes (51, 68-71).

Histopathological examinations have revealed interstitial fibrosis, cell infiltration and necrosis, as well as increased levels of troponin I and II, and B-type natriuretic peptide in the blood (69). Recently, case reports of stress cardiomyopathy (Takotsubo syndrome, also called broken heart syndrome or tip ball syndrome), with symptoms closely resembling those of ACS, have been published. Stress cardiomyopathy is caused by a transient left ventricular systolic dysfunction in the absence of significant atherosclerotic changes in coronary vessels (72). COVID-19 patients with underlying cardiovascular diseases (e.g. hypertension, coronary heart disease, heart failure) displayed more severe clinical outcomes and higher mortalities (69, 72).

The exact mechanisms of how SARS-CoV-2 can cause myocardial injury are at present not fully understood. The proposed processes include a direct damage to cardiomyocytes, severe systemic inflammation with massive release of pro-inflammatory cytokines, myocardial interstitial fibrosis, in addition to atherosclerotic plaque disruption, hypercoagulability state, and hypoxia. Pericytes in the heart express particularly high levels of ACE2. Thus, SARS-CoV-2 infection of the pericytes can lead to local microvascular inflammation and, in consequence, to microvascular dysfunction, contributing to myocardial infarction with nonobstructive coronary arteries (MINOCA). SARS-CoV-2-induced down-regulation of ACE2 in blood vessels may also promote endothelial dysfunction and

inflammation, thus exacerbating existing atherosclerosis. Pulmonary infections can lead to respiratory failure, hypoxemia and decrease in oxygen supply to myocardium. Any imbalance between oxygen supply and cardiac oxygen demand can cause myocardial damage, particularly in patients with preexisting cardiovascular diseases. Oxygen delivery can be worsened by the formation of microthrombi in coronary arteries due to vascular inflammation and hypercoagulability state. Inflammatory factors may be also associated with the development of heart failure, especially in severely ill patients. It was noted that heart failure is associated with an increased risk of mortality (51, 68-70).

As stated above, ACE2 is also expressed in the myocardium, thus the virus can infect cardiomyocytes and lead to myocarditis by direct cytotoxicity. Indeed, analysis of cardiac tissue from autopsy cases demonstrated presence of SARS-CoV-2 RNA within the myocardium. Myocardial inflammation frequently develops 10 – 15 days after the onset of symptoms, and is presumably associated with the cytokine storm, which triggers autoimmune myocarditis (51, 68-71, 73). ACE2 plays a crucial role in Ang II metabolism and Ang(1–7) generation in the heart, so its loss by SARS-CoV-2-induced internalization can exacerbate underlying cardiovascular diseases (43). SARS-CoV-2 virions have also been found in neurons of the brain stem. It is likely that the loss of ACE2 and high viral load can lead to abnormal function or even death of neurons in the vasomotor center, resulting in an inappropriate autonomic regulation of blood pressure, enhanced central sympathetic signaling, alterations in the baroreflex, and exacerbation of hypertension (70, 74).

Hemostatic system

Hypercoagulability is a frequent and early hematological manifestation of coagulopathy in patients with COVID-19, and a predictor of disease worsening. Accumulating clinical evidence indicate that thromboinflammation, the coordinated activation of inflammatory and thrombotic responses to SARS-CoV-2 infection, plays a critical role in severity and mortality of COVID-19 (75). The most prominent manifestation of coagulopathy among patients with COVID-19 is venous thromboembolism (VTE), particularly pulmonary embolism (PE). Cases of PE are more likely to be associated with higher D-dimers levels, admission to intensive care units (ICU) and treatment with mechanical ventilation. Hypercoagulability in patients with COVID-19 also results in cerebral venous thrombosis, arterial thrombosis, microangiopathy, and disseminated intravascular coagulation (DIC), which may occur in patients at the critical stage of the disease and is a relevant predictor of death (36, 75). Up to 71.4% of patients who died from COVID-19 have DIC, while it occurred only in 0.6% of those who survived (76, 77). The incidence of systemic arterial thrombotic events, including acute ACS, myocardial infarction, ischemic stroke, transient ischemic attack and thrombotic limb ischemia, is much lower compared to VTE (78-80). Post-mortem studies report a high frequency of microthrombi in the small arteries and capillaries of the lungs (47). Moreover, these occluding microthrombi were also found in the heart, kidneys and liver in patients with COVID-19 (81).

One of the most common laboratory findings noted in COVID-19 patients requiring hospitalization has been an increase in D-dimers, which was reported in up to 45% subjects. This increased D-dimers level presumably results from thrombosis and fibrinolysis in pulmonary and other vascular beds. Such elevated levels are independent risk factors for death, and patients with D-dimers higher than 1000 ng/mL are about 20 times more likely to die than those with lower levels. In contrast, other conventional coagulation laboratory tests, such as prothrombin time (PT), activated thromboplastin time, and platelet count are often normal or mildly changed on presentation. Other coagulation abnormalities reported in COVID-19 patients include high elevation of factor VIII and plasminogen activator inhibitor-1 (PAI-1) activities, increased fibrinogen and von Willebrand factor levels, tissue factor expression, and thrombin generation. Patients also demonstrate increased platelet activation, and lowered antithrombin, thrombomodulin and protein C activity. Characteristic changes that occur in critically ill COVID-19 patients include severely elevated fibrinogen concentration (600 mg/dL – 900 mg/dL; normal value is 200 mg/dL to 400 mg/dL), increased factor VIII activity (> 300% in many patients), increased thrombin-antithrombin complexes, and low-normal antithrombin and protein C activity (82, 83).

Another parameter associated with COVID-19 is thrombocytopenia, which results from increased platelet consumption, as observed in 5% to 41.7% COVID-19 patients, depending on the study. Thrombocytopenia is usually mild, suggesting a compensatory increase in the production of platelets. Patients with more severe disease tend to demonstrate lower platelet numbers as do non-survivors compared to survivors (84-86). The causes of thrombocytopenia are not fully elucidated. It can result from increased consumption of platelets to form pulmonary thrombi, distraction by cytokines or by autoantibodies whose production can be induced by the virus, megakaryocyte dysfunction or by adverse effects of antiviral drugs (86, 87).

It was suggested that activation of coagulation system originates in the lungs and can further extend to other vascular beds, such as the limbs, gastrointestinal tract, brain and coronary vasculature (50, 51, 68, 84-86, 88, 89). While mechanisms of coagulopathy induced by SARS-CoV-2 infection are not clearly understood, crucial roles have been found to be associated with the pathological hyperactivity of immune system with a massive release of pro-inflammatory cytokines, activation of complement and contact systems, infection and damage of vascular endothelial cells (these cells express ACE2 in abundance), hypoxic vasoocclusion, and RAAS dysfunction with a functional overactivity of ACE-Ang II-AT1 receptor pathway (36, 90, 91). In addition, SARS-CoV-2 may directly induce activation of coagulation through its highly-conserved main proteinase (Mpro). A recent three-dimensional structure analysis demonstrated that the active site of Mpro from SARS-CoV-2 shares structural similarities with the active site of factor Xa and thrombin, and may activate blood coagulation (92).

Hemostatic abnormalities (CAHA) associated with COVID-19 can be divided into three stages (89):

- Stage 1 - patients with mild to moderate symptoms, who can be hospitalized or stay at home. In hospitalized patients without severe symptoms, elevated D-dimers (2- to 3-times higher than normal), normal PT, normal or elevated platelet count and fibrinogen were observed. Pulmonary microthrombi can be present in this stage, but they can be missed on CT as they may be limited to pulmonary microvasculature.
- Stage 2 - patients with more severe symptoms who require intensive care. In these patients markedly elevated D-dimers (3- to 6-times higher than normal), mild prolongation of PT and slightly reduced platelet count were reported. Pulmonary thrombi or emboli may result in filling defects which can be found on CT imaging. Asymptomatic deep vein thrombosis (DVT) in the lower limbs is also possible.
- Stage 3 - patients with severe symptoms, multiorgan failure, venous thromboembolism, and/or ischemia of the gastrointestinal tract, limbs, brain and heart, requiring a higher-level critical care support. In addition, D-dimers are markedly elevated (more than 6-times higher than normal), marked

prolongation of PT, significant thrombocytopenia and decreased fibrinogen were observed. In some cases, extensive pulmonary and systemic thrombosis may be present, including DIC. Intensification of antithrombotic therapy is recommended. Not only anticoagulant, but also fibrinolytic therapy (e.g. tissue plasminogen activator) may be necessary.

