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REVIEW ON COVID-19

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ABSTRACT

This review discusses current evidence regarding the pathophysiology, transmission, diagnosis, and management of COVID-19. Corona virus causes respiratory infection including pneumonia, cold, sneezing and coughing while in animal it causes diarrhea and upper respiratory diseases. Corona virus transmitted human to human or human to animal via airborne droplets. Corona virus enters in human cell through membrane ACE-2 exopeptidase receptor.

KEY WORDS: COVID-19, MERS-CoV, SARS-CoV.

INTRODUCTION

COVID-19 epidemic is the major global health disaster today and the supreme challenge to the universe. Ideally, COVID-19 is an enclosed RNA virus that is distinctly present in people and animals. The virus belongs to the Nidovirales order that consist of families, namely, Roniviridae, Arteriviridae, and Coronaviridae.[1]

Over the past 2 decades, coronaviruses (CoVs) have been associated with significant disease outbreaks in East Asia and the Middle East. The severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) began to emerge in 2002 and 2012, respectively. Recently, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), emerged in late 2019, and it has posed a global health threat, causing an ongoing pandemic in many countries and territories. Several years after the global SARS epidemic, the current SARS-CoV-2/COVID-19 pandemic has served as a reminder of how novel pathogens can rapidly emerge and spread through the human population and eventually cause severe public health crises.[2]

History and Origin

First case of corona virus was notified as cold in 1960. According to the Canadian study 2001, approximately 500 patients were identified as Flu-like system. 17-18 cases of them were confirmed as infected with corona virus strain by polymerase chain reaction. Corona was treated as simple nonfatal virus till 2002. In 2003, various reports published with the proofs of spreading the corona to many countries such as United States America, Hong Kong, Singapore, Thailand, Vietnam etc. Several case of severe acute respiratory syndrome caused by corona and their mortally more than 1000 patient was reported in 2003. When microbiologist was started focus to understand these problems. After a deep exercise they conclude and understand the pathogenesis of disease and discovered as corona virus. COVID-19 was first identified and isolated from pneumonia patent belongs to Wuhan, china.

Characteristics COVID- 19

According to a report published on 24 Jan 2020, corona virus infected patient have many common features such as fever, cough, and fatigue while diarrhea and dyspnea werefound to be as uncommon feature. Many of them patient reported bilateral abnormalities.[3]

Pathophysiology

Coronaviruses are large, enveloped, single-stranded RNA viruses found in humans and other mammals, such as dogs, cats, chicken, cattle, pigs, and birds. Coronaviruses cause respiratory, gastrointestinal, and neurological disease. The most common corona viruses in clinical practice are 229E, OC43, NL63, and HKU1, which typically cause common cold symptoms in immune competent individuals. SARS-CoV-2 is the third coronavirus that has caused severe disease in humans to spread globally in the past 2 decades. The first coronavirus that caused severe disease i.e. severe acute respiratory syndrome (SARS), which was thought to originate in Foshan, China, and resulted in the2002-2003 SARS-CoV pandemic. The second was the coronavirus-caused Middle East respiratory syndrome (MERS), which originated from the Arabian peninsula in 2012. SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona. Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be a natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARSCoV-2 via an intermediate host, such as the pangolin.[4]

Human Coronaviruses

Following four viruses have been identified as common causes common cold symptoms in immune competent individuals and respiratory tract diseases in human. •229E (alpha coronavirus), • NL63 (alpha coronavirus),

• OC43 (beta coronavirus), • HKU1 (beta coronavirus).

