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NOVEL CORONAVIRUS DISEASE – 2019: A REVIEW

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ABSTRACT

The on-going outbreak of novel COVID-19 is a new public health crisis threatening the world. The virus originated in bats or intermediary animals yet unknown and transmitted to humans in Wuhan, China in December 2019.

KEYWORDS:

Etiology and Transmission

Transmission of COVID-19 is due to the inhalation or contact with infected droplets and the incubation period is ranges from 2-14 days.

Symptoms

Sore throat, cough, breathlessness, fatigue, etc. In most of the people the disease is mild or asymptomatic; it may be progressive to pneumonia, ARDS [Acute Respiratory Distress Syndrome] in those people with comorbidities and particularly in old age.

Treatment

The role of antiviral agents is yet to be established, in need to prevent the COVID-19 supportive treatment is essential, that include; home isolation of suspected cases and implement strict infection control measures at hospitals including contact and droplet precautions.

History

In the last few weeks of December 2019, a case of unidentified pneumonia was reported in Wuhan, china. It's symptoms and characteristics were much similar to that of viral pneumonia. After analysing the respiratory samples, the experts from people's republic of China(PRC) declares that it was a Novel coronavirus pneumonia (NCP), later officially named as Covid-19 by WHO (World Health Organization), caused by Novel coronavirus.[1] The committee of Taxonomy of viruses which is at international level named it as 'Severe Acute Respiratory Syndrome Coronavirus 2'(SARS-CoV-2). This viruse is from the beta-coronavirus family, which is a large class of viruses that are prevalent in nature. As compared to 'Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome Coronavirus (SARS-CoV and MERS-CoV, respectively), SARS-CoV-2 has high ability of transmission and infection and less mortality rate[2] Novel Coronavirus was originally gets abbreviated as 2019-nCoV by WHO, by January 7, which was identified from a throat swab sample of a patient[3] On January 30, SARS-CoV-2 declared as a Public Health Emergency of International Concern (PHEIC), by WHO.[4]

The first fatal case of SARS-CoV-2 was reported on 11th January 2020. The massive migration of Chinese people during new year has increased the spread of the disease, cases in other regions of china and other countries too, were reported in people returning from Wuhan. The disease cause to healthcare workers caring for patients was reported on 20th January, then 11 million population of Wuhan was placed under lockdown with restrictions of entry and exit from the region so that it should not spread to larger extent. Soon the lockdown was extended to other regions of Hubei province.[5] *After analysing the genome sequences of SARS-CoV shows that the genome sequence recognition rates of SARS-CoV and bat were 80% and* 96% respectively.[7] This implies that SARS-CoV-2 might originated from bats.[6] A study found that the virus is more relatable to BatCoV RaTG13, a bat coronavirus which was detected previously in a bat species named as Rhinolophus affinis from Yunnan Province, with 96% of genome identity. A study states that there is no evidence of recombination of genome of SARS-CoV-2 with other viruses originating from bat. So, these studies also suggests that bats might be the original hosts of virus.[8,9] According to the Covid-19 coronavirus pandemic worldometer, the total cases of this disease till the date 30 May 2020 are 60,64, Coronavirus recognise it's corresponding receptors on target cells through S proteins on their surface, entry to the cells gives rise to infection. A analysis shows that SARS-COV-2 binds to ACE2(Angiotensin Converting Enzyme) with more than 10 folds have higher affinity than SARS-CoV, at high levels the threshold is required for viruse infection. The mechanism by which SARS-CoV-2 infects the humans is binding of S-protein to ACE2. This results explain that the transmission rate of

SARS-CoV-2 in humans is faster as compared to SARS-CoV. Considering the higher affinity of SARS-CoV-2 binding to ACE2, the ACE2 may be a potential candidate for treatment of Covid-19.[13] This virus became a major pathogen of emerging respiratory disease outbreaks. This family have a large number of single stranded RNA viruses (ssRNA) that can be isolated in different animal species.[18] Under an electron microscope they have crown like appearance due to spike glycoproteins on the envelope. The subfamily Orthocoronavirinae of the coronaviridae family classified into four genera of CoVs as: Alphacoronavirus(alphaCoV), betackronavirus(betaCoV), deltacoronavirus(deltaCoV) and gammacoronavirus(gammaCoV).[19] Generally, some estimations suggests that 2% of the population are healthy carriers of CoV and that viruses are responsible for about 5% to 10% of acute respiratory infections (259, in which deaths are 3,67,474 and 26,85,392 are recovered. The number of active cases is 30,11,393. In India the number of cases reported are 1,75,434, in China it is 82999, in USA it is 17,95,635.*[10]*