Guidelines prepared by the National Institutes of Health (US), International Society on Thrombosis and Hemostasis, American College of Chest Physicians, International Society on Thrombosis and Hemostasis, American Society of Hematology, WHO, National Institute for Health and Care Excellence (UK) recommend the use of routine-dosed thromboprophylaxis (low-molecular-weight heparin and unfractionated heparin) for hospitalized COVID-19 patients, in the absence of contraindications, and routine-dosed thromboprophylaxis for patients in ICU; an increased dose should be considered in high-risk patients. In patients who recovered from COVID-19 and can be discharged from hospital, extended out-of-hospital thromboprophylaxis is not routinely recommended. Nevertheless, in high-risk patients (advanced age, stay in ICU, cancer, previous history of venous thromboembolism, thrombophilia, severe immobility, D-dimers > 2-times the upper normal limit) and those with persistent immobility or high inflammatory activity, or both, anticoagulant thromboprophylaxis could be considered in the absence of increased bleeding (93).

Neurological and psychiatric complications of COVID-19

Emerging evidence suggests that SARS-CoV-2 infection can also be associated with a significant risk of neurological and psychiatric complications. It is estimated that approximately one-third of COVID-19 patients suffer from neuropsychiatric disturbances that can lead to a long-term damage of the nervous system. Almost 20% patients required ICU admission because of neurological complications (94-97). Neurological disorders are much more common in severely ill patients (~45%) than in other subjects (~30%). They are related to disturbances in the function of both the central nervous system (CNS) and the peripheral nervous system (PNS) (94, 98). It is supposed that CNS cases primarily result from the viral infection itself, while those of the PNS are secondary to immunological processes triggered by the SARS-CoV-2 infection (99). Five categories of neurological presentations in COVID-19 patients are distinguished: 1) encephalopathy with delirium/psychosis and no MRI or cerebrospinal fluid (CSF) abnormalities; 2) inflammatory CNS syndromes, including encephalitis and acute disseminated encephalomyelitis; 3) ischemic strokes; 4) peripheral neurological disorders, including Guillain-Barré syndrome and brachial plexopathy; 5) miscellaneous disorders of the CNS (100).

Central nervous system manifestations

Clinical symptoms of disturbances in the function of the CNS may range from mere headache, fever and neck rigidity to more sinister signs like changed personality, aggression, cognitive impairment (disorientation, attention deficit, dysexecutive syndrome), decreased consciousness (including delirium or coma) or seizures. Several studies regard headache and dizziness as the most common neurological symptoms reported by patients affected by COVID-19; they usually appear shortly after infection and have similar frequencies in both severe and non-severe ill patients (96-98). Impaired cognitive functions were often associated with severe infection, older age, higher creatine kinase levels, lower lymphocyte counts and higher blood urea nitrogen (101-103). Among all CNS manifestations, encephalopathy has been mentioned as the major cause of morbidity and mortality in adult and elderly patients, independent of the severity of respiratory complications (101-103). Incidences of 'brain fog' have been reported among patients experiencing milder symptoms who were never hospitalized and presumably did not experience delirium (104). An acute demyelinating encephalomyelitis, Bickerstaff's encephalitis, limbic encephalitis, acute cerebrovascular diseases (ischemic strokes, hemorrhagic strokes) have also been reported among patients of various age groups. Cases of cerebral ataxia, generalized myoclonus and acute transverse myelitis have been noted, but these are rather uncommon (96, 98, 105).

Among neurological manifestations, half of case reports indicate acute cerebrovascular disease. Cerebrovascular events were commonly found in older patients, with concurrent stroke as a potential risk factor (106). However, COVID-19-related strokes have also been reported in young subjects (107). Acute ischemia strokes (AIS) occurred in 1.3 to 4.7% of patients, independently of COVID-19 severity. Acute hypoxic injury was found in the cerebrum and cerebellum under microscopic examination, with a loss of neurons in the cerebral cortex, hippocampus, and cerebellum (108). The mean time of occurrence was 5 to 12 days after the first COVID-19 symptoms. AIS patients with COVID-19 tended to be younger than those without COVID-19, with a higher D-dimers level, a greater likelihood to have cryptogenic stroke subtype, and a higher inpatient mortality. Cryptogenic stroke has been reported in 53 to 67% of AIS in COVID-19 patients. The Global COVID-19 Stroke Registry, including 174 patients from 16 countries, confirmed that AIS patients with COVID-19 had a higher risk of severe disability and death (109). It has been hypothesized that viral neurotropism, endothelial dysfunction, inflammation, hypoxemia, and coagulopathy may all represent possible pathophysiology of cerebrovascular diseases in COVID-19 patients (97).

A growing body of data suggests that psychiatric disorders may be secondary complications of SARS-CoV-2 infection (110-112). Anxiety, depression, post-traumatic stress disorder (PTSD) and insomnia appear to be quite common in COVID-19 survivors. At approximately one month following infection, the reported incidence of depressive symptoms was 31 – 38%, anxiety 22 – 42%, and obsessive-compulsive symptoms 20% (113 – 116). Suicidal ideation was also elevated (117, 118). The prevalence of PTSD among COVID-19 patients ranged from 7.6 to 67.1% (119, 120). The most common risk factors identified to date for PTSD following SARS-CoV-2 infection are younger age, female gender, need for ICU-level care, and having a past psychiatric history (119, 121). In addition, cases of psychosis among people exposed to SARS-CoV-2 infection have been described (101, 112, 122). For example, the ongoing CoroNerve surveillance study identified new onset psychosis in 10 of the first 153 patients with acute COVID-19-related neuropsychiatric complications (101). Importantly, in the era of the COVID-19 pandemic, a significant increase of psychiatric disorders has been observed not only in infected patients, but also in health care workers and across a wide range of society (110).

The virus can invade the brain by the hematogenous and the neuronal route. In the hematogenous route, SARS-CoV-2 infects the epithelial cells of the blood-cerebrospinal fluid barrier and/or the endothelial cells of the blood-brain barrier leading to disruption of the blood-brain barrier integrity and increase in its permeability. In the neuronal route, the virus reaches the CNS by infection of peripheral neurons (94, 99). As ACE2 is expressed on both neurons and astrocytes, SARS-CoV-2 can cause dysfunction in both cell types. Astrocytes secrete inflammatory molecules and neurotrophic factors, and their dysfunction can contribute to neurological symptoms (43).

SARS-CoV-2 may cause neuropsychiatric symptoms by various mechanisms, such as neuroinflammation, cytokine cascade, hypercoagulability, direct brain injury, astrocyte infection, epigenetic changes and oxidative stress (123).

Peripheral nervous system manifestations

PNS manifestations by COVID-19 are comparatively less severe than those of the CNS, and include chemosensory dysfunctions, acute inflammation of the spinal cord, acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome and its variant, Miller-Fisher syndrome), polyneuritis, neuralgia, myalgia, weakness, fatigue, and skeletal muscle damage (myopathy). Depending on the study, methodology and country, 5-98% of SARS-CoV-2-infected patients demonstrate dysfunction of olfaction and taste perception: dysosmia - loss of smell, anosmia - complete loss of smell; dysgeusia - impaired ability to taste, ageusia - complete lack of taste sensation (124). Smell and taste disorders have mostly been reported in asymptomatic individuals, or as the initial stage of SARS-CoV-2 infection with no other symptoms. In many patients they resolved one month after infection (96, 98, 125). Although olfactory dysfunction can commonly occur with viral illness secondarily to mucosal inflammation, COVID-19 appears to be unique in the regard that anosmia and hyposmia develop in the absence of nasal obstruction or rhinorrhea (126). The pathogenesis of olfactory and taste disorders remains unclear. Anosmia may partially result from a local viral injury to olfactory neurons and inflammation in the olfactory epithelium, although it is rarely associated with rhinorrhea and nasal congestion. In addition, olfactory disturbances can result from the effect on the CNS of the virus being transported through the olfactory nerve or changes in function of the olfactory bulb due to inflammation and hypoperfusion caused by the vascular damage (94, 99, 127, 128).