Virology

Coronaviruses are large enveloped, positive single stranded RNA viruses that can be divided into four genera, namely alpha, beta, delta and gamma. A host - derived membrane surrounds the genome, which is encased in a helical nucleocapside. As they are positive-sense single-stranded RNA viruses, they do not need to carry enzymes to initiate infection. The virus genome has been sequenced and these results in conjunction with other reports show that it is 75-80% identical to the SARS-CoV and even more closely related to several bat coronaviruses. Alpha and beta coronaviruses are found in both humans and animals. Gamma and delta coronaviruses have only been identified in animals. Coronaviruses are widespread among birds and mammals, with bats being host to the largest variety of geno types. As a result of genetic recombination occurs between members of the same or different coronavirus groups, new viruses emerge from the animal reservoirs and subsequently jump to human. There are three new coronaviruses have been emerged as a result of this genetic recombination up to now. • MERS-CoV (beta coronavirus) – Middle East Respiratory Syndrome (MERS)

• SARS-CoV (beta coronavirus) – severe acute respiratory syndrome (SARS)• 2019-nCoV (beta coronavirus) - 2019 novel coronavirus acute respiratory disease.

Epidemiology

Currently, it has been reported in all provinces in China and 25 countries worldwide.[5]

Microbiology

Corona virus is spherical or pleomorphic, single stranded, enveloped RNA and covered with club shaped glycoprotein. Corona viruses are four sub types such as alpha, beta, gamma and delta corona virus. Each of sub type coronaviruses has many serotypes. Some of them were affect human of other affected animals such as pigs, birds, cats, mice and dogs.[3] The structures of the coronavirus are more spherical in shape, but their structure has the potential to modify their morphology in response to environmental conditions, being pleomorphic. The capsular membrane which represents the outer envelope usually has glycoprotein projection

and covers the nucleus, comprising a matrix protein containing a positive-strand RNA. Since the structure possesses 5'-capped and 3'-polyadenylated ends, it remains identical to the cellular mRNAs. The structure is comprised of hemagglutinin esterase (HE) (present only in some beta-coronaviruses), spike (S), small membrane (E), membrane (M) and nucleocapsid (N), as shown (Figure **1**). The envelope containing glycoprotein is responsible for attachment to the host cell, which possesses the primary anti-genic epitopes mainly those recognised by neutralising antibodies. The spike S-protein being in a spike form is subjected to a structural rearrangement process so that **fusing** the outer membrane of the virus with the host-cell membrane becomes easier. Recent SARS-CoV work has also shown that the membrane exopeptidase ACE enzyme (angiotensin-converting enzyme) functions as a COVID-19 receptor to enter the human cell.[6]

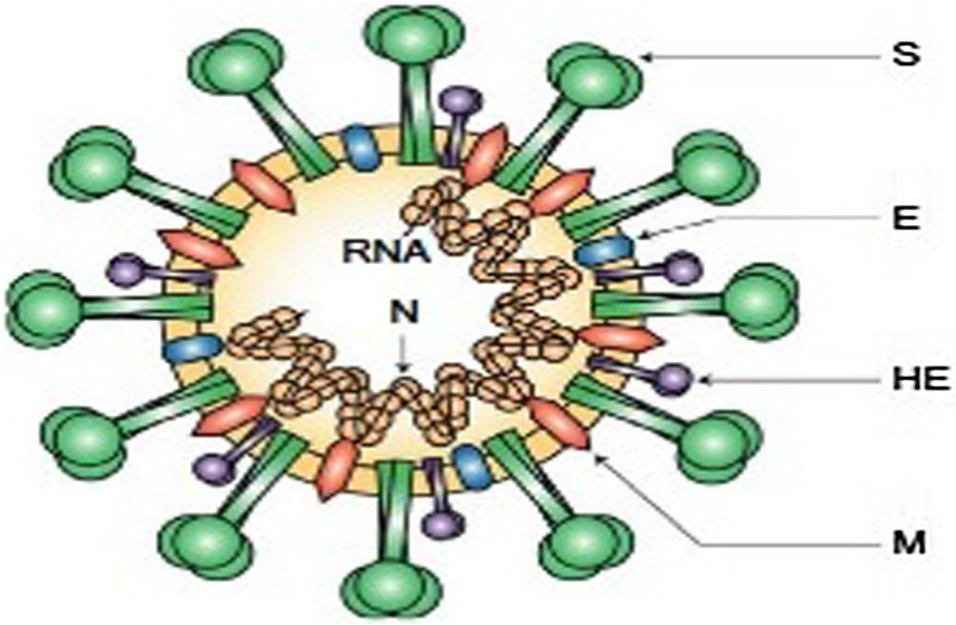

Fig.1

Etiology

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages. Genomic characterization has shown that probably bats and rodents are the gene

sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.

