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A Short Review on COVID-19

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Abstract **Review Article**

Coronavirus disease 2019 (COVID-19) has made a global impact on the daily lives of humanity, devastating health systems and ultimately affecting the world's economy. The coronavirus disease 2019 (COVID-19) is a highly contagious respiratory disease caused by the SARS-CoV-2 virus. SARS-CoV-2 is thought to spread from person to person through droplets released when an infected person coughs, sneezes, or talks. It may also be spread by touching a surface with the virus on it and then touching one's mouth, nose, or eyes, but this is less common. There are four trusted source subtypes of coronavirus - alpha, beta, gamma, and delta and scientists use these classifications to categorize the various species. Among all the corona viruses, seven have affected humans. Four of these are common and cause mild illnesses in the upper and lower airways, nose, sinuses, throat, and lungs. The remaining three can cause more severe illness. This article provides a comprehensive review of this subject with a focus on the history, clinical manifestations, and complications including new insights into the pathophysiology, diagnosis, Management stategies and treatment.

Keywords: COVID-19, Complications, Pathophysiology, diagnosis, treatment.

HISTORY: - [1]

The history of human coronaviruses began in 1965 when Tyrrell and Bynoe found that they could passage virus named B814. It was found in human embryonic tracheal organ cultures obtained from the respiratory tract of an adult with a common cold. The presence of an infectious agent was demonstrated by inoculating the medium from these cultures intranasally in human volunteers; colds were produced in a significant proportion of subjects, but Tyrrell and Bynoe were unable to grow the agent in tissue culture at that time. At about the same time, Hamre and Procknow were able to grow a virus with unusual properties in tissue culture from samples obtained from medical students with colds. Both B814 and Hamre's virus, which she called 229E, were ether sensitive and therefore presumably required a lipid- containing coat for infectivity, but these 2 viruses were not related to any known myxo- or paramyxoviruses. While working in the laboratory of Robert Chanock at the National Institutes of Health, McIntosh *et al.,* reported the recovery of multiple strains of ether-sensitive agents from the human respiratory tract by using a technique similar to that of Tyrrell and Bynoe. These viruses were termed "OC" to designate that they were grown in organ cultures. Within the same time frame, Almeida and Tyrrell performed electron microscopy on fluids from organ cultures infected with B814 and found particles that resembled the infectious bronchitis virus of chickens. The particles were medium sized (80 –150 nm), pleomorphic, membrane-coated, and covered with widely spaced club-shaped surface projections. The 229E agent identified by Hamre and Procknow and the previous OC viruses identified by McIntosh *et al.,* had a similar morphology in the late 1960s; Tyrrell was leading a group of virologists working with the human strains and a number of animal viruses. These included infectious bronchitis virus, mouse hepatitis virus and transmissible gastroenteritis virus of swine, all of which had been demonstrated to be morphologically the same as seen through electron microscopy. This new group of viruses was named coronavirus (corona denoting the crown-like appearance of the surface projections) and was later officially accepted as a new genus of viruses. Ongoing research using serologic techniques has resulted in a considerable amount of information regarding the epidemiology of the human respiratory coronaviruses. It was found that in temperate climates, respiratory coronavirus infections occur more often in the winter and spring than in the summer and fall. Data revealed that coronavirus infections contribute as much as 35% of the total respiratory viral activity during epidemics. Overall, his proportion of adult colds produced by

coronaviruses was estimated at 15%. In the 3 decades after discovery, human strains OC43 and 229E were studied exclusively, largely because they were the easiest ones to work with. OC43, adapted to growth in suckling mouse brain and subsequently to tissue culture, was found to be closely related to mouse hepatitis virus. Strain 229E was grown in tissue culture directly from clinical samples. The 2 viruses demonstrated periodicity, with large epidemics occurring at 2- to 3-year intervals. Strain 229E tended to be epidemic throughout the United States, whereas strain OC43 was more predisposed to localized outbreaks. As with many other respiratory viruses, reinfection was common. Infection could occur at any age, but it was most common in children.

CLASS: - Contagious respiratory disease.

DEFINITION: - [2]

A highly contagious respiratory disease caused by the SARS-CoV-2 virus. SARS-CoV-2 is thought to spread from person to person through droplets released when an infected person coughs, sneezes, or talks. It may also be spread by touching a surface with the virus on it and then touching one's mouth, nose, or eyes, but this is less common.

TYPES OF CORONA VIRUS: - [3]

There are four Trusted Source subtypes of coronavirus — alpha, beta, gamma, and delta and scientists use these classifications to categorize the various species. Among all the coronaviruses, seven have affected humans. Four of these are common and cause mild illnesses in the upper and lower airways, nose, sinuses, throat, and lungs. The remaining three can cause more severe illness. They are:

- **Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV):** Which led to the SARS epidemic in 2002–2003. This virus causes severe acute respiratory syndrome, or SARS. The first cases of this disease in humans occurred in the Guangdong province of China in 2002 trusted Source. In total, SARS spread across 26 countries, causing an epidemic with more than 8,000 cases. Since 2004, there have been no recorded cases of SARS in humans.
- **Middle East Respiratory Syndrome Coronavirus (MERS-CoV):** Which caused an outbreak of MERS that began in 2012. This corona virus causes Middle East respiratory syndrome, or MERS. The first cases occurred in Saudi Arabia in 2012Trusted Source. Approximately 3 or 4 of every 10 people trusted Source with confirmed MERS dies of the disease. A 2019 report from the World Health Organization (WHO) suggests that MERS-CoV may spread through contact with animals, particularly camels. Human-to-human transmission is also possible during close contact with people who are sick. Healthcare workers, for example, may be particularly vulnerable.
- **SARS-CoV-2:** SARS-CoV-2 is the virus that causes COVID-19. The first cases of COVID-19 were identified in the city of Wuhan, China; in 2019.The illness can cause mild to severe symptoms. People with underlying mel conditions and older adults are most at risk of severe COVID-19. SARS-CoV-2, the virus responsible for the COVID-19 pandemic. These four coronaviruses typically trusted Source cause mild respiratory illnesses, such as the common cold, in humans. They are-
  - **229E**
  - **NL63**
  - **OC43**
  - **HKU1**

These viruses are common worldwide and account for around 15–30%Trusted Source of all common colds. They rarely spread to the lower respiratory tract.

STRUCTURES: - [4-7]

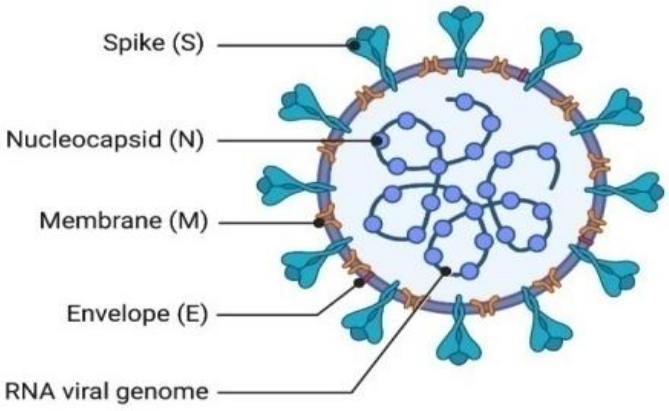

Figure 1: Coronavirus Structure

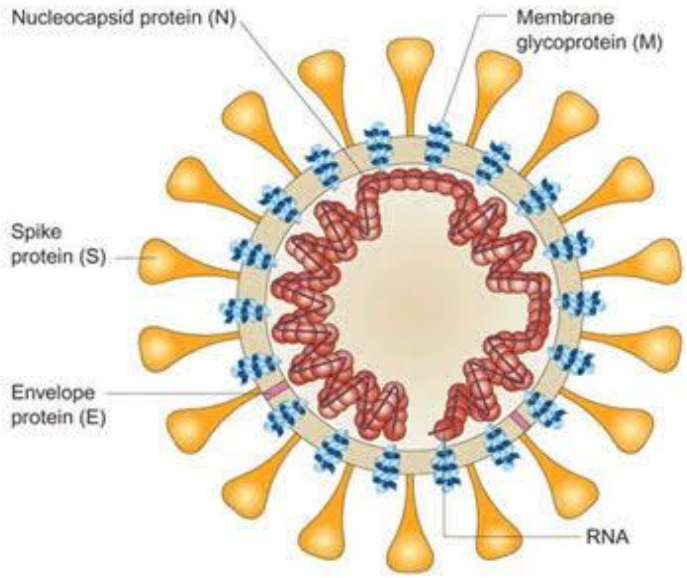

Figure 2: The Crown shaped Coronavirus

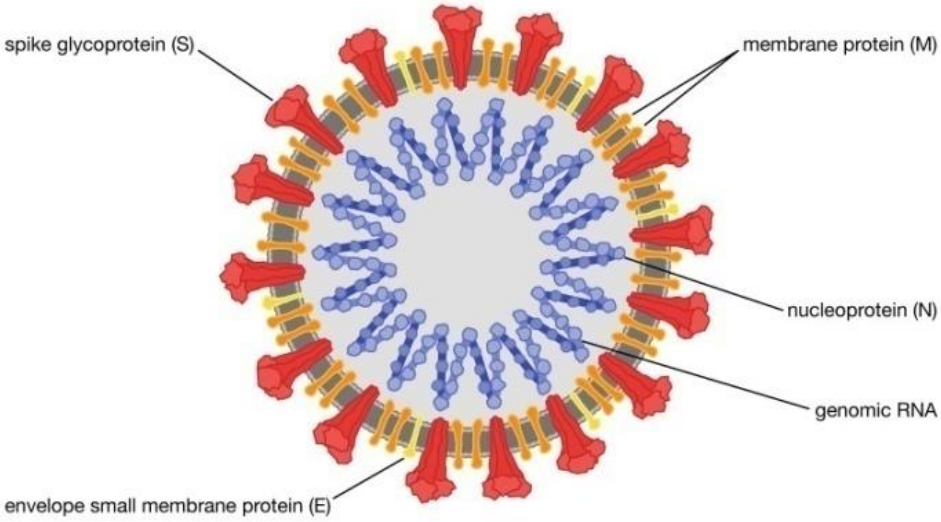

Figure 3: Severe acute respiratory-syndrome coronavirus 2 (SARS-CoV-2)