Structure

In the last few days of february 2020, chinese researchers found that there is only one amino acid different in bonding the domain protein between the coronavirus from pangolins and that is from humans, however comparison of whole genome to date that at most 92% of genetic information was common between pangolins coronavirus and SARS-CoV-2 which is insufficient to prove pangolins are the intermediate host.[15] All characteristics of novel SARS-CoV-2 virus are founded in related coronavirus.[16] The virus can be killed by household soap which destroy its protective envelope.[17] The coronavirus is single stranded RNA virus with a diameter of 80-120nm.[11] The sequence of genomes of SARS-CoV-2 and SARS is approximately 80%, SARS-CoV-2 is closer to the SARS like bat coronavirus (MG772933) than SARS-Cov.[12]

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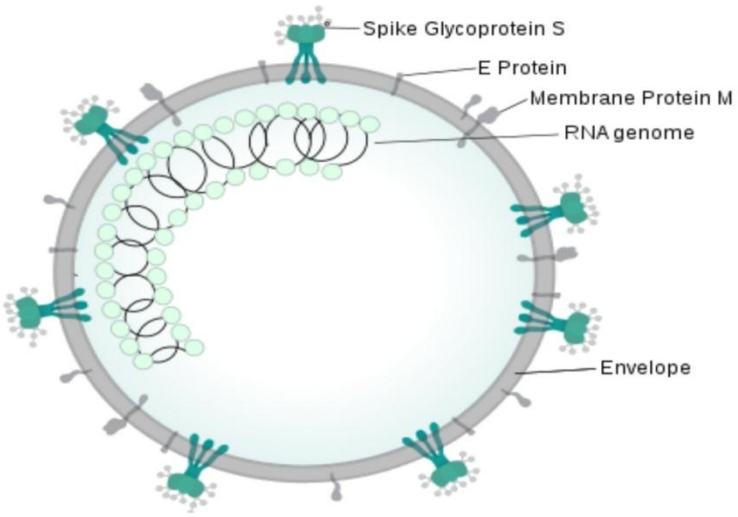
In a single stranded RNA genome, 29891 nucleotides are present which codes for 9860 amino acids. Even if it's origin is not understood entirely, these genomic analysis suggests that SARS-CoV-2 probably evolved from a strain found in bats.[22] The +ssRNA is of 30 kb in length, the largest known RNA viruses. They have 5' cap structure and 3'poly-A-tail. The Synthesis of polyprotein in the host is done as transcription works by the replication-transcriptioncomplex(RCT) is in double-membrane vesicles and by synthesis of subgenomic RNAs sequences. The termination of transcription occurs at transcription regulatory sequences, situated between the Open Reading Frames(ORFs) that work as templ ates which contributes towards 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.[18]

In the structural components of CoVs, there are the spike glycoproteins have two subunits (S1 and S2).[23] This virus is sensitive to ultraviolet radiations and heat. Also they can be effectively deactivated by some lipid solvents like ether (75%), ethanol, chloride containing disinfectants like chloroform and peroxyaceticacid except chlorhexidine.[21]



Etiology and Transmission

The bats are considered as natural carriers of SARS-CoV-2 and pangolins are thought to be intermediate hosts. A analysis by Wuhan Institute of Virology shows that 96% gene sequence is similar in between SARS-CoV-2 and bat coronavirus. This implies that bats are the potential source of SARS-CoV-2[8,9] The droplets which are contaminated are exhaled by infected person are then inhaled by others in lungs or settle on their faces causes new infection.[26] A person is most infectious when he shows symptoms (even less or non-specific), but may be infectious up to two days before symptoms are seen.[25] The droplets with heavy mass, usually settle down to surfaces and don't travel far through the air. COVID-19 transmitted mainly when peoples are in close contact (within two metres or six feet) by small droplets produced during coughing, sneezing and talking.[24,25] A person can transmit the virus even if they don't have any symptoms but it is unclear how often this happens.[24,25,26] An estimate shows that the number of persons infected who are asymptomatic is 40%.[27] It results in the virus being transferred more easily than normal.[24,26] Many initial cases of COVID-19 are linked to market suggesting that SARS-CoV-2 was transmitted from animals to humans.[33] The infected droplets can spread 1-2 m and settled on surfaces. They can remain viable for few days in favorable atmospheric conditions but can be destroyed in few seconds by common disinfectants like sodium hypochlorite and hydrogen peroxide.[34]

