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**Matric number**: 15/MHS06/062

**Course:** MLS 406 {viriology}

**Explain the etiology ,origin, structure and pathphysiology of COVID-19**

Etiology and origin of COVID-19 :

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the ongoing 2019–20 coronavirus pandemic. Common symptoms include fever, cough, and shortness of breath. Other symptoms may include muscle pain, sputum production, diarrhea, sore throat, loss of smell, and abdominal pain. While the majority of cases result in mild symptoms, some progress to viral pneumonia and multi-organ failure. As of 28 March 2020, the overall rate of deaths per number of diagnosed cases is 4.7 percent; ranging from 0.2 percent to 15 percent according to age group and other health problems. In comparison, the mortality rate of the 1918 flu pandemic was approximately 3% to 5%.

Human-to-human transmission of SARS-CoV-2 has been confirmed during the 2019–20 coronavirus pandemic.Transmission occurs primarily via respiratory droplets from coughs and sneezes within a range of about 2 metres (6.6 ft). Indirect contact via contaminated surfaces is another possible cause of infection. Preliminary research indicates that the virus may remain viable on plastic and steel for up to three days, but does not survive on cardboard for more than one day or on copper for more than four hours; the virus is inactivated by soap, which destabilizes its lipid bilayer. Viral RNA has also been found in stool samples from infected people.

Whether the virus is infectious during the incubation period is uncertain. On 1 February 2020, the World Health Organization (WHO) indicated that "transmission from asymptomatic cases is likely not a major driver of transmission". However, an epidemiological model of the beginning of the outbreak in China suggested that "pre-symptomatic shedding may be typical among documented infections" and that subclinical infections may have been the source of a majority of infections.

The virus is spread mainly through close contact and via respiratory droplets produced when people cough or sneeze. Respiratory droplets may be produced during breathing but the virus is not generally airborne.However, a recent study by the National Institute of Health and the New England Journal of Medicine indicates that the virus remains viable in aerosoles for up to 3 hours. For healthcare professionals caring for patients with confirmed Covid-19 infection or suspected Covid-19 infection, the CDC recommends placing the patient in a Airborne Infection Isolation Room (AIIR) in addition to using standard precautions, contact precautions, and airborne precautions. People may also contract COVID-19 by touching a contaminated surface and then their face. It is most contagious when people are symptomatic, although spread may be possible before symptoms appear. The virus can survive on surfaces up to 72 hours. Time from exposure to onset of symptoms is generally between two and fourteen days, with an average of five days. The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab.The infection can also be diagnosed from a combination of symptoms, risk factors and a chest CT scan showing features of pneumonia. The virus has been found in the faeces of as many as 53% of hospitalised people and more anal swab positives have been found than oral swab positives in the later stages of infection. The virus was found in faeces from one to twelve days, and seventeen percent of patients continued to present the virus in faeces after no longer presenting them in respiratory samples, indicating that the viral gastrointestinal infection and the potential fecal-oral transmission can last even after viral clearance in the respiratory tract. Reoccurrence of the virus has also been detected through anal swabs suggesting a shift from more oral positive during the early stages of the disease to more anal positive during later periods.

**Structure and Pathophsiology of Covid-19**

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. For addressing pathogenetic mechanisms of SARS-CoV-2, its viral structure, and genome must be considerations. In CoVs, the genomic structure is organized in a +ssRNA of approximately 30 kb in length — the largest known RNA viruses — and with a 5′-cap structure and 3′-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized. The transcription works through the replication-transcription complex (RCT) organized in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Of note, transcription termination occurs at transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as templates for the production of subgenomic mRNAs. In the atypical CoV genome, at least six ORFs can be present. Among these, a frameshift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps). Apart from ORF1a and ORF1b, other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins. And accessory protein chains. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs.

Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, research underlined that nsp is able to block the host innate immune response.[[7]](https://www.ncbi.nlm.nih.gov/books/NBK554776/) Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described.