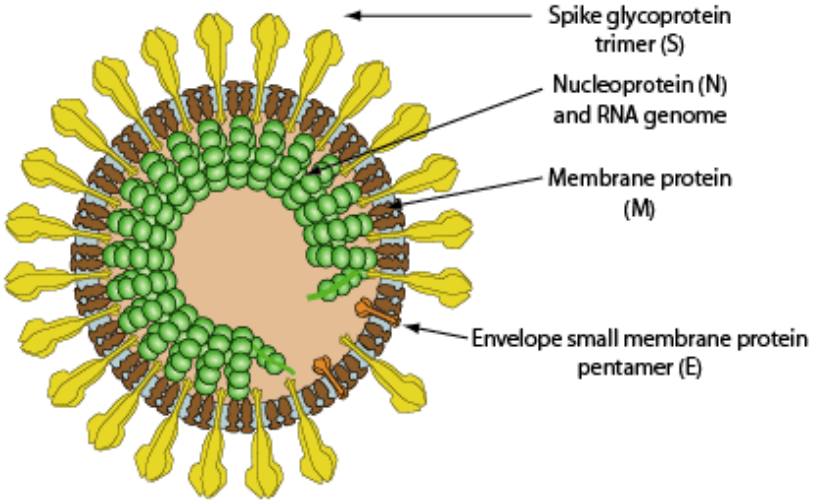

Figure 4: SARS-COV/SARS-COV-2

ETIOLOGY: - [8]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown beta corona virus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019. Corona viruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS], and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS.SARS-CoV-2 belongs to the Sarbecovirus subgenus of the Coronaviridae family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV. Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electrons microscopically. Centers for Disease Control and prevention Citatioends A majority of patients in the initial stages of this outbreak reported a link to the Huanan South China Seafood Market, a live animal or "wet" market, suggesting a zoonotic origin of the virus. An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 January 2020 were linked to the market, whereas only 8.6% of cases after this date were linked to the market. This suggests that person-to-person spread was occurring among close contacts since the middle of December 2019. More recent studies suggest that the virus may have emerged earlier than previously thought in other countries. A zoonotic origin has still not been confirmed. Some studies suggest that SARS-CoV-2 may be a recombinant virus between a bat coronavirus and an origin- unknown coronavirus, with pangolins and minks suggested as possible intermediate hosts. However, there is currently no evidence to demonstrate the possible route of transmission from a bat reservoir to human through one or several intermediary animal species. Further research is required to determine the origin of SARS-CoV-2.

MODE OF TRANSMISSION:

TYPES OF TRANSMISSION: - 3 Types

1. **Symptomatic Transmission:** Transmission mainly occurs via respiratory droplets or aerosols during close contact with an infected symptomatic case. Transmissibility depends on the amount of viable virus being shed and expelled by a person, the type of contact, the setting, and what infection prevention and control measures are in place.
2. **Pre-symptomatic Transmission:** Transmission may occur during the incubation period before symptom onset while there is evidence of transmission from Pre-symptomatic people, there is limited evidence on how frequently this is likely to occur and estimated transmission rates are highly variable. Only 7% of people exposed to a Pre-symptomatic index case became infected in one systematic review. People without symptoms may be Pre-symptomatic, or they may remain persistently asymptomatic.
3. **Asymptomatic Transmission:** Transmission from asymptomatic cases (laboratory-confirmed cases who never develop symptoms) has been reported; however, most of the evidence is based on early data from China and has limitations (e.g., small number of cases, cases may have been Pre-symptomatic). Numerous studies have reported no evidence of asymptomatic transmission from carriers of SARS-CoV-2, including a large study in nearly 10 million residents in Wuhan. Only 1% of people exposed to an asymptomatic index case became infected in one systematic review, suggesting limited infectiousness. Estimating the prevalence of asymptomatic cases in the population is difficult. One living systematic review and meta-analysis found that the interquartile range for the proportion of persistently asymptomatic cases was 14% to 50% across studies; however, heterogeneity was high so the study did not estimate a mean proportion of overall asymptomatic infections. A meta-analysis of over 130,000 people found that 21.7% remained asymptomatic throughout the course of the infection (after excluding Pre-symptomatic cases). Subgroup analysis showed that the overall rate of asymptomatic infections was higher in pregnant women (48.8%) and children (32.1%). African studies reported the highest asymptomatic infection rate, while Asian studies reported the lowest. The pooled percentage of asymptomatic infections has been estimated to be 25.5% to 32.4% among patients infected with the Omicron variant. Healthcare workers may play a role in asymptomatic transmission. About 7.6% of healthcare workers who worked in hospital units with infected patients tested positive for SARS-CoV-2 antibodies; however, only 58% of these workers reported prior symptoms. Although there is some evidence that older children have higher rates of asymptomatic disease than infants <1 year of age, the majority of children present with symptomatic disease and do not appear to be silent spreaders of infection.

ROUTES OF TRANSMISSION:-

- **Respiratory transmission is the dominant mode of transmission**, with proximity and ventilation being the key determinants of transmission risk. Available evidence suggests that transmission

between people occurs primarily when an infected person is in close contact with another person. The virus can spread from an infected person's mouth or nose in small liquid particles (ranging in size from larger droplets to smaller aerosols) when the person coughs, sneezes, sings, breathes heavily, or talks.

- **Close-range contact** can result in inhalation of, or inoculation with, the virus through the mouth, nose, or eyes.
- **Aerosol transmission** can occur in healthcare settings during aerosol-generating procedures. There are also some outbreak reports that suggest aerosol transmission is possible in the community under certain conditions; however, these reports relate to enclosed indoor crowded spaces with poor ventilation where the infected person may have been breathing heavily (e.g., restaurants, choir practice, fitness classes). A detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports. While the air close to, and distant from, patients has been found to frequently be contaminated with SARS-CoV-2 RNA, few of these samples contained viable virus. The risk of transmission is much lower outdoors compared with indoors, with a limited number of studies estimating a transmission rate of <1%. Evidence that nebulizer treatments increase the risk of transmission of coronaviruses similar to SARS-CoV-2 is inconclusive, and there is minimal direct evidence about the risk for transmission of SARS-CoV-2.
- **Fomite transmission (from direct contact with fomites)** may be possible, but there is currently no conclusive evidence for this mode of transmission. In the few cases where fomite transmission has been presumed, respiratory transmission has not been completely excluded. While the majority of studies report identification of the virus on inanimate surfaces, there is a lack of evidence to demonstrate recovery of viable virus. Replication-competent virus is more likely to be identified when polymerase chain reaction cycle threshold for clinical specimens from infected individuals is <30 (i.e., high viral load).
- **Fecal-oral transmission (or respiratory transmission through aerosolized feces)** may be possible, but there is only limited circumstantial evidence to support this mode of transmission.
- **Transmission via other body fluids (including sexual transmission or blood borne transmission)** has not been reported. While the virus has been detected in body fluids (e.g., semen, urine, cerebrospinal fluid, ocular fluids), the presence of virus or viral components does not equate with infectivity. There are limited data about the transmission risk from organ donors. However, there appears to be a low risk of transmission with non-lung (i.e., kidney, liver, heart) organs from SARS-CoV-2-positive donors, irrespective of whether the donor is symptomatic at the time of procurement.
- **Perinatal (vertical) transmission** occurs rarely and transplacental transmission has been documented. There is limited evidence on the extent of vertical transmission and its timing. Further high-quality studies are required to establish whether perinatal transmission occurs. Viral fragments have been detected in breast milk; however, this finding is uncommon and, when it occurs, has been associated with mild symptoms in infants.
- **Nosocomial transmission** was reported in 44% of patients in one systematic review; however, this review was limited to case series conducted early in the outbreak in Wuhan before the institution of appropriate infection prevention and control measures. Hospital-acquired infections accounted for approximately 11.3% of infections in the UK between February and August 2020. This peaked at 15.8% in the middle of May. Rates as high as 25% were reported in some areas in October 2020. Rates were notably higher in residential community care hospitals (61.9%) and mental health hospitals (67.5%) compared with acute and general care hospitals (9.7%). Studies of healthcare workers exposed to index cases (not in the presence of aerosol-generating procedures) found little to no nosocomial transmission when contact and droplet precautions were used. The risk to healthcare workers performing or assisting with a tracheostomy appears to be low. Transmission dynamics in relation to symptoms Transmission is more likely if contacts are exposed shortly before or after symptom onset in the index patient. The risk of transmission to close contacts was higher if exposure occurred between -2 and 3 days from symptom onset in the index patient in one study. Among contacts that became infected, asymptomatic infection was more common if they were exposed to an asymptomatic index patient, suggesting that disease severity in the index patient may be associated with the clinical presentation of disease. The median duration of infectiousness in patients with mild disease in a real-world community setting (pre-Omicron variant) was approximately 5 days (range 3 to 7 days) in one study. Symptom onset was a median of 3 days before peak viral RNA and infectious viral load. Less than 25% of cases shed infectious virus before symptom onset. Two-thirds of cases were still infectious 5 days after symptom onset, and one third were still infectious at 7 days. Onward transmission varies according to specific host and contact factors, and the nature of the exposure.

FACTORS ASSOCIATED WITH INCREASED TRANSMISSION INCLUDE:

- **Environmental Factors:** Indoors, poor ventilation, crowding, close proximity, shared

facilities, cold ambient temperature, low humidity.

