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**OPEN TEST**

**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.

The best way to prevent and slow down transmission is be well informed about the COVID-19 virus, the disease it causes and how it spreads. Protect yourself and others from infection by washing your hands or using an alcohol based rub frequently and not touching your face.

The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it’s important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow).(in reference to WHO.init)

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 Pathophysiology of Covid-19**

Coronavirus virions are spherical to pleomorphic enveloped particles (Fig. 60-3). The envelope is studded with projecting glycoproteins, and surrounds a core consisting of matrix protein enclosed within which is a single strand of positive-sense RNA (Mr 6 × 106) associated with nucleoprotein. The envelope glycoproteins are responsible for attachment to the host cell and also carry the main antigenic epitopes, particularly the epitopes recognized by neutralizing antibodies. OC43 also possesses a haemagglutin. (Courtesy S.Sikotra, Leicester Royal Infirmary, Leicester, England.)

In addition to the SARS coronavirus (treated separately elsewhere in this volume), the complete genome sequences of six species in the coronavirus genus of the coronavirus family [avian infectious bronchitis virus-Beaudette strain (IBV-Beaudette), bovine coronavirus-ENT strain (BCoV-ENT), human coronavirus-229E strain (HCoV-229E), murine hepatitis virus-A59 strain (MHV-A59), porcine transmissible gastroenteritis-Purdue 115 strain (TGEV-Purdue 115), and porcine epidemic diarrhea virus-CV777 strain (PEDV-CV777)] have now been reported. Their lengths range from 27,317 nt for HCoV-229E to 31,357 nt for the murine hepatitis virus-A59, establishing the coronavirus genome as the largest known among RNA viruses. The basic organization of the coronavirus genome is shared with other members of the Nidovirus order (the torovirus genus, also in the family Coronaviridae, and members of the family Arteriviridae) in that the nonstructural proteins involved in proteolytic processing, genome replication, and subgenomic mRNA synthesis (transcription) (an estimated 14–16 end products for coronaviruses) are encoded within the 5′-proximal two-thirds of the genome on gene 1 and the (mostly) structural proteins are encoded within the 3′-proximal one-third of the genome (8–9 genes for coronaviruses). Genes for the major structural proteins in all coronaviruses occur in the 5′ to 3′ order as S, E, M, and N. The precise strategy used by coronaviruses for genome replication is not yet known, but many features have been established. This chapter focuses on some of the known features and presents some current questions regarding genome replication strategy, the cis-acting elements necessary for genome replication [as inferred from defective interfering (DI) RNA molecules], the minimum sequence requirements for autonomous replication of an RNA replicon, and the importance of gene order in genome replication. (Adami C, Pooley J, Glomb J, Stecker E, Fazal F, Fleming JO, Baker SC (1995) Evolution of mouse hepatitis virus (MHV) during chronic infection: quasi-species nature of the persisting MHV RNA. Virology 209:337–346 CrossRefPubMedGoogle Scholar).

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[.[1]](https://www.ncbi.nlm.nih.gov/books/NBK554776/) and accessory proteic chains. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs.

**PATHOPHYSIOLOGY**

Coronaviruses infect many species of animals including humans, causing acute and chronic diseases. This review focuses primarily on the pathogenesis of murine coronavirus mouse hepatitis virus (MHV) and severe acute respiratory coronavirus (SARS-CoV). MHV is a collection of strains, which provide models systems for the study of viral tropism and pathogenesis in several organs systems, including the central nervous system, the liver, and the lung, and has been cited as providing one of the few animal models for the study of chronic demyelinating diseases such as multiple sclerosis. SARS-CoV emerged in the human population in China in 2002, causing a worldwide epidemic with severe morbidity and high mortality rates, particularly in older individuals. We review the pathogenesis of both viruses and the several reverse genetics systems that made much of these studies possible. We also review the functions of coronavirus proteins, structural, enzymatic, and accessory, with an emphasis on roles in pathogenesis. Structural proteins in addition to their roles in virion structure and morphogenesis also contribute significantly to viral spread in vivo and in antagonizing host cell responses. Nonstructural proteins include the small accessory proteins that are not at all conserved between MHV and SARS-CoV and the 16 conserved proteins encoded in the replicase locus, many of which have enzymatic activities in RNA metabolism or protein processing in addition to functions in antagonizing host response.

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. 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. 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**[[iii]](https://www.prosci-inc.com/covid-19/" \l "_edn3" \o ")** 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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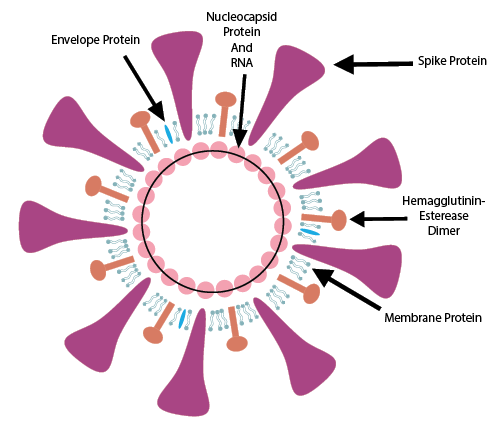
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**Nucleocapsid protein (N)** binds to RNA in vitro and is heavily phosphorylated. N proteins binds the viral genome in a beads on a string type conformation. This protein likely helps tether the viral genome to replicase-transcriptase complex (RTC), 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.*