THE NOVEL CORONAVIRUS. ORIGINS, STRUCTURE, CHARACTERISTICS, PREVENTION

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Abstract

The appearance of the new coronavirus in January 2020 and its rapid spread took the medical world by surprise. The high degree of contagiousness, the severity of the symptoms and the lack of a specific treatment mobilized the medical staff in an unprecedented and superhuman collective effort. More than three months after the pandemic started, new things about COVID-19 disease are still being studied and discovered, and the most appropriate therapeutic protocols are still being sought. This article is intended to be a synthesis of the latest studies on the new coronavirus for a better understanding of the invisible enemy we are fighting during this period.

Keywords: **coronavirus, SARS-CoV-2, COVID-19**

CORONAVIRUSES

Coronaviruses represent the subfamily Orthocoronavirinae in the family Coronaviridae, order Nidovirales, realm Riboviria. The name „coronavirus" is derived from the Latin „corona", which means „crown". The name was coined by June Almeida and David Tyrrell who first observed and studied human coronaviruses, and refers to the characteristic appearance of virions by electron microscopy, which appear surrounded by a halo of the virus's surface proteins, the viral spikes peplomers. (1)(2)

Human coronaviruses were discovered in the 1960s. They were isolated using two different methods in the United Kingdom and the United States. The two strains isolated at that time, B814 and 229E, studied by electron microscopy proved to be related, both having the spikes arranged radially. (1)

Coronaviruses are encapsulated viruses that contain positive-sense, single-stranded RNA and have a helical symmetry nucleocapsid (3). The size of the coronavirus genome varies from about 26 to 32 kilobases, these being among the largest of RNA viruses (4). The large genome gave this family of viruses additional plasticity. Alpha-coronaviruses and beta-coronaviruses infect mammals, and gamma-coronaviruses and delta-coronaviruses mainly infect birds.

BRIEF HISTORY

In terms of evolution, the most recent common ancestor of coronaviruses is estimated to have existed since 8000 BC, although recent genomic research places the coexistence of the virus and its hosts, birds and bats, 55 million years ago. (5). Bats and birds, as warm-blooded flying vertebrates, are an ideal natural reservoir for coronaviruses (bats are the reservoir for alphacoronaviruses and betacoronaviruses, and birds are the reservoir for gammacoronaviruses and deltacoronaviruses). The large number and global range of bat and bird species that host the viruses have allowed the extensive evolution and dissemination of coronaviruses. (5).

There are currently six known species of coronaviruses that can cause infections in humans, one of which contains two subspecies. Four of these species have a seasonal circulation causing about 15% of the usual respiratory infections. (Table 1)

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Human coronaviruses that produce respiratory infections with mild symptoms
Human coronavirus OC43 (HCoV-OC43), β-CoV Human coronavirus HKU1 (HCoV-HKU1), β-CoV Human coronavirus 229E (HCoV-229E), α-CoV Human coronavirus NL63 (HCoV-NL63), α-CoV
Human coronaviruses that produce respiratory infections with severe symptoms
Middle East respiratory syndrome-related coronavirus (MERS-CoV), β-CoV Severe acute respiratory syndrome coronavirus (SARS-CoV), β-CoV Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), β-CoV

Table 1. Human coronaviruses

The viruses that cause severe respiratory infections have been identified recently (SARS-CoV in 2002, MERS-CoV in 2012, SARS-Cov2 in 2019), and have infection mortality rates ranging from 6.8% for SARS-CoV-2 to 37% for MERS. The most common symptoms are fever, irritative dry cough, dyspnea, dysphagia, gastrointestinal disorders (diarrhea). (Table 2)

	MERS-CoV	SARS-Cov	SARS2-CoV
Disease	MERS	SARS	COVID-19
Outbreaks	2012, 2015, 2018	2002-2004	2019-2020
Epidemiology			
Date of first identified case	June 2012	November 2002	December 2019
Location of first identified case	Jeddah, Saudi Arabia	Shunde, China	Wuhan, China
Sex ratio (M:F)	3,3:1	0,8:1	1,6:1
Confirmed cases	2.494	8.096	4.399.070
Deaths	858	774	296.092
Case fatality rate	37%	9,2%	6,7%
Symptoms			
Fever	98%	99-100%	87,9%
Dry cough	47%	29-75%	67,7%
Dyspnea	72%	40-42%	18,6%
Diarrhea	26%	20-25%	3,7%
Sore throat	21%	13-25%	13,9%