- **Host Factors:** Recently infected, high viral load, severe disease, age, presence of comorbidities, immuno-compromised.
- **Behavioral Factors:** Singing/shouting, coughing/sneezing, hugging/kissing, masks etiquette, hand hygiene, duration of contact.
- **Viral Factors:** Changes in the viral genome linked to increased transmissibility.

RISK FACTORS: - [9]

According to the U.S. Centers for Disease Control and Prevention (CDC), as of November 2021, more than 75% of deaths in the U.S. from COVID-19 have been among people age 65 and older. And people in this age group comprise over 42% of those who end up in the hospital due to COVID-19. Here are some reasons why:

- Older adults are more likely to have long-term health problems that can put them at increased risk for severe effects from COVID-19.
- People's immune systems tend to weaken with age, making it more difficult to fight off infections.
- Lung tissue becomes less elastic over time, so respiratory diseases like COVID-19 are particular concerns for older people.
- Inflammation in older people can be more intense, causing organ damage.
- Lung Disease and COVID-19, Regardless of a person's age, some airway and lung diseases can set the stage for a more severe coronavirus infection because of scarring, inflammation or lung damage.

These Include: Chronic obstructive pulmonary disease (COPD), such as Emphysema:

- ✓ Pulmonary Fibrosis.
- ✓ Pulmonary Embolism.
- ✓ Pulmonary Hypertension.
- ✓ Interstitial Lung Disease.
- ✓ Broncho Pulmonary Dysplasia.
- ✓ Heart Disease.

- **Although COVID-19 most often affects the airway and lungs, the heart works to drive oxygen to the body's tissues.** When the lungs are overtaxed due to illness, the heart has to work harder, which creates challenges for people who are already living with conditions such as heart failure, coronary artery disease or cardiomyopathies.
- **The American Heart Association notes** that **viral illnesses** similar to COVID-19 can raise the risk of a heart attack for people with a buildup of plaque in their blood vessels.
- **Research shows that** viral illness can make it more likely for a piece of the plaque lining the vessels to break off and block blood flow to the heart.
- **Cancer, Cancer Treatment and COVID-19 Risk:** People of any age who are currently being treated for cancer or who recently had it are vulnerable to severe COVID-19 if they catch the coronavirus. This is especially true of those with blood cancers such as leukemia.

Cancer treatment, such as chemotherapy or stem cell or bone marrow transplant, can weaken your immune system and make it easier to become infected with contagious diseases such as COVID-19.Talk to your oncologist about when you should be vaccinated for COVID-19 and if you need to receive an additional dose if you are undergoing any of these therapies, since treatments that suppress your immune system may affect how well the vaccines protect you.

- **Pregnancy and COVID-19:** Women who are pregnant and women who recently gave birth who contract COVID- 19 are at higher risk of severe illness, complications and death. COVID-19 may also have negative effects on pregnancy, and it has been linked to higher risk of premature birth and stillbirth. Underlying medical conditions such as heart disease and lung disease can further increase the risk for the mother and the baby. Pregnancy can also trigger changes to the immune system that can make you more vulnerable to respiratory viruses.COVID-19 vaccines are safe, effective and strongly recommended for women who are pregnant.
- **Diabetes as a Risk Factor for COVID-19:** People who have diabetes are at increased risk of getting very sick from the coronavirus that causes COVID-19. Type 1 and type 2 diabetes both cause an increase in blood sugar. Poorly controlled blood sugar can make viral diseases, including COVID-19, more dangerous, possibly because higher blood sugar can create an environment where viruses are likely to thrive. Also, diabetes increases inflammation and weakens the immune system, making it harder for people with the condition to fight off disease in general. People with diabetes should adhere to their medication regimens and do everything possible to keep their blood sugar under control. Having an adequate supply of medications and staying in close touch with your doctor can add to your peace of mind. Also, get vaccinated for COVID-19 and take measures to protect yourself from infection.
- **COVID-19 and People with a Weakened Immune System (Immuno-compromised):** Several diseases and medical treatments can weaken your immune system and put you at risk for coronavirus infection and more serious COVID-19. These include some inherited (genetic) conditions, untreated HIV, long-term steroid use, solid organ or blood stem cell transplants, and some forms of cancer and cancer treatment. Talk to your doctor about your COVID-19 vaccine if you have a weakened immune system. You may benefit from

an additional dose of COVID-19 vaccine to ensure you are protected as much as possible.

- **Mental Health Conditions and Risk of Severe COVID-19:** Researchers have discovered a link between some mental health conditions and increased risk of COVID-19 hospitalization and death. These conditions include mood disorders such as depression and anxiety, as well as schizophrenia and related illnesses and substance use disorders. Experts are still working to understand why and how these conditions increase the risk of severe COVID-19. In the meantime, if you have any of these issues, getting vaccinated can help lower your risk of sever COVID-19.
- **Neurologic Problems and COVID-19: Dementia, Alzheimer's disease and other cognitive and developmental problems** can increase the risk of having a severe case of COVID-19, especially among people living in group care settings. Get vaccinated and take measures to protect yourself from infection.
- **Liver and Kidney Disease and COVID-19:** People with certain chronic liver and kidney conditions may be more likely to experience severe COVID-19. This includes people with hepatitis B or C, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver cirrhosis and chronic kidney disease. Treatments for cancers of the kidneys or liver, such as chemotherapy, can also weaken the immune system and increase your risk of infection.

PATHOPHYSIOLOGY: - [10]

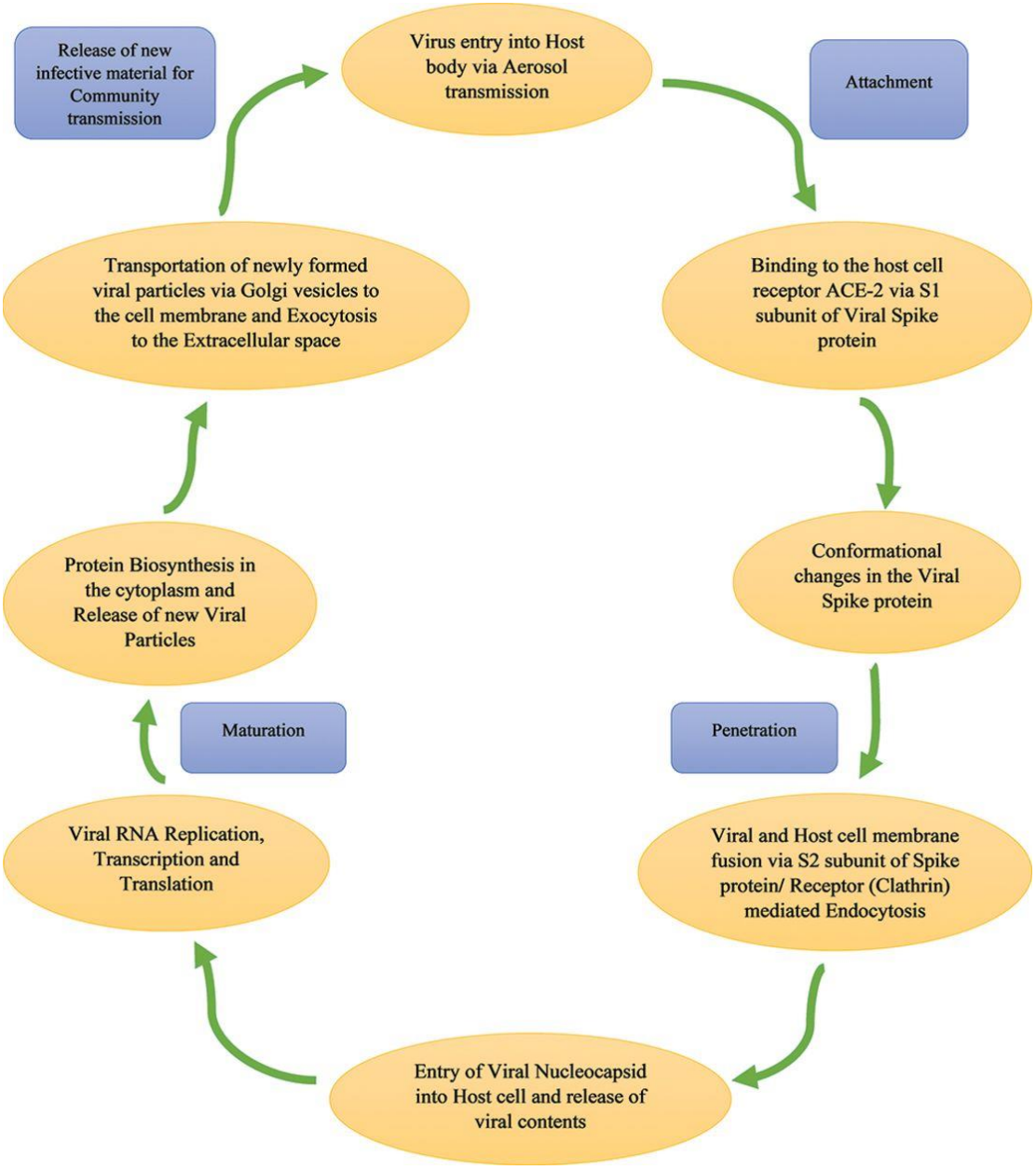

Figure 5: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Viral Life Cycle and Host Cell Invasion

The virus is transmitted via respiratory droplets and aerosols from person to person. Once inside the body, the virus binds to host receptors and enters host cells through endocytosis or membrane fusion. The corona viruses are made up of four structural proteins, namely, the spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins. The S protein is seen to be protruding from the viral surface and is the most important one for host attachment and penetration. This protein is composed of two functional subunits (S1 and S2), among which S1 is responsible for binding to the host cell receptor and S2 subunit plays a role in the fusion of viral and host cellular membranes.ACE-2 has been identified as a functional receptor for SARS-CoV and is highly expressed on the pulmonary epithelial cells.10 It is through this host receptor that the S protein binds initially to start the host cell invasion by the virus. After binding of SARS-CoV-2 to the ACE-2, the S protein undergoes activation via a two-step protease cleavage: the first one for priming at the S1/S2 cleavage site and the second cleavage for activation at a position adjacent to a fusion peptide within the S2 subunit. The initial cleavage stabilises the S2 subunit at the attachment site and the subsequent cleavage presumably activates the S protein causing conformational changes leading to viral and host cell membrane fusion. Post membrane fusion, the virus enters the pulmonary alveolar epithelial cells and the viral contents are released inside. Now inside the host cell, the virus undergoes replication and formation of a negative strand RNA by the pre-existing single-strand positive RNA through RNA polymerase activity (transcription). This newly formed negative strand RNA serves to produce new strands of positive RNAs which then go on to synthesis new proteins in the cell cytoplasm (translation). The viral N protein binds the new genomic RNA and the M protein facilitates integration to the cellular endoplasmic reticulum. These newly formed Nucleocapsids are then enclosed in the ER membrane and transported to the lumen, from where they are transported via golgi vesicles to the cell membrane and then via exocytosis to the extracellular space. The new viral particles are now ready to invade the adjacent epithelial cells as well as for providing fresh infective material for community transmission via respiratory droplets.