In some COVID-19 patients, Guillain-Barré syndrome (GBS) was diagnosed, with neurological symptoms usually occurring 7 – 24 days after respiratory ones. The reported severity varied from a weakness of all four limbs, with or without sensory loss, to leg weakness only, or lower limb paresthesia. The facial nerve was also sometimes affected, resulting in dysphagia. In the majority of patients with GBS, SARS-CoV-2 RNA was detected in a respiratory swab, but not in CSF samples. The mechanism underlying GBS associated with COVID-19 is not clear. It is possible that pro-inflammatory cytokines play a role, which would account for the polyneuropathy; however, this could also result from a direct attack on the nerves by the virus (96, 98, 129).

Gastrointestinal tract

Gastrointestinal symptoms, including nausea, vomiting, diarrhea and loss of appetite, were reported in about 10% of patients with COVID-19. In some patients, the predominant clinical manifestations were gastrointestinal, but not respiratory symptoms. Gastrointestinal manifestations of COVID-19 are more prominent in the intestine. However, there are also few reports about changes localized in the oral cavity, such as ulceration of oral mucosa, gingivitis and hyposalivationn (50, 130).

SARS-CoV-2 has been found to replicate effectively in the epithelium of the human gastrointestinal tract. Both ACE2 and TMPRSS2 are abundantly expressed in the brush border of enterocytes, so the virus can easily infect these cells. Indeed, positive staining for viral proteins has been reported inside gastric, duodenal and rectal epithelial cells. Moreover, in about 20% of patients SARS-CoV-2 RNA was found in the feces. Detectable levels of the viral RNA were demonstrated in the feces even after resolution of respiratory symptoms, suggesting a prolonged presence of the virus in the gastrointestinal tract (45, 51). In addition to the presence of the virus in intestinal cells, mucosal infiltration with plasma cells and lymphocytes has also been recorded. This suggests that the gastrointestinal symptoms can be caused partially by both direct virus cytotoxicity and the cytokine-mediated response. Disturbances of intestinal bacterial flora and abnormalities in blood flow can also contribute to gastrointestinal manifestations (50, 51, 130).

Hepatobiliary system

Studies indicate that 5 to 50% of patients demonstrate elevated levels of liver enzymes (AST, ALT, γ-GT and ALP), hypoalbuminemia, prolonged prothrombin time, increased C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels, and hyperferritinemia (131). Although SARS-CoV-2 was not detected in liver samples, degeneration of hepatocytes, focal necrosis, microvascular steatosis, derangement of intrahepatic portal vein branches, capillary bile duct cholestasis, lobular and portal inflammation were reported. The severity of liver injury was frequently correlated with that of COVID-19. Patients with preexisting liver disease, particularly non-alcoholic fatty liver disease and liver cirrhosis, are subject to a higher risk of severe liver injury and associated mortality (50, 51, 130).

It is suggested that liver injury is related to damage to bile duct cells caused by the virus rather than to hepatocytes. Notably, bile duct cells demonstrate much higher ACE2 expression than liver cells, and the former play key roles in liver regeneration and immune response. Cytokine storm and hypoxia could also contribute to liver damage. In addition, antibiotics, antiviral drugs and steroids used for the treatment of COVID-19 also have the potential for the drug-induced liver injury (130, 132).

Kidney

Acute kidney injury (AKI), characterized by increased level of serum creatinine, proteinuria and hematuria, is rare (~5%) among patients with mild to moderate SARS-CoV-2 infection. In this group kidney abnormalities are usually subclinical (133). On the other hand, AKI was reported in 0.5 – 56.9% of hospitalized patients with COVID-19. Some discrepancies exist between studies; these can result from differences in race, comorbidities, illness severity of participants and/or variations in fluid and hemodynamic management and medication use, as well as from the adopted definition of AKI. AKI was rare on admission, it usually developed in hospital, between day five and nine of hospitalization. Kidney injury was more frequent in patients with the most severe form of the disease, the elderly or those with comorbidities such as hypertension or diabetes (134-136). Infection of podocytes by SARS-CoV-2 and altered RAAS activity can affect the glomerular filtration barrier and result in increased filtration of plasmatic proteins. Tubular injury can also contribute to protein excretion (133).

The mechanism of COVID-19 associated kidney injury remains to be elucidated. It is suggested that more than one factor contributes to the kidney dysfunction. COVID-19 patients frequently suffer from coexisting hypertension and/or diabetes. Fever, tachypnoea and gastrointestinal disturbances can lead to hypovolemia and prerenal AKI. The functional overactivity of ACE-Ang II-AT1 arm of RAAS can lead to vasoconstriction, inflammation and fibrosis in the kidney (43). Cytokines such as IL-6 or TNF-α may participate in kidney injury by inducing apoptosis and increasing vascular permeability. The action of cytokines and coagulopathy can result in microcirculatory

dysfunctions in the kidney. It is also possible that the virus may induce kidney injury by its direct cytotoxic effect. Additionally various drugs (e.g. antiviral medications and antibiotics) are believed to exert nephrotoxic effects (51, 134, 135, 137).

Histopathological examination of the kidney has revealed signs of diffuse injury to the proximal tubules, with a loss of brush border, cytoplasmic vacuoles, degeneration and necrosis. Diffuse erythrocyte aggregation patterns and obstruction of glomerular and peritubular capillaries were also frequently reported. Coronavirus-like particles were found in the cytoplasm of proximal tubule epithelial cells and in podocytes. As histological data were obtained during postmortem analysis, it is difficult to estimate whether these findings are attributed to the direct effects of the virus or they result from sepsis or multiple organ failure (51, 133, 137).

COVID-19 IN CHILDREN

Children form only a small portion (2.1 – 7.8%) of confirmed COVID-19 cases (138). Most of them demonstrate minor symptoms or asymptomatic infection, with only 2 – 6% requiring intensive care treatment. The estimated mortality rate in children is 0.2%. The most common symptoms reported in children were fever, cough, headache, rhinorrhea, gastrointestinal disturbances and myalgia, while anosmia and dysgeusia were less commonly observed (138-140). Unlike adults, the incidence of severe respiratory illness such as ARDS is rare. However, since mid-April 2020, clusters of pediatric cases of severe systemic hyperinflammation leading to multiorgan failure and shock have been reported. This condition was named as SARS-Cov-2-associated multisystem inflammatory syndrome in children (MIS-C) or Pediatric Inflammatory Multisystem Syndrome temporally associated to SARS-CoV-2 infection (PIMSTS). In contrast to acute COVID-19 in children, MIS-C appears to be a condition of higher severity with around two-thirds of cases requiring critical care support. The underlying risk factors of MIS-C appear to be similar to those in adults, with obesity, chronic lung disease (including asthma), cardiovascular disease and immunosuppression being most commonly described (138, 141-143).

The commonly-reported symptoms of MIS-C include persistent fever, asthenia, diffuse erythematous polymorphic rash, non-purulent conjunctivitis, prominent gastrointestinal disturbances, mucosal changes, peripheral edema and conjunctivitis. Many children with MIS-C also present with hypotension and shock from either acute myocardial dysfunction or systemic hyperinflammation/vasodilation (138, 141, 142, 144). Coronary artery dilation has been described in 8.9% of patients, aneurysms in 15.5%, and arrhythmias and left ventricle dysfunction in 63.3% (138). In addition, several pediatric patients presented neurological symptoms. A multicenter study of children diagnosed with MIS-C across US reported that 5% had seizures, coma, encephalitis, demyelinating disorders, and aseptic meningitis (145). In the United Kingdom, of 27 children with MIS-C, four demonstrated new onset neurological symptoms, including encephalopathy, dysarthria, dysphagia, cerebellar ataxia, and peripheral neuropathy leading to global proximal muscle weakness and reduced reflexes (146).