Among the structural elements of CoVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors.[[8]](https://www.ncbi.nlm.nih.gov/books/NBK554776/) Of note, in SARS-CoV-2, the S2 subunit — containing a fusion peptide, a transmembrane domain, and cytoplasmic domain — is highly conserved. Thus, it could be a target for antiviral (anti-S2) compounds. On the contrary, the spike receptor-binding domain presents only a 40% amino acid identity with other SARS-CoVs. Other structural elements on which research must necessarily focus are the ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally different from those of SARS-CoV.

In international gene banks such as GenBank, researchers have published several Sars-CoV-2 gene sequences. This gene mapping is of fundamental importance allowing researchers to trace the phylogenetic tree of the virus and, above all, the recognition of strains that differ according to the mutations. According to recent research, a spike mutation, which probably occurred in late November 2019, triggered jumping to humans. In particular, Angeletti et al. compared the Sars-Cov-2 gene sequence with that of Sars-CoV. They analyzed the transmembrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3 and found that position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine.[[9]](https://www.ncbi.nlm.nih.gov/books/NBK554776/) The matter of viral mutations is key for explaining potential disease relapses.

Research will be needed to determine the structural characteristics of SARS-COV-2 that underlie the pathogenetic mechanisms. Compared to SARS, for example, initial clinical data show less extra respiratory involvement, although due to the lack of extensive data, it is not possible to draw definitive clinical information.

The pathogenic mechanism that produces pneumonia seems to be particularly complex. Clinical and preclinical research will have to explain many aspects that underlie the particular clinical presentations of the disease. The data so far available seem to indicate that the viral infection is capable of producing an excessive immune reaction in the host. In some cases, a reaction takes place which as a whole is labeled a 'cytokine storm'. The effect is extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. It also stimulates the production of acute phase proteins and plays an important role in thermoregulation, in bone maintenance and in the functionality of the central nervous system. Although the main role played by IL-6 is pro-inflammatory, it can also have anti-inflammatory effects. In turn, IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer. It is also implicated into the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.

**STRUCTURE**

The structure of COVID-19 (SARS-CoV-2) consists of the following: a spike protein (S), hemagglutinin-esterease dimer (HE),  a membrane glycoprotein (M), an envelope protein (E) a nucleoclapid protein (N) and RNA as seen in the figure below.

**Spike protein (S)** is heavily glycosylated, utilizes an N-terminal signal sequence to gain access to the ER and mediate attachment to host receptors. It is the largest structure and makes the distinct spikes on the surface of the virus. For most coronaviruses, S protein is cleaved by a host cell furin-like protease into two separate polypeptides S1 and S2; **RNA** is the genome of the virus.

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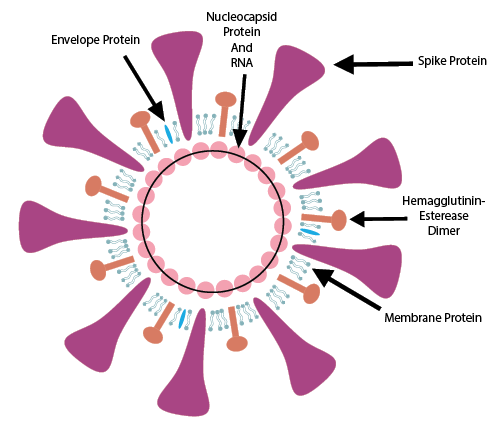
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**Nucleocapsid protein (N)** binds to RNA in vitro and is heavily phosphorylated. N proteins binds the viral genome in a beads on a string type conformation. This protein likely helps tether the viral genome to replicase-transcriptase complex (RTC), and subsequently package the encapsulated genome into viral particles.

**Envelope protein (E)** is found in small quantities in within the virus. It is most likely a transmembrane protein and with ion channel activity. The protein facilitates assembly and release of the virus and has other functions such as ion channel activity. It is not necessary for viral replication but it is for pathogenesis.

**Membrane protein (M)** is the most abundant structural protein. It does not contain signal sequence and exists as a dimer in the virion. It may have two different conformations to enable it to promote membrane curvature as well as bind to nucleocapsid.

**Hemagglutinin-esterase dimer protein (HE)** is present in a subset of betacoronaviruses. The protein binds sialic acids on surface glycoproteins. The protein activities are thought to enhance S protein-mediated cell entry and virus spread through the mucosa.



*Fig. 1 – The structure of the C19 Virus.*