Asymptomatic Phase

The SARS-CoV-2 which is received via respiratory aerosols binds to the nasal epithelial cells in the upper respiratory tract. The main host receptor for viral entry into cells is the ACE-2, which is seen to be highly expressed in adult nasal epithelial cells. The virus undergoes local replication and propagation, along with the infection of ciliated cells in the conducting airways. This stage lasts a couple of days and the immune response generated during this phase is a limited one. In spite of having a low viral load at this time, the individuals are highly infectious, and the virus can be detected via nasal swab testing.

Invasion and Infection of the Upper Respiratory Tract

In this stage, there is migration of the virus from the nasal epithelium to the upper respiratory tract via the conducting airways. Due to the involvement of the upper airways, the disease manifests with symptoms of fever, malaise and dry cough. There is a greater immune response during this phase involving the release of C-X-C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and IFN-λ) from the virus-infected cells.27 The majority of patients do not progress beyond this phase as the mounted immune response is sufficient to contain the spread of infection.

Involvement of the Lower Respiratory Tract and Progression to Acute Respiratory Distress Syndrome (Ards)

About one-fifth of all infected patients progress to this stage of disease and develop severe symptoms. The virus invades and enters the type 2 alveolar epithelial cells via the host receptor ACE-2 and starts to undergo replication to produce more viral Nucleocapsids. The virus-laden pneumocytes now release many different cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumor necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemo attractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α). This 'cytokine storm' acts as a chemo attractant for neutrophils, CD4 helper T cells and CD8 cytotoxic T cells, which then begin to get sequestered in the lung tissue. These cells are responsible for fighting off the virus, but in doing so are responsible for the subsequent inflammation and lung injury. The host cell undergoes apoptosis with the release of new viral particles, which then infect the adjacent type 2 alveolar epithelial cells in the same manner. Due to the persistent injury caused by the sequestered inflammatory cells and viral replication leading to loss of both type 1 and type 2 pneumocytes, there is diffuse alveolar damage eventually culminating in an acute respiratory distress syndrome.

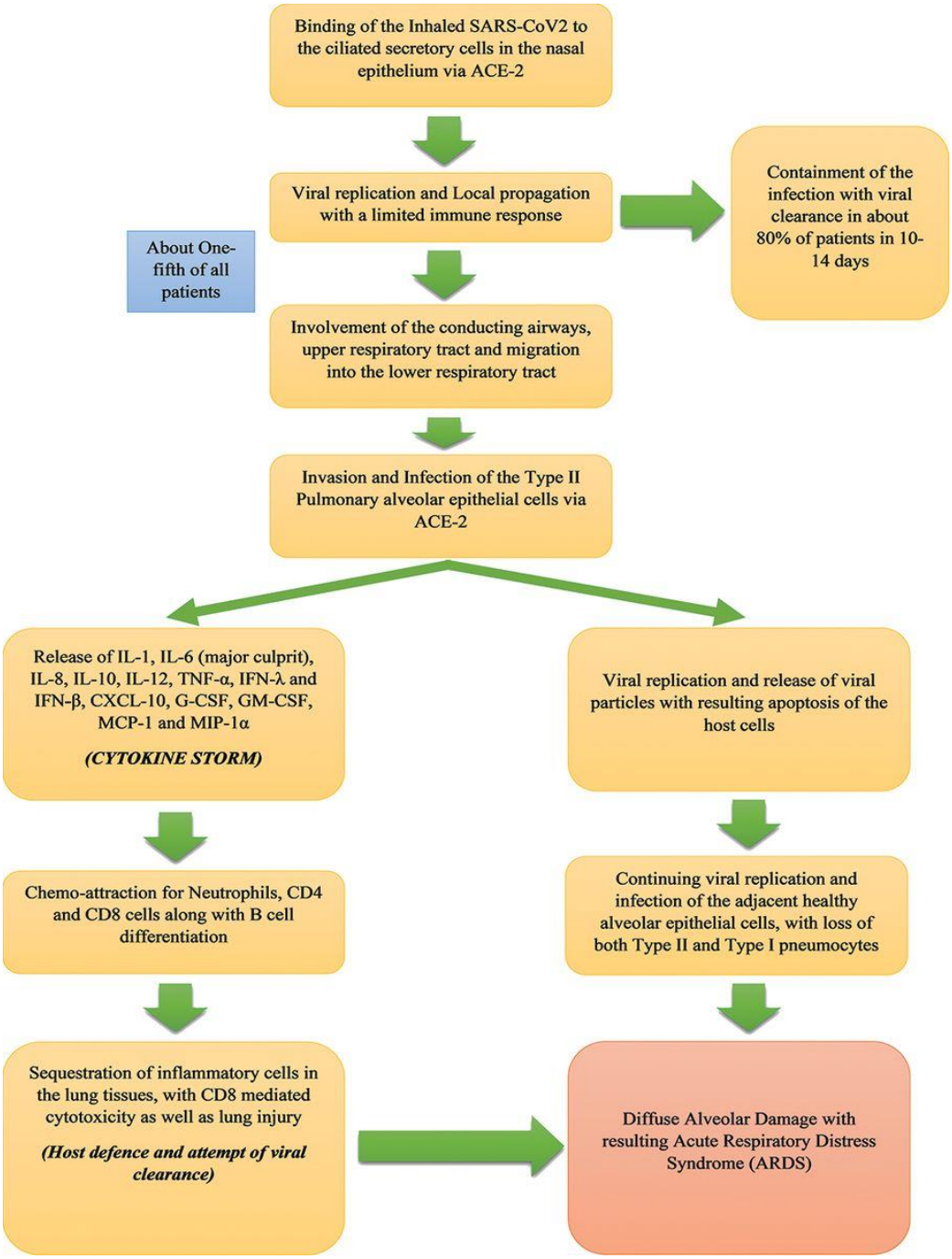

Figure 6: Pathophysiology of COVID-19.

CXCL-10, C-X-C motif chemokine ligand 10; IFN, interferon: IL, interleukin; MCP-1, monocyte chemo attractant protein-1; MIP-1a, macrophage inflammatory protein-1a; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2: TNF-a, tumor necrosis factor-a; G-CSF, granulocyte colony-stimulating factor, GM-CSF, granulocyte- macrophage colony- stimulating factor.

Viral Transmission and Clinical Features

COVID-19 Virus is mainly spread from person to person via respiratory droplet transmission, which occurs when a person is in close contact with someone who is actively coughing or sneezing. This occurs through exposure of the mucosal surfaces of the host, that is, eyes, nose and mouth, to the incoming infective respiratory droplets. Transmission of the virus may also occur through fomites used by or used on the infected individual such as bed sheets, blankets, kitchen utensils, thermometers and stethoscopes. Airborne transmission has not been reported for COVID-19, except in specific circumstances in which procedures that generate aerosols are performed, that is, endotracheal intubation, bronchoscopy, open suctioning, nebulisation with oxygen, bronchodilators or steroids, bag and mask ventilation before intubation, tracheostomy and cardiopulmonary resuscitation. The incubation period of COVID-19, which is the time period from exposure to the virus to symptom onset, is 5–6 days, but can be up to

14 days. During this period, also known as the 'pre-symptomatic' period, the infected individuals can be contagious and transmit the virus to healthy individuals in the population. The patients of COVID-19 belong mostly to the 40–70 years age group, and most commonly present with fever, body aches, breathlessness, malaise and dry cough, although patients may present with asymptomatic, mild, moderate or severe disease .Some patients may also present with gastrointestinal symptoms such as abdominal pain, vomiting and loose stools. The complications seen in patients with COVID-19 infection are caused mostly due to the 'cytokine storm'.

SINGS AND SYMPTOMS: - [11]

Signs and symptoms of coronavirus disease 2019 (COVID-19) may appear 2 to 14 days after exposure. This time after exposure and before having symptoms is called the incubation period. You can still spread COVID-19 before you have symptoms (presymptomatic transmission).

Common signs and symptoms can include:

- ✓ Fever.
- ✓ Cough.
- ✓ Tiredness.

Early symptoms of COVID-19 may include:

- ✓ A loss of taste or smell.

Other symptoms can include:

- ✓ Shortness of breath or difficulty breathing.
- ✓ Muscle aches.
- ✓ Chills.
- ✓ Sore throat.
- ✓ Runny nose.
- ✓ Headache.
- ✓ Chest pain.
- ✓ Pink eye (conjunctivitis).
- ✓ Nausea.
- ✓ Vomiting.
- ✓ Diarrhea.
- ✓ Rash.