MIS-C has been found to show similarities with Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome. However, accumulating clinical evidence indicates that MIS-C is distinct from Kawasaki disease, with features including an age at onset of more than 7 years, a higher proportion of African or Hispanic children being affected, and diffuse cardiovascular involvement suggestive of a generalized immune-mediated disease (142, 147-149). Patients with MIS-C had increased concentrations of CRP, troponin, ferritin, D-dimers, brain natriuretic peptide (BNP), *N*-terminal pro B-type BNP, or IL-6; neutrophilia, or low platelet or lymphocyte counts (143, 150). The presence of oral or oropharyngeal changes, such as red or swollen lips, often associated with systemic rash and conjunctivitis, may be early indicators of MIS-C, and should be considered suggestive of MIS-C in the setting of COVID-19 infection (148, 151). A study by Feldstein *et al.* (145) analyzed a case series of patients younger than 21 years hospitalized at 66 US hospitals. Of 1116 patients, 539 were diagnosed with MIS-C and 577 with COVID-19. Compared with patients with COVID-19, these with MIS-C were more likely to be 6 to 12 years old (40.8% vs. 19.4%), to have cardiorespiratory involvement (56.0% vs. 8.8%), cardiovascular without respiratory involvement (10.6% vs. 2.9%), and mucocutaneous without cardiorespiratory involvement (7.1% vs. 2.3%). A total of 398 patients (73.8%) with MIS-C and 253 (43.8%) with COVID-19 were admitted to ICU, and 10 (1.9%) with MIS-C and 8 (1.4%) with COVID-19 died during hospitalization.

Importantly, the time-line of molecular diagnosis and spectrum of severe complications associated with MIS-C differ from those seen in pediatric COVID-19 cases. Firstly, MIS-C starts appearing around one month after a COVID-19 peak in the population. Secondly, only a third of the reported MIS-C cases were positive for SARS-CoV-2 based on RT-PCR test; most cases were positive with an antibody test, indicating past infection. The delay in presentation of MIS-C symptoms, the low proportion of patients who were SARS-CoV-2 positive by RT-PCR, and the high proportion who were antibody positive suggest that MIS-C is not mediated by the direct viral invasion, but instead coincides with the development of acquired immune responses to SARS-CoV-2. Time from infection to onset of MIS-C symptoms varies among studies, from a few days to months (138). The most widely-recommended medication to treat MIS-C was intravenous immunoglobulin followed by corticosteroids, with heparin or low molecular weight heparin being used primarily in severe cases. In addition, in severe cases, anakinra and vasopressors are frequently recommended (138, 150, 152).

PHARMACOLOGICAL TREATMENT OF COVID-19

Current WHO recommendations for management of COVID-19 patients

According to COVID-19 Clinical management Living guidance, published by the WHO on 25 January 2021 (153), the following management is recommended for patients with COVID-19:

- Treatment of a mild COVID-19 should be symptomatic. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used for fever and pain. Adequate nutrition and appropriate rehydration of patients is also recommended. Antibiotics for treatment or prophylaxis should not be used.
- Patients with moderate COVID-19 pneumonia may require hospitalization, but in some cases can be treated at home. The decision about localization of a patient should be individualized depending on the clinical presentation, requirement for supportive care, potential risk factors for severe disease and home conditions. Hospitalization is preferred for patients with high risk of health deterioration. Non-hospitalized patients should be warned that if symptoms of complications develop (e.g. difficulty breathing or chest pain), they should seek urgent professional care. For non-hospitalized patients with COVID-19 with risk factors for progression to severe disease, the use of pulse oximetry monitoring at home is suggested. If there is no

clinical suspicion of a bacterial infection, antibiotics should not be prescribed.
• Patients with severe COVID-19 require hospitalization. In more serious cases, they have to be placed in ICU. In this group, administration of oxygen is necessary and treatment depends on the patient's condition.

DRUGS CURRENTLY RECOMMENDED BY THE WHO AND EMA FOR TREATMENT OF COVID-19

Since September 2020, the WHO has published several living guidelines on drugs to prevent and treat COVID-19. In the last version of "Therapeutics and COVID-19: living guideline" published 24 September 2021 by the WHO (154) the following recommendations are given:
• "a strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19;
• a strong recommendation for IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe and critical COVID-19;
• a conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19;
• a conditional recommendation against remdesivir in hospitalized patients with COVID-19;
• a strong recommendation against hydroxychloroquine in patients with COVID-19 of any severity;
• a strong recommendation against lopinavir/ritonavir in patients with COVID-19 of any severity;
• a recommendation against ivermectin in patients with COVID-19 of any severity, except in the context of a clinical trial;
• a conditional recommendation to use casirivimab and imdevimab in non-severe patients, the condition being patients' risk of severe disease: patients at highest risk represent good candidates for use of the intervention.
• a conditional recommendation to use casirivimab and imdevimab in patients with severe and critical infection, the condition being seronegative status. "

In March 2021-June 2021, the European Medicines Agency (EMA) granted conditional marketing authorization for some monoclonal antibodies against the spike protein of the SARS-CoV-2 virus (155). The following medicines are approved for the use in the European Union, but are still under rolling review:
• bamlanivimab / etesevimab
• casirivimab / imdevimab
• regdanvimab
• sotrovimab.

Moreover, EMA has already started evaluation of an application to extend the use of two medicines, anakinra and baricitinib, for the treatment of COVID-19. Data from clinical studies indicate that these drugs may be useful in hospitalized patients with COVID-19 (155).

Fig. 1 presents molecular targets for medicines currently used for the COVID-19 treatment.

IL-6 RECEPTOR BLOCKERS - TOCILIZUMAB AND SARILUMAB

IL-6 is a key inflammatory cytokine which is highly elevated in severely-ill COVID-19 patients (156), so the IL6/IL-6 receptor (IL-6R) signaling pathway appears as a promising target for alleviation of inflammatory symptoms. Tocilizumab and sarilumab are strongly recommended by the WHO for patients with severe or critical COVID-19 (154). These two medicines are human monoclonal antibodies against IL-6R. By binding to both soluble (sIL-6R) and membrane-bound (mIL-