- Common human CoVs: HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alphaCoVs). They can cause common colds and self-limiting upper respiratory infections in immunocompetent individuals. In immunocompromised subjects and the elderly, lower respiratory tract infections can occur.
- Other human CoVs: SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively). These cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations. Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 10% and 35%, respectively.
- Thus, SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. In this regard, although high temperature decreases the replication of any species of virus.[8]

Mode of spreading

Peoples can get the infection through close contact with a person who has symptoms from the virus includes cough and sneezing. Generallycorona virus was spread via airborne zoonotic droplets. Virus was replicated in ciliated epithelium that caused cellular damage and infection at infection site. According to a study published in 2019, Angiotensin converting enzyme 2 (ACE.2), a membrane exopeptidasein the receptor used by corona virus in entry to human cells.[3]

Transmission of SARS-CoV-2 Infection

Prolonged exposure to an infected person (being within 6 feet for at least 15 minutes) and briefer exposures to individuals who are symptomatic (eg. coughing) are associated with higher risk for transmission, while brief exposures to asymptomatic contacts are less likely to result in transmission. Contact surface spread (touching a surface with virus on it) is another possible mode of transmission. Transmission may also occur via aerosols (smaller droplets that remain suspended in air). [4]

Diagnosis

Clinical factors are utilised to evaluate the necessity for testing. This involves close interaction with a disease-confirmed client within fourteen days of symptoms. Also, it may

include travel history to an infected region within fourteen days of symptoms beginning. Precisely, WHO endorses gathering samples from individuals with COVID-19. Then, the samples are evaluated for viral RNA by means of the polymerase chain reaction. When the test outcome shows positive, it is suggested to repeat the test for the purpose of verification. On the other hand, if the test confirms negative, this warrant repeat testing. Also, chest X-ray and CT imaging are used to identify COVID-19 in suspect individuals with adverse molecular diagnosis.[1]

The symptoms of COVID-19 remain very similar to those of the other respiratory epidemics in the past, which include SARS and MERS, but here the range of symptoms includes mild rhinitis to septic shock. Some intestinal disturbances were reported with the other epidemics, but COVID -19 was devoid of such symptoms. When examined, unilateral or bilateral involvement compatible with viral pneumonia is observed in the patients, and bilateral multiple lobular and sub segmental consolidation areas were observed in patients hospitalised in the intensive care unit.[6]

Clinical diagnosis

Clinical diagnosis COVID-19 is based on clinical manifestations, molecular diagnostics of the viral genome by RT-PCR, chest x-ray or CT scan, and serology blood tests.

There are two types of tests for COVID-19 during this pandemic: One type is PCR tests, as a molecular diagnostic technique based on viral genetic material that can diagnose an active COVID-19 infection. The early detection of COVID-19 via PCR depends on the presence of a sufficient amount of viral genome in the patient sample and the sensitivity of the RT-PCR assay. So, optimized or screening methods that able to detect the 2019-nCoV even in low viral titers are fairly necessary. The Coronaviruses have four subfamilies including alpha, beta, gamma, and delta. The alpha and beta coronaviruses originate from mammals, while gamma and delta coronaviruses have been identified in pigs and birds. Beta-coronaviruses are also called bat-coronavirus. Bioinformatics analysis shows that RNA sequence of 2019-nCoV is more than 90% similar to a bat-coronavirus RaTG13. It has been reported that the beta-coronaviruses cause severe disease while the alpha-coronaviruses cause asymptomatic or mildly symptomatic disease. 2019-nCoV is closely related to the B lineage of the beta-coronaviruses, which are known to cause severe disease and fatalities.[7]