Children have similar symptoms to adults and generally have mild illness. The severity of COVID-19 symptoms can range from very mild to severe.

- ❖ Some people may have only a few symptoms.
- ❖ Some people may have no symptoms at all, but can still spread it (asymptomatic transmission).
- ❖ Some people may experience worsened symptoms, such as worsened shortness of breath and pneumonia, about a week after symptoms start.
- ❖ Some people experience COVID-19 symptoms for more than four weeks after they're diagnosed. These health issues are sometimes called post-COVID-19 conditions.
- ❖ Some children experience multisystem inflammatory syndrome, a syndrome that can affect some organs and tissues, several weeks after having COVID-19. Rarely, some adults experience the syndrome too.
- ❖ People who are older have a higher risk of serious illness from COVID-19, and the risk increases with age.
- ❖ People who have existing medical conditions also may have a higher risk of serious illness.
- ❖ Certain medical conditions that may increase the risk of serious illness from COVID-19 include:

- Serious heart diseases, such as heart failure, coronary artery disease or cardiomyopathy.
- Cancer.
- Chronic obstructive pulmonary disease (COPD).
- Type 1 or type 2 diabetes.
- Overweight, obesity or severe obesity.
- High blood pressure.
- Smoking.
- Chronic kidney disease.
- Sickle cell disease or thalassemia.
- Weakened immune system from solid organ transplants or bone marrow transplants.
- Pregnancy.
- Asthma.
- Chronic lung diseases such as cystic fibrosis or pulmonary hypertension.
- Liver disease.
- Dementia.
- Down syndrome.
- Weakened immune system from bone marrow transplant.
- HIV or some medications.
- Brain and nervous system conditions, such as strokes.
- Substance use disorder.

CLINICAL COMPLICATIONS: - [12]

If some people about 1 in 6 will have complications, including some that are life-threatening. Many of these complications may be caused by a condition known as cytokine release syndrome or a cytokine storm. This is when an infection triggers your immune system to flood your bloodstream with inflammatory proteins called cytokines. They can kill tissue and damage your organs, including your lungs, heart and kidneys. COVID-19 complications may include the following:

- ❖ **Acute Respiratory Failure:** When you have acute respiratory failure, your lungs might not pump enough oxygen into your blood or might not take enough carbon dioxide out. Both of these problems can happen at the same time. In several studies of those who died of COVID-19, acute respiratory failure was the leading cause of death.
- ❖ **Pneumonia:** Some who catch the new corona virus get severe pneumonia in both lungs. COVID-19 pneumonia is a serious illness that can be deadly. When you have pneumonia, the air sacs in your lungs become inflamed, making it harder to breathe. Scientists who have studied images of very ill

COVID-19 patients' lungs found them filled with fluid, pus, and cell debris. In those cases, patients' bodies weren't able to transfer oxygen to the blood to keep their systems working properly.

- **Acute Respiratory Distress Syndrome (ARDS):** Acute respiratory distress syndrome (ARDS) was one of the most common complications of COVID-19.With ARDS, the lungs are so severely damaged that fluid begins to leak into them. As a result, the body has trouble getting oxygen into the bloodstream. You may need mechanical help to breathe -- such as a ventilator -- until your lungs recover.
- **Acute Liver Injury:** Research shows that the most seriously ill patients run the greatest risk of liver damage. Scientists aren't sure yet whether the virus harms the liver or if it happens for another reason. Acute liver injury and liver failure are life-threatening complications. ("Acute" means it happens suddenly).
- **Acute Cardiac Injury:** Studies of many hospitalized with COVID-19 found that some developed heart problems, including arrhythmias and high levels of other cardiac ailments. But it's not clear whether the virus itself affected patients' hearts, or if the damage happened simply because the illness caused such stress on their bodies' overall.COVID-19 also could cause cardiac problems that last long after people have recovered from the coronavirus infection. But since the illness is so new, that's not clear yet.
- **Secondary Infection:** A secondary infection means that you get an infection unrelated to the first problem you had. In this case, it means someone with COVID-19 gets infected with something else. A review of several studies done so far on hospitalized COVID-19 patients found that secondary infection is a possible -- but not common -- complication. Sometimes, a person fighting off, or recovering from, a virus gets infected by bacteria. Strep and staph are common culprits. This can be serious enough to raise the risk of death.
- **Acute Kidney Injury:** This doesn't seem to be a common complication, but if it happens, it's serious. If your kidneys stop working properly, doctors will start treatment to stop the damage. You might get dialysis (in which a machine filters your blood) until your kidneys get back to working normally. But sometimes, the damage doesn't heal and people get chronic kidney disease, which would need to be managed long term.
- **Septic Shock:** Sepsis happens when your body's reaction to an infection misfires. The chemicals released into your bloodstream to battle the illness don't trigger the right response, and instead your organs are damaged. If the process isn't stopped, you can go into what's called septic shock. If your blood pressure drops too much, septic shock can be fatal.
- **Disseminated Intravascular Coagulation:** When you have disseminated intravascular coagulation, or DIC, the body's blood-clotting response doesn't work right. Abnormal clots form, which can lead to internal bleeding or organ failure. DIC is not uncommon among those who have died or COVID.
- **Blood Clots:** A condition called disseminated intravascular coagulation (DIC) causes your body's blood-clotting response to work differently than it should. Unusual clots form, which can lead to internal bleeding or organ failure and death. A Dutch study found that nearly a third of people who were in the intensive care unit (ICU) for COVID-19 had blood clots. Some were in patients' legs (deep vein thrombosis or DVT), lungs (pulmonary embolism or PE), or arteries. But none of the patients had DIC. Some researchers say the coronavirus may be causing a new clotting condition, COVID-19-associated coagulopathy (CAC). It's marked by different protein levels in your blood than the ones caused by DIC.
- **Multi System Inflammatory Syndrome in Children:** Some children and teens have been hospitalized with a condition called multisystem inflammatory syndrome in children (MIS-C) or pediatric multisystem inflammatory syndrome (PMIS). Doctors are still learning about it, but they think it's linked to the new coronavirus. Symptoms include fever, belly pain, vomiting, diarrhea, rash, headache, and confusion. They're similar to those of toxic shock syndrome or Kawasaki disease, which causes inflamed blood vessels in children.
- **Chronic Fatigue:** Some people who've had COVID-19 develop a condition similar to chronic fatigue syndrome. They may have a brain fog, severe fatigue, pain, trouble thinking, or dizziness.
- **Rhabdomyolysis:** This is an extremely rare condition, but it's one COVID-19 researchers are watching. In rhabdomyolysis, your muscles break down and tissue dies. As cells fall apart, a protein called myoglobin floods your bloodstream. If your kidneys can't flush it out of your blood quickly enough, it can overwhelm them and cause.

DIAGNOSIS: - [13]

You develop symptoms of coronavirus disease 2019 (COVID-19) or you've been exposed to the COVID-19 virus; contact your health care provider. Also let your health care provider know if you've had close contact with anyone who has been diagnosed with COVID-19.Factors used to decide whether to test you for the virus that causes COVID-19 may differ depending on where you live. Depending on your location, you may need to be screened by your clinic to determine if testing is appropriate and available. In the U.S., your health care provider will determine whether to conduct tests for the virus that causes COVID-19 based on your signs and symptoms, as well as whether you have had close contact with someone diagnosed with COVID-19. Your health care provider may also consider

testing if you are at higher risk of serious illness or you are going to have a medical procedure. If you have had close contact with someone with COVID-19 but you've had COVID-19 in the past month, you don't need to be tested. If you've been fully vaccinated and you've had close contact with someone with COVID-19, get tested 5 days after you've had contact with them.

- **To Test for the COVID-19 Virus:** A health care provider takes a sample from the nose (nasopharyngeal swab), throat (throat swab) or saliva. The samples are then sent to a lab for testing. If you're coughing up sputum, that may be sent for testing. The FDA has authorized at-home tests for the COVID-19 virus. These are available only with a doctor's prescription The U.S. Food and Drug Administration (FDA) approved these types of tests for diagnosing COVID-19:
- **RT-PCR Test:** Also called a molecular test, this COVID-19 test detects genetic material of the virus using a lab technique called reverse transcription polymerase chain reaction (RT-PCR). A health care professional collects a fluid sample by inserting a long nasal swab (nasopharyngeal swab) into your nostril and taking fluid from the back of your nose. A sample may be collected by using a shorter nasal swab (mid-turbinate swab) or a very short swab (anterior nares swab). In some cases, health care professional inserts a long swab into the back of your throat (oropharyngeal swab). Or you may spit into a tube to produce a saliva sample. Results may be available in minutes if analyzed onsite in 1 to 3 days — or longer in locations with test processing delays — if sent to an outside lab. RT- PCR tests are very accurate when properly performed by a health care professional, but the rapid test can miss some cases.
- **Antigen Test: -** This COVID-19 test detects certain proteins in the virus. Using a long nasal swab to get a fluid sample, some antigen tests can produce results in minutes. Others may be sent to a lab for analysis. A positive antigen test result is considered accurate when instructions are carefully followed. But there's an increased chance of false-negative results — meaning it's possible to be infected with the virus but have a negative result. Depending on the situation, the health care provider may recommend a RT-PCR test to confirm a negative antigen test result. A RT-PCR test called the Flu SC2 Multiplex Assay can detect any of three viruses at the same time: the COVID-19 virus, influenza A and influenza B (flu). Only a single sample is needed to check for all three viruses. This could be helpful during the flu season. But a negative result does not rule out the possibility of any of these infections. So the testing process may include more steps, depending on symptoms, possible exposures and your provider's clinical judgment.