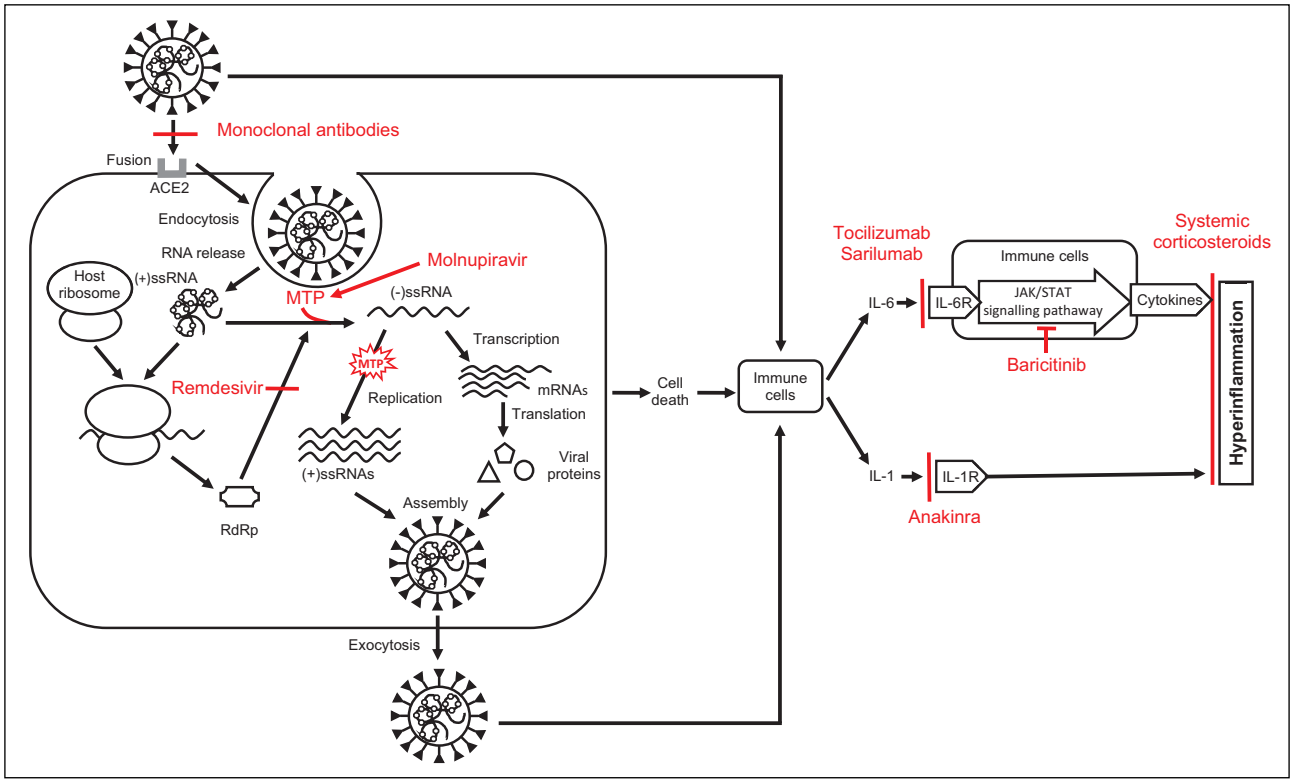

Fig. 1. Molecular targets for medications currently used to treat COVID-19. Red lines represent inhibition of different steps in COVID-19 by medicines. (MTP – NHC triphosphate, active form of molnupiravir). For details see text.

6R) forms of the receptor they inhibit sIL-6R- and mIL-6R-mediated signaling (154, 157, 158).

Originally tocilizumab has been used in the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis and Cytokine Release Syndrome. It was shown to reduce the rate of progression of joint damage and to improve physical function (158). Sarilumab is indicated for moderate to severe RA in adult patients, in whom it reduces the number of tender and swollen joints, and decreases pain severity and CRP level (157).

The Immune Modulation Therapy domain of the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) indicated that tocilizumab and sarilumab decrease mortality and the need for mechanical ventilation in COVID-19 patients (159). It was suggested that these two antibodies may shorten the duration of mechanical ventilation and hospitalization. Better effects were observed in patients who received respiratory support or non-invasive ventilation (oxygen by nasal cannula, face mask, high-flow nasal oxygen) than in those who required invasive mechanical ventilation. A significant decrease in mortality was found only in patients who received both IL-6R antagonists and a systemic corticosteroid. These results were confirmed by a meta-analysis of the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group and other studies (159-162). The most common side effects of tocilizumab are upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased levels of transaminases. Serious infections, complications of diverticulitis and hypersensitivity reactions were also reported (158).

In the treatment of COVID-19 patients, tocilizumab is typically administered as a single intravenous dose (8 mg/kg up to a maximum of 800 mg); however, the dose was repeated after 12 to 48 hours in major clinical trials when the clinical response was inadequate. Sarilumab is administered in a single dose of 400 mg intravenously. Dosing is the same regardless severity of COVID-19. Although the drug is administered subcutaneously in the treatment of RA, this route is not recommended in the case of COVID-19 (153, 157). The most common adverse effects of sarilumab are neutropenia, increased transaminase levels, erythema and pruritus at the site of injection, and upper respiratory tract and urinary tract infections (157).

Therapy with IL-6R blockers increases the risk of active tuberculosis, invasive fungal infections and infections by opportunistic pathogens. Thus, potential risks and benefits of therapy should be weighed carefully, and patients should be monitored for signs and symptoms of infection (154).

SYSTEMIC CORTICOSTEROIDS

In severe COVID-19, organ injuries are caused, at least partially, by inflammation. Patients may have markedly elevated levels of CRP, IL-1, IL-6 and other inflammatory markers. Various therapeutic interventions have been proposed to modulate inflammatory organ injury, among them corticosteroids. The current body of clinical evidence indicates that inhibition of inflammation-mediated lung damage can prevent the development of respiratory failure and death. In an early phase of the pandemic, reports on efficacy of corticosteroids in COVID-19 patients were contradictory. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial was designed to evaluate effects of potential treatments, including dexamethasone, in hospitalized patients with COVID-19. Dexamethasone used for up to ten days decreased mortality in patients receiving invasive mechanical ventilation (29.3% vs. 41.4% in the usual care group) or receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2% in the usual care group). However, benefits were only observed in patients receiving respiratory support. Clinical improvements were clear in those patients who were treated after at least seven days from the onset of symptoms, when inflammatory-mediated lung injury is more common (163). In SARS-CoV-2 infection, viral replication is more intensive early in the course of the disease, with the rate decreasing with time. While dexamethasone may be harmful if administered during periods of intensive virus replication, it can be beneficial if applied when inflammation is the predominant cause of the lung injury (50, 163).

Earlier randomized control trials demonstrated that corticosteroids decrease mortality, shorten the duration of mechanical ventilation and improve oxygenation in patients with ARDS (164, 165). They inhibit inflammation, with a decrease in the levels of pro-inflammatory mediators and chemokines being observed in bronchoalveolar lavage and plasma. Moreover, it is possible that in critically-ill patients, the response of the hypothalamus-pituitary-adrenals axis to stress is impaired and administration of a stress dose of corticosteroids may increase survival (164, 166).

Since September 2020, the WHO has strongly recommended administration of systemic corticosteroids to patients with severe and critical COVID-19. They can be administered orally or intravenously, especially in patients with a suspected intestinal dysfunction. Recommendations were based on clinical trials in which the majority of patients received dexamethasone 6 mg daily. The treatment lasted 5 to 14 days, typically not more than 10 days, and generally was discontinued after discharge. Hydrocortisone (50 mg every 8 hours; *i.v.*), methylprednisolone (10 mg every 6 hours; *i.v.*) or prednisone (40 mg daily; p.o.) can be used as alternatives to dexamethasone. Dosing is the same in patients with severe or critical COVID-19. For patients with non-severe COVID-19, the WHO suggest not using systemic corticosteroids, as corticotherapy did not yield any obvious benefits in this group (153, 154).

MONOCLONAL ANTIBODIES AGAINST THE SPIKE (S) PROTEIN OF SARS-COV-2 VIRUS

Neutralizing monoclonal antibodies (MAbs) that target the spike (S) glycoprotein of SARS-CoV-2 virus are potential candidates for therapeutic treatment against COVID-19. Three of such antibodies, i.e., bamlanivimab, casirivimab and imdevimab, were approved by the U.S. Food and Drug Administration Agency (FDA) on November 2020 (167).

Monoclonal antibodies against the S protein are conditionally approved for the treatment of patients with mild to moderate COVID-19, aged at least 12 years, who do not require supplemental oxygen therapy, and who are at risk of progressing to severe COVID-19. The antibodies bind to the S protein, thus blocking the protein binding to the host receptor (ACE2) and preventing the entrance of the virus to the host cells.

Bamlanivimab and etesevimab

Bamlanivimab (LY3819253 or LY-CoV555) and etesevimab (LY3832479 or LY-CoV016) are monoclonal antibodies that bind to the S protein at two different but overlapping sites (168, 169).

Bamlanivimab can be used in monotherapy, where it accelerates the natural decline in the viral load. It also decreases the number of hospitalizations and visits to emergency departments (170). In the Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE) trial, it was shown that the combined bamlanivimab with etesevimab therapy decreases the viral load, reduces the number

of hospitalizations and deaths in high-risk COVID-19 patients (170).