Table 2. Characteristics of human coronavirus strains
MERS-CoV, SARS-CoV, SARS-CoV-2 and related diseases (1)(6)(7)

SARS-CoV-2

Initially, the virus was presented in the media as „Wuhan Coronavirus" but starting with January 2020, at the recommendation of the WHO, the provisional term 2019-nCov was used, from „2019 novel coronavirus" (new coronavirus 2019). On February 11th 2020, the International Committee on Taxonomy of Viruses, based on existing rules establishing the hierarchical relationships between coronaviruses based on five conserved nucleic acid sequences, showed that the differences between 2019-nCoV and the SARS-CoV virus that caused the 2003 epidemic are insufficient to consider them different species of viruses. As a result, they identified 2019-nCoV as a strain of *Severe acute respiratory syndrome coronavirus* and thus 2019-nCoV received the official name of SARS-CoV-2. (8)

Research into the natural reservoir of the virus that caused the SARS epidemic in 2002-2004 has highlighted the existence of numerous SARS-like

strains in bats, most of them in the horseshoe nose bat species Rhinolophus. Phylogenetic analysis indicated 80% similarities between samples taken from *Rhinolophus sinicus* bats and SARS-CoV-2. Viruses collected in Yunnan Province from *Rhinolophus affinis* bats are 96% similar to SARS-CoV-2, and coronavirus from pangolin is 92% similar to SARS-CoV-2. (9)

A study conducted on February 7th 2020 in China identified that pangolin coronavirus strains are 99% similar to SARS-CoV-2. In this study, the coronavirus strain isolated from Malaysian pangolin showed 100%, 98.2%, 96.7% and 90.4% amino acid overlap with 2019-nCoV in the E, M, N and S genes, respectively. In particular, the receptor-binding domain of the S protein of the Pangolin-CoV is virtually identical to that of 2019-nCoV, with a difference of only one amino acid. The comparison of available genomes suggests that 2019-nCoV could have originated from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus (from bats). (10)

A phylogenetic analysis performed at the end of January 2020 on the 42 SARS-CoV-2 genomes sequenced up to that date showed that they were „very related, with at most seven mutations in relation to a common ancestor", which suggests that the first human infection occurred in November or December 2019. By May 7th 2020, 4690 SARS-CoV-2 genomes had been sequenced on six continents and are publicly available. (11)

VIRUS STRUCTURE

Each SARS-CoV-2 virion has a diameter of 50-200 nanometers. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as proteins S (spike), E (envelope), M (membrane) and N (nucleocapsid); protein N contains the RNA genome, and proteins S, E and M together create the viral envelope. The spike protein, which was visualized at atomic level using cryogenic electron microscopy, is the protein responsible for enabling the virus to attach and fuse with the membrane of a host cell. (12)

Protein modeling experiments on the virus spike protein have suggested that SARS-CoV-2 has an affinity for angiotensin 2 converting enzyme in human cells (ACE2), using this as a cellular entry mechanism. In January 2020, two groups of researchers from China and the United States demonstrated independently and experimentally that ACE2 can act as a receptor for SARS-CoV-2. Studies have shown that SARS-CoV-2 has a higher affinity for human ACE2 than the original SARS virus strain. SARS-CoV-2 can also use basigin to enter cells. (13) Basigin (or CD147) is a transmembrane glycoprotein involved in the development of tumors, erythrocyte invasion by plasmodium, and viral infection.

After a SARS-CoV-2 virion attaches to a target cell, the TMPRSS2 protease (transmembrane protease, serine 2) of the cell cuts open the virus's spike protein, exposing a fusion peptide and the host receptor ACE2. The virion then releases RNA into the cell and forces the cell to produce and dissseminate copies of the virus, which infect more cells. (13)

COVID-19

The disease caused by SARS-CoV-2 is called COVID-19 (Coronavirus disease 2019). The usual symptoms include fever, cough, loss of appetite, marked fatigue, dyspnea, myalgias, nausea, vomiting, diarrhea. Less common symptoms include chest pain, palpitations, anosmia and lack of taste. Studies in the literature show different percentages of these symptoms depending on the geographical area, the number of patients included in the study and the age of the subjects. According to the Centers for Disease Control and Prevention (CDC), the signs and symptoms at the onset of the disease vary, but during the course of the disease most patients develop the symptoms in Table 3. (14) Elderly people or those with multiple comorbidities may have a late onset of fever; in this sense, there were described cases when only 44% had a fever at the time of admission in the hospital but later, during hospitalization, 89% had a fever. (14)