TREATMENT: -

PREVENTIVE MEASURES: - [14]

- **Hand-Washing:** Regular hand-washing is one of the main ways to help prevent the transmission of coronavirus. People should use plenty of soap and water to wash their hands for at least 20 seconds Trusted Source, especially after traveling on public transport, being in a public place, coughing, sneezing, blowing their nose, If a person is not able to use soap and water, they can use a hand sanitizer containing at least 60%Trusted Source alcohol. Washing the hands with soap or hand sanitizer helps kill any viruses on the hands that people may have come into contact with.
- **Avoiding Touching the Face:** People should avoid touching their eyes, nose, and mouth with their hands, especially if they are unwashed. This can help limit the spread of germs and reduce the likelihood of them getting sick. The hands come into contact with several surfaces throughout the day, and they may pick up viruses this way. A new report suggests that SARS-CoV-2 can remain on certain surfaces for up to 3 days. If a person then touches their face, viruses can transfer to the eyes, nose, or mouth and enter the body.
- **Limiting Contact with Others:** People should take care to avoid coming into close contact with others — especially those who are older, unwell, or have symptoms of the virus. The Centers for Disease Control and Prevention (CDC) recommend staying 6 feet. Trusted Source away from anyone who is coughing or sneezing. This is because when a person coughs or sneezes, small droplets containing the virus leave their mouth and nose. Other people can then breathe these droplets in and catch any virus that the droplets may contain. If a person lives within a community where coronavirus is present, the relevant government will likely have additional instructions on how to implement social distancing. These may include staying home from work or working from home, avoiding contact with anyone who is not a member of the household, prohibiting large gatherings of people, closing nonessential services, including bars and restaurants.
- **Staying Home if Unwell:** If a person has mild symptoms of COVID-19, they can self-isolate by staying at home and avoiding contact with others. Even if a person is unsure whether they have COVID-19, a common cold, or something else, it is best to stay inside and rest.
- **Calling Ahead for Medical Attention:** Anyone with a fever, cough, or difficulty breathing in an area with a COVID-19 outbreak should seek medical advice. Calling ahead before visiting a healthcare facility allows healthcare providers to reduce the risk of the virus spreading to others. For example, they may have the person use a designated entrance

at the hospital, which helps keep them away from vulnerable patients

- **Prevention Tips while Traveling:** If a person is traveling, all of the above prevention advice still applies and may help reduce the risk of contracting the virus. The CDC Trusted Source recommend that anyone at high risk of COVID-19 complications avoid cruise and air travel .People at lower risk can assess the potential risks of traveling, then decide whether it is best to postpone or cancel their travel plans. While the situation is constantly developing, many countries discourage nonessential travel and some have closed their borders certain groups.
- **Prevention in the Household:** The most valuable prevention method for the household is keeping all surfaces clean. A person should clean all surfaces that people touch regularly, including light switches, door handles, and countertops. To do so, they can use water and a household detergent. For surfaces that are visibly dirty, a person may wish to use a detergent and then a disinfectant. If a person in the household develops COVID-19, they can take the following steps to help prevent it from spreading:
  - Staying in a separate room or bedroom.
  - Using a separate bathroom if possible.
  - Cleaning and disinfecting bathroom surfaces after using them.
  - Wearing a face mask when using communal areas.
  - Not sharing food and drink with people who do not have the illness.
  - Wearing gloves while cleaning and disinfecting any shared surfaces.

Figure 7: Tips to Prevent Coronavirus Transmission

MANAGEMENT STRATEGIES: - [14]

As no vaccine is presently available for COVID-19, the treatment is mainly symptomatic and supportive in most cases. Initially, the patient presenting to the emergency is categorized into mild, moderate or severe according to the symptoms on presentation. Most patients present with mild-to-moderate symptoms such as fever, persistent dry cough, body aches and occasional

breathlessness. A small fraction of patients may also present with acute respiratory failure and acute respiratory distress syndrome with associated sepsis or multiorgan failure. The complete management protocol for patients with COVID-19.

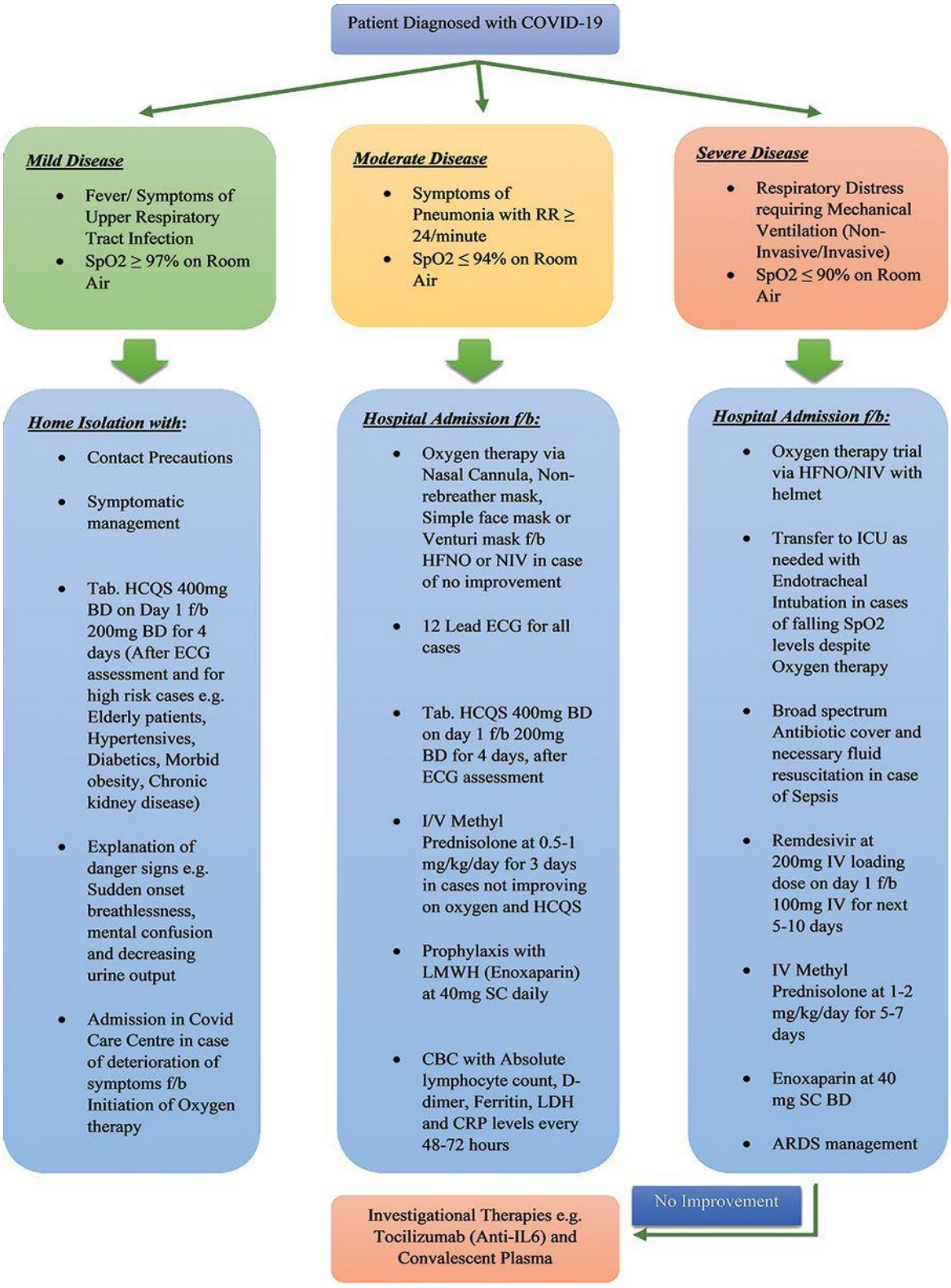

Figure 8: Treatment protocol for patients with COVID-19

HCQS- Hydroxychloroquine, ECG- Electrocardiogram, HFNO- High flow nasal oxygen, RR-Respiratory rate, SpO2- Oxygen saturation, NIV-Non-invasive ventilation, IV- Intravenous, LMWH- Low molecular weight heparin, CBC- Complete blood count, ICU-Intensive care unit, ARDS-Acute respiratory distress syndrome, LDH-Lactate dehydrogenase, CRP- C-reactive protein.