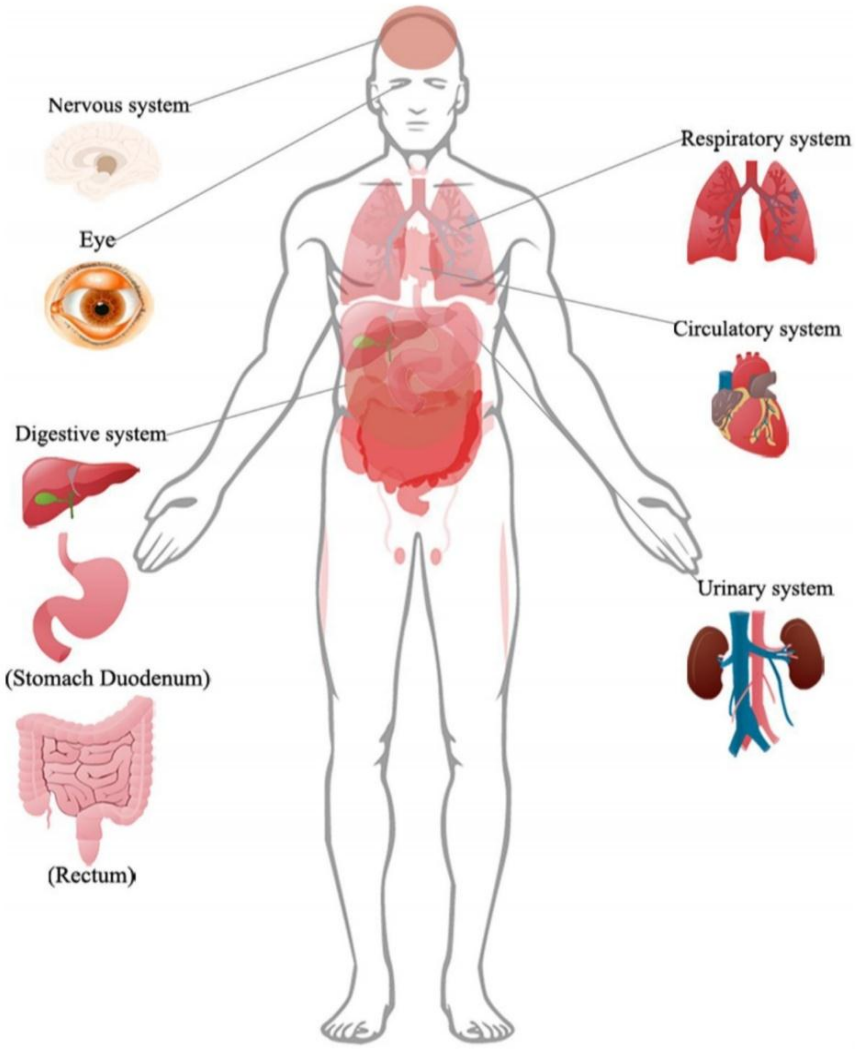
Sputum and saliva carry large amount of viruses.[24,25,26,28] A study shows that COVID-19 do not spread through sexual contact, kissing and intimate contact and faeco-oral routes are suspected to transmit the virus.[29,30] Some medical procedures produces aerosols.[31] The WHO's initial estimates that the R0 (basic reproduction rate) were 1.5-2.5 however a more recent review found the basic R0 (without control measures) to be higher at 3.30 and median R0 is to be 2.80.[32] After January 1, less less than 10% patients had exposed to market and more than 70% patients had no exposure to market.[33] The Basic Case Reproduction rate (BCR) lies in range of 2 to 6.50 in various modelling studies.[35] In addition to this, researchers have detected SARS-CoV-2 in stool, gastrointestinal tract, saliva and urine samples. Based on bioinformatics, the digestive tract may be a route of SARS-CoV-2 infection.[36] The SARS-CoV-2 has been detected many times in the gastrointestinal tissue of patients of COVID-19.[37] A study of nine pregnant women having COVID-19 indicates that the possibility of transmission between mother and infant during late pregnancy was temporarily excluded.[38] These are some causes, symptoms and ways of transmission of Covid-19.