Bamlanivimab (700 mg) and etesevimab (1400 mg) administered together as a single dose in a short-term infusion have been approved by FDA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. These two antibodies should not be used in patients who are hospitalized due to COVID-19 or require oxygen therapy (167). On 9 September 2021 FDA has authorized the emergency use of bamlanivimab and etesevimab, administered together, as a post-exposure prophylaxis (prevention) for COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death (167). The combination bamlanivimab/etesevimab should be administered as soon as possible after a positive test for SARS-CoV-2 and within ten days of the symptoms onset. As serious hypersensitivity reactions were reported, patients should be monitored during administration and observed for at least one hour after the end of infusion. Most frequent adverse effects of these drugs are nausea and vomiting, diarrhea, dizziness, headache and pruritus. Serious hypersensitivity reactions, including anaphylaxis, and infusion-related reactions were observed in clinical trials (167).

After administration of bamlanivimab, some cases of COVID-19 exacerbation were reported, including symptoms like fever, hypoxia, difficulty breathing, arrhythmia, fatigue and altered mental status. Some patients required hospitalization. Currently, it is not known whether these symptoms were related to administration of bamlanivimab or resulted from progression of COVID-19 (171).

Casirivimab/imdevimab (REGN-COV2 antibody combination; Ronapreve)

Casirivimab (REGN10933) and imdevimab (REGN10987) are human monoclonal antibodies that bind to distinct and non-overlapping regions of the receptor binding domain (RBD) of the S protein. The antigen-binding fragment of casirivimad binds at the top of RBD, overlapping almost completely the region hosting the binding site for ACE2, while imdevimab acts on the side of RBD endowed with low probability of interfering with ACE2. By blocking RBD, these antibodies prevent the binding of the S protein to ACE2. Binding casirivimab and imdevimab to two non-overlapping epitopes minimizes the risk of decreased effectiveness due to viral variation, and the development of resistant mutants (172). These two antibodies are intended to be used as combination and should not be used in monotherapy. They are prepared in a form of a combined cocktail marked as REGN-COV2 (173-175).

Originally REGN-COV2 was recommended only for patients with mild to moderate COVID-19. In the fifth version of Therapeutics and COVID-19: living guideline published by the WHO on 24 September 2021 a conditional recommendation was added to use casirivimab and imdevimab in patients with severe and critical infection, the condition being seronegative status (154). On 16 November 2021 EMA recommended Ronapreve for the treatment of COVID-19 in adults and adolescents aged 12 years and older and weighing at least 40 kg who do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe form of the disease (176).

REGN-COV2 is administered intravenously (a short-term infusion) in a single dose (154):

- from 600 mg of each antibody (total dose 1200 mg) to 1200 mg of each antibody (total dose 2400 mg) for patients with mild to moderate COVID-19;
- from 1200 mg of each antibody (total dose 2400 mg) to 4000 mg of each antibody (total dose 8000 mg) for patients with severe to critical COVID-19.

Until now, Ronapreve treatment has not been associated with any adverse effects when administered at the recommended dose. Nevertheless, as a risk of serious allergic reactions exists, patients should be monitored during the infusion, and at least one hour after its completion (177). The effectiveness of REGN-COV2 was evaluated in the COV-2067 study, a randomized, double-blinded, placebo-controlled clinical trial involving 799 adult patients with COVID-19. Treatment with REGN-COV2 resulted in a statistically significant decrease in the viral load after seven days. The reduction was bigger in patients with a higher baseline viral load and in those whose immune response has not yet been initiated. In addition, patients treated with REGN-COV2 demonstrated lower numbers of physician visits/telemedicine consultations and hospitalizations compared to a placebo group. The greatest benefits were observed in patients with the following risk factors: older than 50 years, obese, with co-existing diseases. Importantly, the administration of casirivimab/imdevimab may lead to worsening of clinical outcomes in hospitalized patients requiring high flow oxygen or mechanical ventilation (173, 175, 177, 178). Ronapreve was also found to be effective at preventing people from getting infected and developing symptoms after contact with contagious persons. Amongst people who tested negative for SARS-CoV-2 following contact, fewer subjects given Ronapreve developed symptoms within 29 days of their test results (1.5%; 11 out of 753) compared with those given placebo (7.8%; 59 out of 752) (176).

Regdanvimab (Regkirona)

Regdanvimab is a recombinant human monoclonal antibody that binds to the RBD of the S protein (179-181). Results of an ongoing CT-P59 3.2 Part 1 study indicate that regdanvimab may decrease the rate of hospitalization. Also, patients treated with regdanvimab were found to demonstrate a shorter time to clinical recovery and greater reduction in viral shedding in nasopharyngeal swabs in comparison to a placebo group. In this study no deaths were reported (180). Among patients at increased risk of their illness becoming severe, 3.1% of patients treated with Regkirona (14 out 446) were hospitalized, required supplemental oxygen or died within 28 days of treatment compared with 11.1% of patients on placebo (48 out of 434) (180).

Regdanvimab is administered intravenously (a short-term infusion) in a single dose of 40 mg/kg. Patients should be monitored during administration and observed for at least one hour after the end of infusion. Treatment should be started no later than seven days after the onset of symptoms (181). Commonly-reported side effects of regdanvimab ($\geq$ 1/100 to $<$ 1/10) were neutropenia and hypertriglyceridemia. Hyperkaliemia, dyslipidemia, headache, rash, hepatitis, proteinuria, fever were reported with a frequency less than 1/1000. Infusion-related fever and dyspnea (mild to moderate) were reported in 0.5% of patients. In hospitalized patients requiring high flow oxygen or mechanical ventilation, regdanvimab may worsen clinical outcomes (181).

On 16 November 2021 EMA recommended Regkirona for treating adults with COVID-19 who do not require supplemental oxygen and who are also at increased risk of their disease becoming severe (182).

Sotrovimab (Xevudy; VIR-7831 or GSK4182136)

Sotrovimab is a human monoclonal antibody that binds to RBD of the S protein (183). This region is highly conserved, so the risk that the virus may develop resistance to sotrovimab due to mutations is relatively low. Sotrovimab contains an LS modification of the Fc domain, which prolongs its half-life and improves bioavailability in the mucosa of the respiratory tract (183).

In the COMET-ICE trial, non-hospitalized patients with COVID-19 received sotrovimab or placebo. A 85% reduction in hospitalization or deaths in patients receiving sotrovimab compared to placebo was reported (183-185).

Sotrovimab is administered intravenously (a 30 min infusion) in a single dose of 500 mg. Severe allergic reactions are very rare; nevertheless anaphylaxis after infusion was reported, thus patients should be monitored during infusion and at least one hour after infusion. The drug is well-tolerated; adverse effects were mild to moderate. Most frequently diarrhea was reported, it occurred in about 1% of patients. Other side effects, such as headache, nausea and dyspnea occurred in less than 1% of patients (183, 185).

On 2 December 2021 the Medicines and Healthcare Products Regulatory Agency (MHRA; the United Kingdom) authorized Xevudy (sotrovimab) for use in people who have mild to moderate COVID-19 infection and at least one risk factor for developing severe illness. Such risk factors include obesity, older age (> 55 years), diabetes mellitus, or heart disease (186).

ANTIVIRAL DRUGS

Remdesivir (Veklury)

Remdesivir was originally introduced in 2017 against the Ebola virus (187). Its spectrum of antiviral activity also includes the RNA viruses *Filoviridae*, *Pneumoviridae*, *Paramyxoviridae* and *Coronaviridae* (50, 188). In *in vitro* studies, remdesivir inhibited replication of SARS-CoV-2 in primary human airway epithelial cells and in the Calu-3 human lung epithelial cell line (189).

Remdesivir, an adenosine analog, is a potent inhibitor of RNA-dependent RNA polymerase (RdRp). It is a prodrug, being transformed inside the host cells into remdesivir triphosphate (RTP), an analogue of adenosine triphosphate (ATP) which inhibits viral RNA polymerases. RTP is incorporated into the viral RNA leading to delayed termination during the replication phase (50, 188).