Prevention

The WHO and other agencies such as the CDC have published protective measures to mitigate the spread of COVID-19. This involves frequent hand washing with handwash containing 60% of alcohol and soap for at least 20 seconds. Another important measure is avoiding close contact with sick people and keeping a social distance of 1 metre always to everyone who is coughing and sneezing. Not touching the nose, eyes and mouth was also suggested. While coughing or sneezing, covering the mouth and nose with a cloth/tissue or the bent elbow is advised. Staying at home is recommended for those who are sick, and wearing a facial mask is advised when going out among people. [6] Since there is no precise treatment for this disease, prevention is critical. Again, proper ventilation with good sunlight to destroy the virus is recommended at home. Hence, it is accurate to state that prevention of COVID-19 includes isolation, proper ventilation, hand hygiene and use of personal protective equipment, especially as surgical masks, eye protection, gloves, and gowns.

Treatment

The initial step in treating those suspected to have COVID-19 is adequate isolation in order to prevent spread to other contacts, clients, and healthcare providers. The mild disease should bead ministered at home through staying hydrated, proper nutrition, monitoring fever and cough. Besides, the repetitive usage of antibiotics and antivirals, mainly oseltamivir, should be evaded among those with COVID-19 symptoms. This portrays that there is no specific treatment for this ailment.[1]

Targeting the Virus and the Host Response

The following classes of drugs are being evaluated or developed for the management of COVID-19: antivirals (eg, remdesivir, favipiravir), antibodies (eg, convalescent plasma, hyperimmune immunoglobulins), anti-inflammatory agents (dexamethasone, statins), targeted immunomodulatory therapies (eg, tocilizumab, sarilumab, anakinra, ruxolitinib), anticoagulants (eg, heparin), and antifibrotics (eg, tyrosine kinase inhibitors). It is likely that different treatment modalities might have different efficacies at different stages of illness and in different manifestations of disease. Viral inhibition would be expected to be most effective early in infection, while, in hospitalized patients, immunomodulatory agents may be useful to prevent disease progression and anticoagulants may be useful to prevent thromboembolic complications. More than 200 trials of chloroquine/hydroxychloroquine, compounds that inhibit viral entry and endocytosis of SARS-CoV-2 in vitro and may have beneficial

immunomodulatory effects in vivo, have been initiated, but early data from clinical trials in hospitalized patients with COVID-19 have not demonstrated clear benefit. A clinical trial of 150 patients in China admitted to the hospital for mild to moderate COVID-19 did not find an effect on negative conversion of SARS-CoV-2 by 28 days (the main outcome measure) when compared with standard of care alone. Two retrospective studies found no effect of hydroxychloroquine on risk of intubation or mortality among patients hospitalized for COVID-19. One of these retrospective multi center cohort studies compared in-hospital mortality between those treated with hydroxychloroquine plus azithromycin (735 patients), hydroxychloroquine alone (271 patients), azithromycin alone (211 patients), and neither drug (221 patients), but reported no differences across the groups. Adverse effects are common, most notably QT prolongation with an increased risk of cardiac complications in an already vulnerable population. These findings do not support off-label use of (hydroxy)chloroquine either with or without the coadministration of azithromycin. Randomized clinical trials are ongoing and should provide more guidance. Most antiviral drugs undergoing clinical testing in patients with COVID-19 are repurposed antiviral agents originally developed against influenza, HIV, Ebola, or SARS/MERS. Use of the protease inhibitor lopinavir-ritonavir, which disrupts viral replication in vitro, did not show benefit when compared with standard care in a randomized, controlled, open-label trial of 199 hospitalized adult patients with severe COVID-19. Among the RNA-dependent RNA polymerase inhibitors, which halt SARS-CoV-2 replication, being evaluated, including ribavirin, favipiravir, and remdesivir, the latter seems to be the most promising. The first preliminary results of a double-blind, randomized, placebo-controlled trial of 1063 adults hospitalized with COVID-19 and evidence of lower respiratory tract involvement who were randomly assigned to receive intravenous remdesivir or placebo for up to 10 days demonstrated that patients randomized to receive remdesivir had a shorter time to recovery than patients in the placebo group (11 vs 15 days). A separate randomized, open-label trial among 397 hospitalized patients with COVID-19 who did not require mechanical ventilation reported that 5 days of treatment with remdesivir was not different than 10 days in terms of clinical status on day 14. The effect of remdesivir on survival remains unknown. Treatment with plasma obtained from patients who have recovered from viral infections was first reported during the 1918 flu pandemic. A first report of 5 critically ill patients with COVID-19 treated with convalescent plasma containing neutralizing antibody showed improvement in clinical status among all participants, defined as a combination of changes of body temperature, Sequential Organ Failure Assessment score, partial pressure of oxygen/fraction of inspired oxygen, viral load, serum antibody titer,