NON -PHARMACOLOGICAL THERAPY: - **[15, 16]**

- **Oxygen Therapy:** Oxygen therapy should be used for the treatment of hypoxemia. Hypoxemia is characterized as an O2 concentration below the normal range of 85 to 100 mmHg in arterial blood. Hypoxemia is defined by the British Thoracic Society as PaO2 < 60 mmHg or SaO2 < 90% (Al-Shaqsi and Brockway 2013).Oxygen therapy is used as an alternative to relief of respiratory symptoms caused by COVID-19. It is recommended for respiratory and symptomatic support. Hypoxemic patients should receive oxygen therapy immediately and maintain a blood oxygen saturation level (SaO2) of at least 90% (in pregnant women, saturation should be between 92 and 95%) (Li *et al.*, 2020b). The Ministry of Health recommends oxygen therapy in patients with severe acute respiratory syndrome and breathing difficulties, hypoxemia or shock (BRASIL 2020c).
- **Invasive Ventilation:** Invasive ventilatory support is "positive pressure ventilation applied through an endotracheal or tracheostomy tube" (Buckley and Gillham 2007). According to current evidence, to improve symptoms caused by SARS-CoV-2, patients with ARDS due to respiratory viral infections (RVI) should be treated with invasive ventilation as a pulmonary protection strategy with low tidal volumes (6 mL/kg of predicted body weight) and plateau pressure < 30 to 35 cmH2O (Arabi *et al.*, 2020; BRASIL 2020c).Evidence from meta-analysis studies shows that higher levels of positive end-expiratory pressure (PEEP) are associated with better survival among the subgroup of patients with ARDS (defined by PaO2/FiO2 ≤ 200 mmHg) (Xu *et al.*, 2020). Titration of PEEP to obtain optimal oxygenation, possibly without aggressive recruitment maneuvers, remains a reasonable strategy for most patients (Arabi *et al.*, 2020).It is noteworthy that endotracheal intubation must be performed by an experienced physician, using personal protective equipment (PPE) (Li *et al.*, 2020b).
- **High-Flow Nasal Cannula:** Adequate tissue oxygenation must be maintained in patients with acute respiratory failure (ARF) and oxygen supplementation is essential for this. The high-flow nasal cannula is a new air supply device capable of delivering up to 100% oxygen. The nasal cannula improves the clinical condition of patients with ARF in intensive care units (ICUs) and emergency departments (Kang *et al.*, 2015).The high-flow nasal cannula has been indicated for patients with COVID-19 as a way to prevent intubation in patients who have respiratory arrest with acute hypoxemia (Arabi *et al.*, 2020; Singhal 2020). Patients with mild hypoxemia should be placed in a nasal cannula with a flow rate of 5 L/min. If the patient's condition worsens, the high-flow nasal cannula should be considered, starting with 20 L/min and gradually increasing to 50–60 L/min. The oxygen fraction must be adjusted according to SaO2 (Guo *et al.*, 2020).The purpose of the article of Barrasa *et al.*, (2020) was to report the epidemiology of the first patients with COVID-19 hospitalized in ICUs in the city of Vitoria in Spain. The study consisted of 48 patients, 3 received high-flow nasal therapy (HFNT) and 45 underwent intubation. The seven-day mortality of patients who required intubation was less than 15%. And after 15 days of admission to the ICU, half of the patients remained intubated and 33% died. The authors conclude that a properly implemented oxygenation strategy could save lives. Robba *et al.*, (2020) undertook a systematic review aimed at providing guidance on respiratory management for patients with COVID-19. The author's hypothesis is that respiratory management should be customized according to the phenotype presented by the patient, which can be divided into three distinct types:

(1) Good compliance, but severe hypoxemia;
(2) Atelectasis and derecruitment are predominant; and
(3) Typical computed tomography (CT) pattern of moderate-to-severe ARDS, with alveolar edema and low compliance. The authors argue that high-flow nasal cannula (HFNC) should be used preferentially in relation to non-invasive oxygenation (NIO), as it reduces the risk of intubation. In addition, the risk of viral contamination by NIO is higher. Regarding ventilatory strategies, the authors consider that for the type phenotype moderate levels of PEEP should be used, for patients with type 2 phenotype the approach should be moderate to high levels of PEEP and for patients with type 3 phenotype should be applied the general principles used for ARDS.

- **High-Frequency Oscillatory Ventilation:** High-frequency oscillatory ventilation (HFOV) is characterized by being a form of respiratory therapy at very high rates. Higher frequencies result in lower tidal volumes and decrease the amplitude of alveolar pressure oscillations. The efficiency provided by HFOV is due to the change in the distribution dynamics of the gas flow in relation to conventional ventilation. This mechanical ventilation technique has alternative mechanisms for the gas exchange process, such as molecular diffusion, Taylor dispersion, turbulence, asymmetric velocity profiles, among others (Pillow 2005). HFOV has been used as a rescue therapy for patients who do not respond to conventional ventilation. However, a meta-analysis with 1552 patients (55% with pneumonia) found that the effect of treatment with HFOV depended on the baseline severity of hypoxemia with damage among patients with mild to moderate ARDS, but possibly decreased mortality in patients with very severe ARDS (Arabi *et al.*, 2020).This treatment is possibly not used extensively for patients with COVID-19, because articles were searched in complementary databases

and additional and specific articles about COVID-19 were not found.

- **Non-Invasive Ventilation:** Non-invasive ventilation (NIV) is a ventilatory support technique and, as its name indicates, does not use invasive methods, avoiding complications associated with orotracheal intubation. Thus, non-invasive pressure ventilation contributes to the preservation of airway defenses, speech and swallowing functions and prevention of airway trauma (Pamidi and Mokhlesi 2012). The two main types of NIV are positive pressure and negative pressure. The use of positive pressure is aimed at directly inflating the lungs. Negative pressure is applied to the abdomen and chest in order to draw air into the lungs through the upper airways. The mode most used in intensive care units (ICU) is the positive pressure model (Pardo 2007). In this type of respiratory therapy, a mask, nasal or facial, is used as an interface between the patient and the mechanical ventilator (Pardo 2007). Face masks have a better seal, however, they are considered less comfortable than nasal masks. In addition, sealed helmets and tents have been widely used, as they create a positive pressure environment, making the patient more comfortable (Pardo 2007).
- **Extracorporeal Membrane Oxygenation:** Extracorporeal membrane oxygenation (ECMO) is characterized as a way of replacement cardiopulmonary support. Its operating mechanism consists of draining blood from the vascular system, using a mechanical pump, causing it to circulate outside the body. At this time, a membrane allows O2 to enter, hemoglobin becomes saturated with oxygen and CO2 is removed. Then, the blood is re infused into the body's circulation. The flow rate through the membrane determines oxygenation and CO2 elimination and can be controlled by adjusting the countercurrent gas through the oxygenator (Schmidt *et al.,* 2013). The ECMO technique is indicated in three cases: respiratory support, cardiac support and cardio respiratory support. This method has its application defined for adult, pediatric and neonatal patients (Extracorporeal Life Support Organization 2020). Some authors claim that ECMO is associated with better results when used in patients with limited organic failure and good pre-morbid functional status. The use of ECMO can be considered in patients who do not improve with the use of other strategies to support oxygenation, considering the individual characteristics of the patient as well as the risk-benefit ratio of the decision to use the intervention (Arabi *et al.,* 2020). ECMO is recommended for patients who have the most severe acute respiratory distress syndrome (SARDS) (Li *et al.,* 2020b). In addition, ECMO can also be used in patients with refractory hypoxemia, as long as it is performed in centers with experience in handling ECMO, these recommendations were reinforced by the WHO (Guo *et al.,* 2020).The use of ECMO is highly indicated in patients who are at high risk of death, if there is ARF and any of the following conditions are found, PaO2/FiO2 below 80 mmHg for more than 6 h; PaO2/FiO2 less than 50 mmHg for more than 3 h; and pH < 7.25 with PaCO2 > 60 mmHg for more than 6 h (Extracorporeal Life Support Organization 2020). Riera *et al.,* (2020) conducted a case series study to assess the performance of the ECMO group. Nineteen patients diagnosed with COVID-19 were analyzed. The patients were transferred to the ICU of the University Vall d'Hebron Hospital, after cannulation in the hospitals of origin. The adverse effects presented were the following: 1 patient presented pulse less electrical activity (PEA) during transport; 9 patients had thrombotic events during extracorporeal membrane oxygenation and 13 patients had hemorrhagic events. The results showed that 12 patients were discharged from the hospital and 4 patients died. The authors concluded that recovery from extracorporeal membrane oxygenation can rescue healthy young patients with severe COVID-19 disease.
- **Inhaled Nitric Oxide:** Like HFOV, inhaled nitric oxide does not appear to be used extensively for patients with COVID-19, because articles were searched in complementary databases and additional and specific articles about COVID-19 were not found and, mainly, in some articles their use was not is indicated. Ferrari *et al.,* (2020) describe in their study the response to inhaled nitric oxide (INO) in 10 critically ill patients due to COVID-19 exposed to mechanical ventilation. The effect of inhaled nitric oxide would be to dilate blood vessels in the region of ventilation. The authors concluded that the administration of inhaled nitric oxide did not show a significant improvement in relation to artery oxygenation. Longobardo *et al.,* (2020) conducted a cohort study with 99 patients diagnosed with COVID-19 and ARDS and with 91 patients admitted with ARDS not caused by COVID-19. A comparison was made between 27 patients diagnosed with COVID-19 and ARDS and 20 patients with ARDS not caused by COVID-19 and the two groups were administered inhaled nitric oxide (INO). The time between hospital admission and administration of INO, age, and PaO2/FiO2 rate was similar between groups. The results showed that the increase in the PaO2/FiO2 rate was lower in the group of patients diagnosed with COVID-19 and with ARDS. However, in patients in the group diagnosed with COVID-19 and ARDS, where thrombosis was limited, the PaO2/FiO2 rate was increased after INO application. The authors conclude that the response in relation to the PaO2/FiO2 rate was much lower in the group of patients diagnosed with COVID-19 and ARDS.
- **Intravenous Infusion:** Currently, up to 80% of hospitalized patients receive intravenous therapy at some point during admission. This therapy allows the administration of medications, fluids, parenteral

nutrition and blood products via the peripheral or central intravenous route, through a catheter (Waitt and Waitt 2004).The early intravenous infusion of immunoglobulin has been used as one of the supportive treatments for patients of COVID- 19, being recommended for critically ill patients, as it increases the ability to fight infection (Li *et al.*, 2020b).Some studies have used immunoglobulin concomitantly with low molecular weight heparin anticoagulation therapy. However, this use was not recommended, as it presented some abnormalities (Chen *et al.*, 2020).Studies are still incipient for intravenous infusion, with some limitations, such as tests on a few confirmed patients with COVID-19 and reports based only on professional experiences (Li *et al.*, 2020b)

- **Passive Immunotherapy:** Treatment with intravenous immunoglobulin (IgIV) was introduced in the 1950s as a replacement therapy for patients with congenital antibody deficiency (Boros *et al.*, 2005). The technique of IgIV therapy consists of extracting antibodies present in the blood of donors, already immunized, to be injected into another person's vein (Hughes *et al.*, 2012), being immediately bioavailable in the circulation (Dhar 2009). They are sterile immunoglobulin G (IgG), purified and manufactured from human plasma, typically containing more than 95% unmodified IgG (Dhar 2009).Passive immunotherapy based on monoclonal antibodies is considered an effective method for the clinical treatment of infectious diseases. Hence, it becomes an alternative in the treatment of COVID-19. SARS-CoV and SARS-CoV-2 use the same surface receptors as the host cell, so potential input blocking agents for SARSs can be evaluated as possible blockers for SARS-CoV-2 (Shanmugaraj *et al.*, 2020). Monoclonal antibodies, directed to the spike protein in SARS-CoV and MERS-CoV, showed promising results in vitro and in vivo, which can be potentially effective against SARS-CoV-2. However, no monoclonal antibodies have been successfully marketed, due to the scale production of monoclonal antibodies being laborious, costly and time consuming.