In October 2020, remdesivir was approved by FDA for treatment of COVID-19 in adult and pediatric patients at least 12 years old and weighing at least 40 kilograms. Remdesivir was the first drug to receive FDA approval for use in COVID-19 patients (190). It was approved for treatment of hospitalized patients who require oxygen supplementation, i.e. non-invasive ventilation, at the beginning of treatment (190, 191).

Initially, the Adaptive COVID-19 Treatment Trial (ACTT) indicated that remdesivir may shorten time to clinical improvement in COVID-19 patients and decrease mortality (192, 193). However, the WHO Guideline Development Group found insufficient evidence that remdesivir meaningfully reduces mortality and the need for mechanical ventilation and decreases time to clinical improvement. Moreover, remdesivir has to be administered only intravenously and the global availability of this drug is currently limited. Therefore, the WHO conditionally recommended against administering remdesivir in addition to the usual care. There is no evidence that remdesivir is ineffective; rather there is insufficient data that its use is really beneficial and further investigations are necessary (154).

In the treatment of COVID-19, remdesivir is administered by intravenous infusion: a loading dose of 200 mg at the first day, followed by 100 mg once daily. The duration of treatment was between five and ten days (154, 191). The most common adverse effects of remdesivir include prolongation of prothrombin time, increased levels of transaminases, headache, nausea and rash. Hypersensitivity reactions including anaphylaxis were also reported; therefore, patients have to be observed during and after infusion (191).

Molnupiravir (Lagevrio)

Molnupiravir was invented at the Drug Innovation Ventures at Emory University (Atlanta, GA, US), and is being developed by Merck & Co, Inc. in collaboration with Riggeback Biotherapeutics. Similar to remdesivir, molnupiravir targets the RdRp of SARS-CoV-2. Molnupiravir is an isopropylester prodrug of the nucleoside analog β-D-N^4-hydroxycytidine (NHC) which is cleaved in plasma by host esterases to NHC - a cytidine analog. NHC is distributed to various tissues and subsequently converted to NHC trisphosphate (MTP). NHC is a broad-spectrum antiviral compound that *in vitro* inhibited the replication of multiple viruses (e.g., Chikungunya virus, Venezuela equine encephalitis virus, respiratory syncytial virus, hepatitis C virus, norovirus, influenza A and B viruses, Ebola virus, and human coronaviruses) (194). MTP can be used by the RdRp as a substrate instead to cytidine trisphosphate (CTP) or, less frequently, uridine trisphosphate (UTP). The drug inhibits viral replication by a two-step mechanism known as 'lethal mutagenesis'. In the first step RdRp incorporates molnupiravir monophosphate (M) instead of C or U when it uses the positive-strand genomic RNA (+gRNA) as a template to synthesize the negative-strand genomic RNA (-gRNA) and subgenomic RNA (-sgRNA). In the second step, the M-containing RNA can be used as a template for the synthesis of +gRNA or positive-strand subgenomic mRNA (+sgmRNA). M–A pairing induced mutagenesis by increasing G to A and C to U transition frequencies (195-197).

Molnupiravir can be used for the treatment of mild-to-moderate COVID-19 in adults with a positive SARS-CoV-2 diagnostic test, the symptoms onset within five days, and who have at least one risk factor for developing severe illness. The drug is administered orally, usually at a dose of 800 mg, twice daily for five days. Available data indicate that molnupiravir is well tolerated, with nausea, insomnia and increased levels of ALT being reported in a small group of patients. Results of an ongoing phase 3 clinical trials showed that the drug can significantly decrease the progression of COVID-19 by hospitalization and/or death (198). In November 2021 the MHRA authorized molnupiravir for the treatment of mild-to-moderate COVID-19 in adults with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness (199). However, as β-D-N^4-hydroxycytidine has recently been demonstrated to be mutagenic to hamster CHO-K1 cells (200), careful studies on its safety when used in humans are urgently needed.

ANAKINRA

In July 2021 EMA started evaluating an application to extend the use of anakinra for treatment of COVID-19 in adult patients with pneumonia who are at risk of severe respiratory failure. Anakinra is currently indicated for treatment of autoinflammatory disorders: RA, periodic fever syndromes and Still's disease (201).

Anakinra is an antagonist of the IL-1 receptor (IL-1R). By blocking the binding of IL-1α and IL-1β to IL-1R it prevents IL-1-induced production of nitric oxide, PGE_2 and collagenase by synovial cells, fibroblasts, and chondrocytes. In patients with RA, the drug decreases pain and the number of tender joint, and improves physical function. Anakinra decreases the number of attacks and normalizes body temperature in periodic fever syndromes. In patients with Still's disease, it induces resolution of fever and rash (201, 202).

Although anakinra is administered subcutaneously when treating autoinflammatory diseases, it is given intravenously in patients with COVID-19. The CORIMUNO-ANA-1 trial was the first to examine effects of anakinra in COVID-19 patients with pneumonia. In the trial, anakinra was administered to patients with mild to moderate stage of the disease; however, no benefits were recorded. It was hypothesized that as the patients enrolled in the trial had an appropriate immune response to the virus, no benefits could be gained from the use of a drug which modulates the immune response (203).

In a trial undertaken by Cavalli and coworkers (204) anakinra was administered to a group of 29 patients with moderate to severe COVID-19 pneumonia, ARDS and hyperinflammation, who required a non-invasive respiratory support. Patients were treated outside ICU; they obtained hydrochloroquine and lopinavir/ritonavir without corticosteroids and any other anti-inflammatory drugs. Anakinra was administered intravenously at a high dose of 5 mg/kg, twice daily. After 21 days of therapy, the patients demonstrated better respiratory function and higher rate of survival than those with the standard treatment. It was believed that the high-dose of anakinra improved respiratory functions by suppressing inflammation (204). A meta-analysis of available data regarding the use of anakinra in hospitalized patients with moderate to severe COVID-19 pneumonia demonstrated that mortality was significantly lower in patients treated with anakinra than in those receiving standard of care with or without placebo standard. Benefits are observed especially in patients with signs of hyperinflammation (e.g. CRP > 100 mg/L) (205). Anakinra showed a significant survival benefit when given without dexamethasone, but not with dexamethasone co-administration. Importantly, anakinra is well tolerated even at high doses. Moreover, in comparison with other cytokine-blocking agents anakinra has a short half-life (four to six hours) and its level decreases rapidly after discontinuation. Hence, the drug is relatively safe in critically ill patients (204). Most frequent side effects of anakinra, when used in autoinflammatory diseases, are reactions at the injection site, headache, increased serum cholesterol level, thrombocytopenia and neutropenia. Although the product information indicates that the common side effects of anakinra can be serious secondary infection, this was not observed in patients with COVID-19, maybe due to the shorter duration of therapy (201, 205).

BARICITINIB

In April 2021 EMA began evaluating an application to extend the use of baricitinib for treatment of COVID-19 in hospitalized patients who require supplemental oxygen. Currently, this drug is indicated for treatment of moderate to severe active RA and atopic dermatitis (AD) in adult patients (206).

Baricitinib is a selective, reversible inhibitor of Janus kinases, JAK1 and JAK2. JAK kinases are involved in intracellular Janus kinase -signal transducer and activator of transcription (JAK-STAT) signaling pathway. They phosphorylate and activate signal transducers and activators of transcription (STATs), which then activate the expression of genes encoding proteins involved in hematopoiesis, inflammation and function of immune system. Inhibition of JAK kinases may decrease an unwanted inflammatory response (207, 208). The COV-BARRIER trial was designed to evaluate the efficacy and safety of baricitinib in combination with the standard care for treatment of hospitalized adults with COVID-19 (systemic corticosteroids, mainly dexamethasone). The patients demonstrated elevations in at least one inflammatory marker (CRP, D-dimers, LDH, ferritin) and did not require invasive mechanical ventilation. Baricitinib was administered orally (or crushed for nasogastric tube) at a dose of 4 mg daily (2 mg in patients with a baseline eGFR ≥ 30 to 60 mL/min/1.73 m^2). Treatment lasted for up to 14 days or until discharge from hospital. It was shown that although baricitinib did not significantly inhibit progression of the disease, it markedly reduced mortality in comparison to the control group. The 28-day all-cause mortality was 8% (n = 62) for baricitinib and 13% (n = 100) for placebo. The 60-day all-cause mortality was 10% (n = 79) for baricitinib and 15% (n = 116) for placebo. The frequencies of serious adverse events, serious infections, and venous thromboembolic events were similar between the two groups (209).