Fever	83-99%
Cough	59-82%
Marked fatigue	44-70%
Loss of appetite	40-84%
Dyspnea	31-40%
Myalgia	11-35%

Table 3. COVID-19 symptoms

As is usually the case with infectious diseases, there is a delay between when a person is infected and

the onset of symptoms, an interval called the incubation period. The incubation period for COVID-19 is usually five to six days, but can range from two to fourteen days, although 97.5% of people who develop symptoms will do so within 11.5 days of infection. However, there is a part of the population does not develop symptoms at all after infection; these asymptomatic carriers, not matching with the case definition, are not tested and can transmit the disease to the community.

Among the severe complications of the disease we mention pneumonia, acute respiratory distress syndrome, multi-organic failure, septic shock and death. Cardiovascular complications include arrhythmias, myocarditis, heart failure and hypercoagulability with thrombosis / infarctions. The neurological manifestations that must be mentioned are represented by encephalitis, seizures, stroke and Guillain-Barré syndrome. In children, toxic-septic shock and symptoms similar to those of Kawasaki disease were observed.

The lung is the most affected organ in COVID-19 because the virus attaches and invades host cells through angiotensin converting enzyme 2 (ACE2), which is found in large amounts in the type II alveolar cells of the lungs. The spikes of the virus attach to ACE2 resulting in the fusion of the lipid membrane of the virus with the membrane of the host cell and thus the virus enters the cell. The density of ACE2 in each tissue correlates with the severity of the disease in the tissue. As alveolar disease progresses, respiratory failure may develop leading to exitus.

SARS-CoV-2 can also cause respiratory failure by affecting the respiratory centers in the brainstem, which is possible given that other coronaviruses have been detected in the central nervous system (CNS). Although the virus was detected in cerebrospinal fluid at autopsy, the exact mechanism by which it invades the CNS remains unclear and it is assumed that initially the virus would invade peripheral nerves and then the CNS, given the low levels of ACE2 in the brain (only in the vascular endothelium and in the vascular smooth muscle cells). (15) (16)

The virus also affects the gastrointestinal organs, as ACE2 is expressed in abundance in the glandular cells of the gastric, duodenal and rectal epithelium, as well as in the endothelial cells and the enterocytes of the small intestine.

The virus can cause acute myocardial damage and chronic damage to the cardiovascular system. Acute heart damage was found in 12% of infected people hospitalized in Wuhan, China, especially in those with severe forms of the disease. Rates of cardiovascular symptoms are high due to the systemic inflammatory response and immune system disorders during the course of the disease, but acute myocardial injury may also be related to ACE2 receptors in the heart. A high incidence of thrombosis (31%) and venous thromboembolism (25%) was found in ICU (Intensive Care Units) patients with COVID-19 infections, which may be related to a poor prognosis. Vascular endothelial dysfunction and blood clot formation (as suggested by high levels of D-dimers) are thought to play a significant role in mortality, blood clots leading to pulmonary emboli and cerebral ischemic events, complications leading to the death of patients infected with SARS-CoV-2. The infection appears to trigger a chain of vasoconstrictor responses in the body, with constriction of blood vessels in the pulmonary circulation further decreasing oxygen saturation in the context of viral pneumonia. (16)

Another common cause of death is kidney complications — SARS-CoV-2 directly infects kidney cells, as confirmed in post-mortem studies. Acute kidney damage is a common complication and cause of death; this is more significant in patients with already impaired renal function, especially in people with pre-existing chronic conditions such as high blood pressure and diabetes, which cause long-term nephropathy. (17) The risk of people on dialysis from contracting the virus is higher given the fact that they go to dialysis centers three times a week.

TRANSMISSION

COVID-19 is a disease that is transmitted by air, more easily than the influenza virus, through saliva droplets caused by coughing, sneezing or speech, which people who are a short distance from the source of infection can inhale.