routine blood biochemical index, ARDS, and ventilatory and extracorporeal membrane oxygenation supports before and after convalescent plasma transfusion status. However, a subsequent multicenter, open-label, randomized clinical trial of 103 patients in China with severe COVID-19 found no statistical difference in time to clinical improvement within 28 days among patients randomized to receive convalescent plasma vs standard treatment alone (51.9% vs 43.1%). However, the trial was stopped early because of slowing enrollment, which limited the power to detect a clinically important difference. Alternative approaches being studied include the use of convalescent plasma-derived hyperimmune globulin and monoclonal antibodies targeting SARS-CoV-2. Alternative therapeutic strategies consist of modulating the inflammatory response in patients with COVID-19. Monoclonal antibodies directed against key inflammatory mediators, such as interferon gamma, interleukin 1, interleukin 6, and complement factor 5a, all target the overwhelming inflammatory response following SARS-CoV-2 infection with the goal of preventing organ damage. Tyrosine kinase inhibitors, such as imatinib, are studied for their potential to prevent pulmonary vascular leakage in individuals with COVID-19. Studies of corticosteroids for viral pneumonia and ARDS have yielded mixed results. However, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which randomized 2104 patients with COVID-19 to receive 6 mg daily of dexamethasone for up to 10 days and 4321 to receive usual care, found that dexamethasone reduced 28-day all-cause mortality (21.6% vs 24.6%; age-adjusted rate ratio, 0.83 [95% CI, 0.74-0.92]; $P < .001$). The benefit was greatest in patients with symptoms for more than 7 days and patients who required mechanical ventilation. By contrast, there was no benefit (and possibility for harm) among patients with shorter symptom duration and no supplemental oxygen requirement. A retrospective cohort study of 201 patients in Wuhan, China, with confirmed COVID-19 pneumonia and ARDS reported that treatment with methylprednisolone was associated with reduced risk of death (hazard ratio, 0.38 [95% CI, 0.20-0.72]). Thromboembolic prophylaxis with subcutaneous low molecular weight heparin is recommended for all hospitalized patients with COVID-19. Studies are ongoing to assess whether certain patients (ie, those with elevated D-dimer) benefit from therapeutic anticoagulation.[3]

CONCLUSION

COVID-19 outbreak has challenged almost all sectors due to the spread of the disease at an alarming rate across the globe notably, COVID-19 is an RNA virus that poses a threat to public health. Currently, the disease has caused thousands of infections and deaths. Ideally,

the rapid spread of the ailment calls for strong investigation and isolation protocols to avert additional spread. Fundamentally, no confirmed medicine or vaccine has been created to improve the health of patients with the condition.

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