In a retrospective multicenter study undertaken by Cantini and coworkers (210), it was found that the combination of baricitinib with lopinavir/ritonavir and hydrochloroquine resulted in decreased mortality (0% vs. 6.4%) and ICU admission (0.88% vs. 17.9%), and increased discharge rate at week one (9.7% vs. 1.3%), in comparison to the control group (lopinavir/ritonavir and hydrochloroquine without baricitinib). In this study hospitalized patients with moderate COVID-19 were taken into account. The therapy with baricitinib started in the early phase of disease, seven days from the symptoms onset. The most common adverse effects of baricitinib, when used in RA and AD, include infections of the upper respiratory tract and urinary tract, gastritis, nausea and abdominal pain, hypercholesterolemia and thrombocytosis. In patients with COVID-19, increases of transaminase levels, urinary infections and oral candidiasis have been reported (210).

The recommendations for use of the presented above medications in treating COVID-19 are given in *Table 2*.

VACCINES CURRENTLY APPROVED BY THE WHO FOR PROPHYLAXIS OF COVID-19

The safest and most cost-effective way to prevent COVID-19 illness and death, and the best option to combat anticipated future variants, is preventative vaccination. According to the draft landscape of COVID-19 candidate vaccines released by the WHO, as of 23 July 2021, 108 candidates were in clinical evaluation and more than 184 in various stages of preclinical evaluation (211).

COVID-19 vaccines being developed around the world are mainly of two different forms, the first being classical vaccine platforms, including live-attenuated viruses, whole-inactivated viruses, protein subunits and virus-like particles, and the second being next-generation vaccine platforms, including viral DNA vaccines, RNA vaccines, viral vectors, and antigen-presenting cells (212). Among various vaccine types, those based on T cells, dendritic cells, viral vector replicating combined with antigen presenting cell, are still in their initial phase, and no product has been confirmed with adequate safety so far (213). The molecular targets for the development of vaccines against SARS-CoV-2, dominated by the S protein, and options for designing the best vaccination strategies are summarized in a recent elegant review by Martinez-Flores and coworkers (214). At present all COVID-19 vaccines are administered intramuscularly. For individuals ages 5 to 17 who are eligible to receive a COVID-19 vaccination, the Pfizer-BioNTech

COVID-19 Vaccine (Comirnaty) by Pfizer-BioNTech is the only vaccine currently approved (215). For children 5 through 11 years of age it is administered as a two-dose (10 μg) primary series, three weeks apart; this dose is lower than that used for individuals 12 years of age and older (30 μg) (216, 217).

As a protection against SARS-CoV-2 infection after vaccination has begun to decrease over time, there is a possibility to get an addition dose of a vaccine, so-called a booster shot. The booster is designed to help people maintain their level of immunity for a longer time.

Centers for Disease Control and Prevention (CDC0 US) recommends a COVID-19 booster for the following groups (218):
A. Pfizer-BioNTech or Moderna COVID-19 Vaccines
(1) People ages 50 years and older, residents ages 18 years and older of long-term care settings should get a booster shot at least six months after the second dose of the vaccine;
(2) People who are ages 18 years and older may get a booster shot based on their individual risks and benefits. The additional dose should be given at least six months after the second dose of the vaccine.

Table 2. Use of medications in COVID-19 of different severity. Shaded boxes indicate the category of disease severity in which a drug is recommended (for dosing see text).

Medications currently recommended to treat COVID-19	**Severity of COVID-19**			
	Mild	Moderate	Severe	Critical
Monoclonal antibodies				
REGN-COV2			Seronegative patients	
Anakinra				
Barticinib				
Remdesivir				
Systemic corticosteroids				
ll-6 receptor blockers				

Table 3. Vaccines against COVID-19 that according to the WHO have met the necessary criteria for safety and efficacy (211).

Vaccine platform description	**Developer**	**Type of candidate vaccine; name, dose/injection volume**	**No. of doses required**	**Schedule**	**Efficiency against symptomatic infection (based on phase 3 clinical trial results)** (220)
Inactivated virus	Sinovac Research and Development Co., Ltd	CoronaVac; inactivated SARS-CoV-2 vaccine (vero cell). 0.5 ml	2	Day 0 + 14	50 – 84%
	Sinopharm & China National Biotec Group Co & Beijing Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (vero cell), vaccine name BBIBP-CorV. 8 μg	2	Day 0 + 21	78.1%
	Hyderabad-based Bharat Biotech International Limited	COVAXIN, inactivated SARS-CoV-2 vaccine; 6 μg	2	Day 0 + 28	77.8%
Viral vector (non-replicating)	AstraZeneca & University of Oxford	ChAdOx1-S-(AZD1222); Vaxzevria (previously COVID-19 Vaccine AstraZeneca)*; 5×10^{10} viral particles	1 – 2	Day 0 + 28	76% after a single dose; 81.3% after the second dose
	Janssen Pharmaceuticals/ Johnson & Johnson	Ad26.COV2.S; Janssen (Johnson & Johnson) COVID-19 Vaccine*#. 1×10^{11} viral particles	1 – 2	Day 0 or Day 0 + 56	66.1% after 28 days in one-dose regimen
RNA based vaccines	Pfizer/BioNTech & Fosun Pharma	BNT162b2 (3 LNP-mRNAs); Comirnaty*# 10 μg (0.2 ml) for children 5 – 11 years old, 30 μg (0.3 ml) for individuals 12 years of age and older	2	Day 0 + 21	52% after the first dose, 95% after the second dose
	Moderna & National Institute of Allergy and Infectious Diseases (NIAID)	mRNA-1273; Spikevax (previously COVID-19 Vaccine Moderna)*#. 100 μg	2	Day 0 + 28	94.1% after the second dose

Vaccines authorized in the European Union* and the United States# to prevent COVID-19.

B. Johnson & Johnson/Janssen COVID-19 Vaccine

All people ages 18 years and older who received a J & J/Janssen COVID-19 vaccine at least 2 months ago should get a booster shot, for a total of two shots. A list of vaccines against COVID-19 evaluated by the WHO that have met the necessary criteria for safety and efficacy (219) is presented in *Table 3*.

CONCLUDING REMARKS

Since 2020, the world is struggling with the COVID-19 pandemic. Although only a fraction of patients has a severe disease, because of the large number of people infected, even this small percentage is a huge burden for the health service. The lack of effective treatment made it necessary to introduce a lockdown, which led to economic disturbances and impaired social ties. The introduction of vaccines in 2021 raised hope for controlling the pandemic, but rapid mutations of the virus reduce the effectiveness of this method of fighting with it. Preventive measures, such as wearing masks, keeping social distancing and washing hands, still play an important role in the fight against pandemic. Along with the progress of pandemic amount of research on the virus, antiviral therapy, immunomodulatory drugs and vaccines is increasing.

This survey presents problem of COVID-19 from different points of view. Complexity of SARS-CoV-2 virus contributes to its high contagiousness and allows rapid variability, which makes difficult to develop effective drugs and vaccines. COVID-19 is the multisystemic disease and its varied course - from asymptomatic to very severe - is a great challenge for clinicians. We describe the course of the disease not only in adults but also in pediatric patients - in the latter group COVID-related serious complications may arise after the end of the acute phase of the disease. The article also discusses current therapeutic approaches and vaccines available at the time of writing. Although, as we emphasized, a great progress has been made in this field, further multidisciplinary studies are still needed to understand the complex processes underlying the development of COVID-19. Their results will form the basis for the development of new strategies for the prevention and treatment of SARS-CoV-2 infection.

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