Speaking out loud releases more droplets than normal speech. A study in Singapore found that sneezing can propel droplets up to 4.5 meters. Research from March 2020 claim that the current advice regarding the distance traveled by droplets, depending

on their size, is based on experiments from 1930 that did not take into account the effects of exhaled hot and humid air surrounding the droplets. Exhalation, sneezing and coughing do not only consist of mucosalivary droplets following short-range semi-ballistic emission trajectories, but consist primarily of a multiphase turbulent cloud (puff) that enters the surrounding air and captures and transports within it groups of droplets of different sizes. The humid and warm local atmosphere within the turbulent gas cloud allows the droplets contained to escape evaporation much longer than isolated droplets. Under these conditions, the lifespan of a droplet could be considerably extended by a factor of up to 1000, from a fraction of a second to minutes. Due to the advancing force of the cloud, the pathogen-carrying droplets are propelled much farther than if they were emitted in isolation, without being trapped inside a turbulent cloud. Given the various combinations between the physiological characteristics of patients and environmental conditions, such as humidity and temperature, the gas cloud and its pathogen content can travel 7-8 m with a maximum speed of 10-30 m / s. Large droplets settle on the surface of objects in about 3-6 seconds up to a maximum distance of 1.5 meters, while small droplets remain suspended in the air for a longer period, up to 3 hours. (18)

Direct contact with contaminated surfaces can infect a person if afterwards they take their unwashed / not-disinfected hand to their mouth, nose or eyes. The conjunctival mucosa is considered an entry gateway, so medical personnel who come into contact with infected people must also wear goggles or medical visors.

An analysis of existing studies on the persistence of coronaviruses on surfaces showed that SARS-CoV-2 survives on plastic surfaces for 72 hours, on stainless steel for 48 hours, on cardboard for 24 hours and on copper surfaces for only 4 hours. Studies on the persistence of other coronaviruses have shown different values, ranging from 3 to 9 days (see Table 4). Temperatures of 30-40 degrees Celsius reduce the persistence of the virus on surfaces. In contrast, temperatures of 4 degrees Celsius increased the persistence of the virus on surfaces to at least 28 days. (19)

Virus	Year of study	Material	Persistence
SARS-CoV-2	2020	Aerosols	3 hours
		Plastic	72 hours
		Stainless steel	48 hours
		Copper	4 hours
		Cardboard	24 hours
Other Coronaviruses	2020	Aerosols	3 hours
		Plastic	72 hours
		Copper	8 hours
		Cardboard	8 hours
	2020	Paper	5 minutes – 5 days
		Glass	5 days
		Plastic	2-9 days
		Silicon rubber, Latex	5 days
	2015	Ceramic	5 days
		Glass	5 days
		Brasses containing copper	<40 minutes
		Copper	120 minutes
		Zinc	60 minutes

Table 4. Persistence of coronaviruses on surfaces (19)

People are most contagious when they have symptoms (even if they are mild or nonspecific), but they can be infectious up to two days before the onset of symptoms (pre-symptomatic transmission). They remain contagious for about seven to twelve days in mild and moderate cases, and on average two weeks in severe cases.

In February 2020 in China it was estimated that an infected person could infect an average of another 2 – 2.5 people (R_0). The basic reproduction number R_0 in epidemiology is defined as the expected number of cases of disease directly generated by a positive case in a population in which all individuals are susceptible to infection. This definition refers to a population in which no other individual is infected or immunized. R_0 is not a constant for each pathogen, but is generated from a mathematical model that takes into account various modifiable factors. The interpretation of an R_0 value is always made taking into account the local

factors and the model used. For example in Germany the R_0 for SARS-CoV-2 in April was 0.9, and in May, after relaxing the restrictions (thus changing the conditions of the mathematical model used), it reached 1.1. (20) (21) The most important aspect of using R_0 is to evaluate if a new infectious disease has epidemic potential and to determine the proportion of the total number of citizens who need to be immunized against that disease in order to eradicate it. A subunitary R_0 value means that the disease will not be able to spread in the population, while a supraunitary value indicates a contagious nature of the disease. The higher the R_0 value, the harder it is to control the epidemic. A recent study analyzing cases of COVID-19 in China determined an average R_0 of 5.7 for the first months of 2020 (confidence interval 3.8-8.9). (22) (23) Table 5 shows the R_0 values for several infectious diseases.