PHARMACOLOGICAL TREATMENT: - [17]

The Following Drugs are used for the Treatment of COVID-19-

Remdesivir, Favipiravir, Molnupiravir, PF-07321332, Paxlovid, convalescent plasma, Sotrovimab, Banlanivimab, Etesevimab, Casirivimab, Imdevinab, AZD7442, Ciganilmab, Tixagevimab, Evusheld, BRII-196, BRII- 198, Dexamethasone, Corticosteroids, Tocilizumab, Sarilumab, Anakinra, Canakinumab, Baricitinib, Tofacitinib, Ruxolitinib, Adalimumab, Certolizumab, Infliximab, Etanercept, Golimumab, Itolizumab, Ravulizumab, Lemilumab, Ivermectin, Colchicine, Vitamin D, Metformin, Fluvoxamine, Azithromycin, Hydroxychloroquine, Lopinavir/Ritonavir.

ALTERNATIVE TREATMENT: - [18]

Alternative remedies include teas, essential oils, tinctures, herbal therapies such as oleander/oleandrin, and silver products such as colloidal silver. But there is no scientific evidence that any of these alternative remedies can prevent or cure COVID-19.

VACCINES: - [19-22]

As of 8 April 2022, WHO has evaluated that the following vaccines against COVID-19 have met the necessary criteria for safety and efficacy:

- AstraZeneca/Oxford vaccine.
- Johnson and Johnson.
- Moderna.
- Pfizer/BionTech.
- Sinopharm.
- Sinovac.
- COVAXIN.
- Covovax.
- Nuvaxovid.
- CanSino.

Table 1: List of vaccines according to WHO

❖ Oxford/AstraZeneca COVID-19 vaccine	A very rare adverse event called Thrombosis with Thrombocytopenia Syndrome (TTS) the benefit of vaccination in protecting against COVID-19 far outweighs the risks. Guillain-Barré syndrome (GBS) has been reported very rarely following vaccination. The AstraZeneca vaccine has an efficacy of 72% against symptomatic SARS-CoV-2 infection
❖ Pfizer BioNTech (BNT162b2) COVID-19 vaccine	The Pfizer BioNTech vaccine against COVID-19 has very high efficacy against severe disease and moderate efficacy against symptomatic SARS-CoV-2 infection. A very rare serious adverse event is myocarditis, which is mainly observed in young males aged 18-35 after the second dose.
❖ COVAXIN vaccine against COVID-19	Safety and efficacy of the vaccine and has recommended its use for people aged 18 and above. Safety data is currently limited for persons above 60 years of age. Vaccine efficacy against severe disease is 93%. In adults aged less than 60 years, efficacy was 79%; and in those aged 60 years and over it was 68%.
❖ Sinopharm COVID-19 vaccine	Safety and efficacy of the vaccine and has recommended its use for people aged 18 and above. Safety data are limited for persons above 60 years of age efficacy of

	79% against symptomatic SARS-CoV-2 infection 14 or more days after the second dose. It was not designed and powered to demonstrate efficacy against severe disease in persons with comorbidities, in pregnancy, or in persons aged 60 years and above
❖ ModernaCOVID-19 (mRNA-1273) vaccine	A very rare serious adverse event is myocarditis, which is mainly observed in young males aged 18-35 after the second dose. The Moderna vaccine after two doses and a first booster dose has been shown to have very high effectiveness against severe disease
❖ Janssen Ad26.COV2.S COVID-19 vaccine	This vaccine has also undergone review by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) and found to be safe for use. A rare serious adverse event is the "thrombosis with thrombocytopenia syndrome" and "Guillain-Barre Syndrome" the vaccine efficacy of 2 doses, 2 months apart, was 94%. In comparison, the single dose vaccine efficacy in the USA was 72%.
❖ Novavax vaccine against COVID-19	SAGE has thoroughly assessed the data on the safety and efficacy of the vaccine and has recommended its use for people aged 12 and above. Very rare serious adverse events of myocarditis and pericarditis. The efficacy of the vaccine against mild, moderate, and severe disease is 90%
❖ Sinovac-CoronaVac COVID-19 vaccine	Safety and efficacy of the vaccine and has recommended its use for people aged 18 and above. Safety data is currently limited for persons above 60 years of age. efficacy of 51% against symptomatic SARS-CoV-2 infection, 100% against severe COVID-19, and 100% against hospitalization starting 14 days after receiving the second dose.
❖ CanSino Biologics Ad5-nCoV-S [recombinant] COVID-19 vaccine	Safety and efficacy of this vaccine and has recommended its use for people aged 18 and above. Thrombosis with thrombocytopenia syndrome (TTS). Efficacy of 58% against symptomatic disease and 92% against severe COVID-19.

Some national regulators have also assessed other COVID-19 vaccine products for use in their countries. Take whatever vaccine is made available to you first**,** even if you have already had COVID-19. It is important to be vaccinated as soon as possible once it's your turn and not wait. It is safe and effective to mix-and-match different COVID-19 vaccines. The current COVID-19 vaccines provide strong protection against serious illness and death caused by the Omicron and Delta variants of the virus that causes COVID-19. Being fully vaccinated will also help reduce the likelihood of new variants emerging.

- **WHO SHOULD GET VACCINATED**:- **COVID-19 vaccines with WHO EUL are safe for most people 18 years and older,** including those with pre-existing conditions, including auto-immune disorders. These conditions include: hypertension, diabetes, asthma, pulmonary, liver and kidney disease, as well as chronic infections that are stable and controlled.
- **If you are pregnant, want to get pregnant in the future or are currently breastfeeding, getting vaccinated is important to protect you and your current or future family.** Many people around the world have now been vaccinated against COVID-19 while pregnant or breastfeeding, and no safety concerns have been identified for them or their babies. In fact, getting vaccinated while pregnant helps to protect your baby; this may also be the case if you get vaccinated while breastfeeding. You should still get vaccinated if you are menstruating on the day of your appointment.
- **If you are immuno-compromised, you should be prioritised for an additional dose of COVID-19 vaccine after 1 to 3 months.** People with compromised immune systems don't always develop sufficient immunity against COVID-19 after one or two doses, so an additional dose can help to protect them. You should also get a booster dose if recommended.

WHO SHOULD NOT GET VACCINATED: - It **is safe for most people to get vaccinated against COVID-19.** However, you should not be vaccinated if:

- You have a history of severe allergic reactions/anaphylaxis to any of the ingredients of the COVID-19 vaccine, in order to avoid possible adverse effects.
- You have a fever over 38.5ºC on the day of your vaccine appointment. Postpone until you have recovered.
- You currently have confirmed or suspected COVID-19. Wait until you have completed the mandated isolation period and your acute symptoms have passed to get vaccinated.

If you are on blood thinners, it is safe for you to get vaccinated but let the person vaccinating you know.

WHAT TO EXPECT AFTER GETTING VACCINATED:-

Some People will Experience Mild Side Effects after being vaccinated against COVID-19

Common side effects to COVID-19 vaccines include a fever, head or body aches and a sore arm.

These symptoms usually go away within a day or two. You can manage any side effects with rest, plenty of non-alcoholic liquids and taking medication to manage pain and fever, if needed. We do not recommend taking medication for pain before being vaccinated, as we don't know how this will affect how well the vaccine works.

CONCLUSION

Coronavirus disease 2019 (COVID-19) has caused a serious global health concern due to its rapid spread, high morbidity, mortality, and economic challenge all over the world. This article reviews the history, types of corona virus, clinical signs and symptoms, complications, diagnosis, etipathogenesis and management including preventive measures as well as the vaccines profile. The development of vaccines for a novel disease like this will always be a challenge as it has to gain the trust of the scientific community first. Early diagnosis, effective treatment, and preventive measures are the cornerstones of disease management. Although the efficacy of the vaccines varies significantly up to 95.0%, it was observed that a combination of immunity following natural infection with SARS-CoV-2 and vaccine-induced immunity has not been sufficient to prevent the emergence and rapid spread of coronavirus variants such as the Delta (B.1.617.2) and Omicron (B.1.1.529)– 'variants of concern'. Thus, mutated strains of SARSCoV- 2 continue to emerge worldwide, and concerns about the vaccine's efficacy are arising. However, current data suggests that people who are completely vaccinated, exhibit mild non-life threatening symptoms and are less likely to be symptomatically infected and thereby less prone to spreading the virus. Presently, it is not clear whether and how permanent protective immunity can be achieved or if second-generation vaccines with greater immune protection and more durable immunity will be needed. However, the goal at this time remains to increase vaccine production all over the world and get as many people vaccinated as possible. Although the vaccine helps prevent severe illness and death, it is still unknown how effective it is in preventing infection and the spread of the virus, so further studies are needed in this regard. Vaccines must be accepted by the public. This will need to be coupled with multiple preventive measures such as wearing a mask, social distancing, and frequent hand hygiene, for everyone including those that are vaccinated.

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