Mechanism

An acute viral infection in humans with a incubation period of days is produced by SARS-CoV-2, this is similar to SARS-CoV with a incubation period of few days.[53,54] The host range of virus is ruled by multiple molecular interactions, including receptor interaction. The spike(S) of protein receptor binding domain of SARS-CoV-2 was shown structurally which is similar to that of SARS-CoV, despite amino acid variation at some key residues. Generally, the spike protein of virus is divided into S1 and S2 domain, in which S1 is responsible for receptor binding and S2 is for cell membrane fusion.[55] The lungs are the most affected organs by COVID-19 because the virus accesses the host cells via the enzyme angiotensin converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells of lungs.[39] This virus have a special surface glycoprotein called ‘spike’(peplomer) to connect to ACE2 and enter the host cells.[40] As the alveolar disease progresses, respiratory failure might be there followed by death.[41] Respiratory failure may be caused by SARS-CoV-2 through affecting the brainstem as other coronaviruses have been found to be invade the central nervous system (CNS). While virus has been detected in CerebroSpinal Fluid (CSF), the exact mechanism by which it enters the CNS remains unclear. Invasion of peripheral nerves gives rise to low levels of ACE2 in

brain.[42,43] The virus also affects gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric duodenal and rectal epithelium.[44] The virus can cause acute heart injury and damage to the cardiovascular system.[45]

Autopsies of patients who died due to COVID-19 have found diffuse alveolar damage (DAD), and lymphocytes containing inflammatory infiltrates within the lungs.[46] Although SARS-CoV-2 has a tropism for ACE2 expressing epithelial cells of respiratory tract, persons with severe COVID-19 have symptoms of systemic inflammation, Clinical laboratory findings of elevated IL-7, IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF), interferon-gama inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-alpha (MIP-alpha), and tumour necrosis factor -alpha (TNF-alpha) indicative of cytokine release syndrome (CRS) suggest an underlying immunopathology.[47] In addition to that, people having COVID-19 and Acute Respiratory Distress Syndrome (ARDS) have classical serum biomarkers of CRS, including elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and ferritin.[48] The identification of several key residues (GIn493 and Asn501) that allows the binding of SARS-CoV-2 receptor binding domain with ACE2 further support that SARS-CoV-2 has acquired capacity for person-to-person transmission.[56] Systematic inflammation results in allowing inflammatory lymphocytic and monocytic infiltration, vasodilation of lung of heart. In particular pathogenic GM-CSF secreting T-cells were shown to corelate with the recruitment of inflammatory IL-6-secreting monocytes and severe lung pathology in COVID-19.[46] Some data are available about microscopic lesions and pathophysiology of COVID-19.[49,50] There are four types of viral pneumonia as:Minor pneumonia: minor serous, exudation. Mild pneumonia: pulmonary oedema, pneumocytes, hyperplasia, interstitial inflammation with lymphocytic infiltration and multinucleated big cell formation. Severe pneumonia: diffuse alveolar damage (DAD) with diffuse alveolar exudates. DAD is the reason for acute respiratory distress syndrome (ARDS) and severe hypoxemia. Healing pneumonia: organization of alveolar cavities and pulmonary interstitial fibrosis plasmocytosis.[51] This is a part of mechanism by which COVID-19 invades in our body.



Effects and Symptoms

There is a delay between the moment when a person is infected and the time he or she developes symptoms. This period is called as incubation period. The average incubation period for COVID-19 is five to six days but generally ranges from one to fourteen days.[58,71] Some most common symptoms are fever, dry cough, tiredness. On other side the less common symptoms are sore throat, pains, diarrhoea, conjunctivitis, headache, loss of taste and smell, rashes or discolouration of fingers or toes. Some serious symptoms are difficulty in breathing or shortness of breath, chest pain or pressure and loss of speech or movement.[72] The time on exposure to onset of symptoms is around five to seven days typically but may range from two to fourteen days.[57,60] It is most contagious in first couple of days and after appearance of symptoms, although spread is possible even before symptoms appears and people who do not show symptoms.[58/61] A study found that 44% people had fever when they presented to the hospital, while 90% went on to develop fever at some point during their hospitalization.[62/64] Symptoms such as vomiting, nausea, diarrhoea have been detected in varying percentages.[65,66,67] This are some types of symptoms occurred when a person get infected by coronavirus.

Symptom	Range
Fever	83–99%
Cough	59–82%
Loss of appetite	40–84%
Fatigue	44–70%
Shortness of breath	31–40%
Coughing up sputum	28–33%
Muscle aches and pains	11–35%

Treatment

With the past investigations, the drugs are evaluated into therapeutic treatment for SARS and MERS[81] Isolation and caring includes oxygen therapy, fluid management and antibiotics treatment for secondary bacterial infection is recommended.[80] Mild illness should be solved at home with counseling about danger signs and symptoms. The general principle are maintenance of hydration and nutrition and controlling fever and cough.

Provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated in hypoxic patients. Renal replacement therapy may required in some cases. Antibiotics and antifungals are needed if co- infections are suspected or proven.[73,74] Antiviral therapy includes oseltamivir, ganciclovir and lopinavir, ritonavir was given to 75% of patients. The time period of non-invasive ventilation was 4-22d and mechanical ventilation for 3-20d. In the case series of children discussed earlier, all children recovered recoverd with basic treatment and did not need intensive care.[76] Antiviral drugs like ribavirin, lopinavir-ritonavir have been used on based on the experience with SARS and MERS. A study in patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone.[75] Other than these drugs, arbidol(an antiviral drug in Russia and China), intravenous, immunoglobulin, interferons, chloroquine and plasma of patients recovered from COVID-19.[77,78,79]

Antiviral Western Medical Treatment

Xiao et al. found that remdesivir was effective in controlling of COVID-19 in vitro. while, chloroquine has been found to have immunomodulatory activity and

could inhibit SARS-CoV-2 in vitro.[82] Controlled clinical trials have shown that chloroquine was effective for treating the person having COVID-19.[83] A large number of tests and trials are carried out on Remdesivir in some hospitals, the efficacy of drug us uncertain at present. Arbidol, a small indole derivative molecule, was found to inhibit viral fusion of influenza A and B viruses and hepatitis C viruses.[84] In addition, the nucleoside analogue like lopinavir/ritonavir, neuraminidase inhibitor, Remdesivir and peptide EK1 could be used for treatment of COVID-19.[85]

Chinese medical treatment

The Chinese medicine also have a important role in the treatment of COVID-19. A. study by the Shanghai institute of Materia Medica and Wuhan Institute of Virology, found that shuanghuanglian oral liquid could inhibit SARS-CoV-2, previous studies shown that baicalin, chlorogenic acid and forsythin in that oral liquid have certain inhibitory effects on bacterias and viruses.[86,87] It may work on the mechanism that these components play a therapeutic role by reducing the inflammatory response effectively caused due to the viruses and bacterias.[88]

Immunoenhancement therapy

Interferons are also acts as effective inhibitors of SARS and MERS-CoV replication.[89] These findings suggest that interferons can be used in the treatment. Immunoglobulin might be the safest immunomodulator for long term in all age groups and could helps to inhibit the production process of pro-inflammtory cytokines and increases production of anti-inflammatory mediators.[90] Apart from that, thymosin alpha-1(Ta1) can be an immune booster for patients with SARS effectively controlling the spread of disease.[91]

Convalescent plasma therapy

In a retrospective study, it is founded that convalescent plasma therapy is more effective than severe doses of hormonal shock in patients with severe SARS, reducing mortality and shortening hospital stays.[92] On other side, from the perspective of immunology, most of the patients who recoverd from COVID-19 wil produce specific antibodies against SARS-CoV-2, and their serum is used to prevent re-infection. At the same time, antibodies can inhibit the reproduction in the acute phase of infection and helps in clearing the virus.[93] Theoretically, viraemia peaks during the first week of most viral infection, and it should be more effective to give convalescent plasma early in the disease course.[94]

Auxiliary blood purification treatment

According to the recent studies, the key receptor of SARS-CoV-2, ACE2, is highly expressed in human kidney (nearly 100 times higher than in lung). Kidney night be the main target of attack for SARS-CoV-2. Early continuous blood purification treatment could reduce renal work- load and help to promote the recovery of renal function.[95] Therefore, blood purification technology could be used to remove inflammatory factors, eliminate cytokine storms, correct electrolyte imbalances and maintain acid-base balance to control person's capacity load in an effective manner.[96]

This are some methods of treatment to overcome the COVID-19.

Precautions

To prevent spread of COVID-19 following measures should be taken:

1) We should clean our hands 2-3 times in a couple of hours.
2) The proper distance (at least one meter) should be maintained from be maintained from the person who is coughing and sneezing**.**
3) Cover your mouth and nose with handkerchief or bent elbow while coughing.
4) Don't touch your eyes, nose and mouth.
5) Don't go outside if you feel unwell, stay home.
6) If you have fever, cough or difficulty in breathing, quickly consult your doctor.

CONCLUSION

The COVID-19 infection is like pneumonia and also named as Novel Coronavirus pneumonia (NCP). It is important to find out a vaccine on this virus as it causes a deadly disease. This is believed that this virus is originated from bats as the genome sequence of them is relatable. This virus spreads through intimate contact with the infected person. We have to be careful while going outside as the vaccine is not available. The use of mask is mandatory. Our surroundings should be sanitized in a couple of hours and social distancing should be maintained.

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