Disease	R_0
Measles	12-18
Varicella (Chickenpox)	10-12
Mumps	10-12
COVID-19	3,8-8,9
SARS	3,1-4,2
Influenza (1918 pandemic strain)	1,4-2,8
Influenza	0,9-2,1
MERS	0,3-0,8

Table 5. Values of R_0 for various infectious diseases (23)

It is considered that of the total infected persons, 30% are asymptomatic, 55% develop moderate forms of the disease, 10% severe forms of the disease and 5% will have critical symptoms. The period in which these people are contagious depends on the form of the disease they develop. Asymptomatic people are contagious 14 days after contacting the virus. People who develop mild forms of the disease are contagious 21 days after contact with the virus, and people with severe or critical forms are contagious for 25 days. We must mention that in the case of these last three categories, the first 5 days of contagion are asymptomatic. (24)

PREVENTION

The main measures in the population that need to be taken to prevent infection with the new coronavirus are general measures that relate to personal hygiene and social distancing.

Hand washing is recommended to be performed as often as possible, with soap and water, for at least 20 seconds, including in the interdigital spaces and fingertips: after returning from shopping, after sneezing or coughing (although the WHO recommends people to cough in the elbow fold), after using the toilet, after blowing the nose, before meals. When soap and water are not available, alcohol-based disinfectant solutions are recommended, with alcohol concentration of at least 65-70%, that will be used according to the manufacturer's recommendations, generally 10ml for one minute.

Disinfection of surfaces, including mobile phones, keyboards, door handles, is performed with solutions containing 62-71% ethanol, 50-100% isopropanol, 0.1% sodium hypochlorite, 0.5% hydrogen peroxide. Chlorhexidine has not been shown to be effective in killing the virus. (25)

Although initially the WHO recommendations were that only people with symptoms of respiratory infection should wear protective face masks, probably also due to limited resources of protective materials, today more and more governments recommend the population to wear protective masks when leaving home, in some countries this being mandatory.

Social distancing is a measure of infection control that minimizes physical contact between individuals. This involves transport restrictions, the closure of schools, workplaces, restaurants, malls, theaters, stadiums, parks. People are advised to stay in their homes for as long as possible, to reduce the number of rides to the city and to reduce the interactions with other people. Measures such as limiting the number of people who can enter a store, the number of people who can attend a funeral, limiting the number of people who can form a group outdoors have been taken with the intention of limiting contact between people.

Recently, the term of „social distancing" has been renamed „physical distancing", as the goal is to reduce physical contact with others but to maintain social connections using means of distance communication such as text messages, voice and video calls, emails.

In Romania, all citizens of the country, including people at risk, i.e. patients with chronic diseases

and people over 65, benefited during this period from the possibility of remote medical consultations both from the family doctor and from the doctor from the specialized outpatient clinic, following the medical act the patient receiving directly by phone or email the electronic prescription necessary for the purchase of medicines, or the medical leave note in order to motivate absences from work.

The physical distancing measures resulted in a decrease in the spread of the virus in the population, the time thus gained being used by the authorities for the purchase of protective materials and for equipping hospitals with the necessary equipment and drugs in the treatment of the disease. The return to pre-existing social conditions must be gradual, with small steps, with regular reassessments of the situation. Any explosion in the number of cases will lead to a step backwards, to a tightening of restrictions.

In this regard, the WHO has developed a guide with recommendations for the gradual relaxation of the strict measures taken by the states of the world in the fight against the new coronavirus. WHO Europe highlights 4 key components for considering the elimination of large-scale restrictive measures: epidemiological and public health measures, the ability to manage a dual health system, understanding population behavior, economic and social implications. The 6 criteria that countries must take into account in order to manage the relaxation period are listed in Table 6. (26)

Countries need to take the issue very seriously and ensure that:
1. evidence shows COVID-19 transmission is controlled;
2. public health and health system capacities are in place to identify, isolate, test, trace contacts and quarantine them;
3. outbreak risks are minimized in high-vulnerability settings, particularly in homes for older people, mental health facilities and crowded places of residence;
4. workplace preventive measures are established, including physical distancing, handwashing facilities and protective masks;
5. importation risks can be managed; and
6. communities have a voice and are aware, engaged and participating in the transition

Table 6. WHO Europe criteria for easing restrictive measures (26)

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