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Origin, Spread, Diagnostic tests and treatment for Covid-19

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ABSTRACT

An acute respiratory disease, caused by a novel coronavirus (SARS-CoV-2, the coronavirus disease 2019 (COVID-19) has spread throughout China and received worldwide attention. On 30 January 2020, World Health Organization (WHO) officially declared the COVID-19 epidemic as a public health emergency of international concern. COVID-19 is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 is now a pandemic affecting many countries globally. Most of these types of viruses have an origin in animals. The COVID-19 virus (also called SARS-CoV-2) is a new virus in humans. The most common symptoms of COVID-19 are fever, dry cough, and tiredness. Some patients may have aches and pains, nasal congestion, sore throat or diarrhea. These symptoms are usually mild and begin gradually. The disease spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. You are more likely to infect others in the early stages of the disease when you just have mild symptoms; therefore early self-isolation is very important. If you do not have symptoms, but have been exposed to an infected person, self-quarantine for 14 days. The goal of the self-quarantine is to prevent transmission. Since people who become ill with COVID-19 can infect people immediately self-quarantine can prevent some infections from happening. Studies have shown that the COVID-19 virus can survive for up to 72 hours on plastic and stainless steel, less than 4 hours on copper and less than 24 hours on cardboard. In some cases, patients were given an antiretroviral drug: lopinavir boosted with ritonavir (LPV/r). These studies were mostly carried out in HIV-negative individuals.

Keywords: Coronaviruses, COVID-19, Origin, Outbreak Spread.

ARTICLE

Corona represents crown-like spikes on the outer surface of the virus thus; it was named as a coronavirus. Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length. The severe acute respiratory syndrome coronavirus (SARS-CoV), H5N1

influenza A, H1N1 2009 and Middle East respiratory syndrome coronavirus (MERS-CoV) cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality. These viruses were thought to infect only animals until the world witnessed a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, in China. This virus was reported to be a member

of the β group of coronaviruses. The novel virus was named as Wuhan coronavirus or 2019 novel coronavirus (2019-nCoV) by the Chinese researchers.

HISTORY

There are various theories about where the very first case may have originated. The first known case may trace back to 1 December 2019 in Wuhan Hubei, China. Within a month, the number of coronavirus cases in Hubei gradually increased. According to official Chinese sources these were mostly linked to the Huanan sea food market, which also sold live animals, and one theory is that the virus came from one of these animals. A pneumonia cluster of unknown cause was observed on 26 December and treated by the doctor in Hubei Provincial Hospital, On 30 December; a group of doctors at Wuhan Central Hospital alerted their colleagues of a "SARS-like coronavirus".

During the early stages of the outbreak, the number of cases doubled approximately every seven and a half days. In early and mid-January 2020, the virus spread to other Chinese provinces helped by the Chinese New Year migration and Wuhan being a transport hub and major rail interchange. On 20 January, China reported nearly 140 new cases in one day, including two people in Beijing and one in Shenzhen Later official data shows 6,174 people had already developed symptoms by then, and more may have been infected. A report in the lancet on 24 January indicated human transmission, strongly recommended personal protective equipment for health workers, and said testing for the virus was essential due to its "pandemic potential". On 30 January, the WHO declared that the coronavirus was a public health emergency for international concern

By 26 March, the United States had overtaken China and Italy with the highest number of confirmed cases in the world corona virus genome indicates the majority of COVID-19 cases in New York came from European travellers, rather than directly from China or any other Asian country.

ORIGIN

Based on virus genome sequencing results and evolutionary analysis, bat has been suspected as natural host of virus origin, and SARS-CoV-2 might be transmitted from bats via unknown intermediate hosts to infect humans. It is clear now that SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV to infect humans. Several studies suggested that bat may be the potential reservoir of SARS-CoV-2 suggesting that bat CoV and human.

Epidemiology

Data provided by the WHO Health Emergency Dashboard (March 14, 06.00 am CET) report 142,320 confirmed cases worldwide since the beginning of the epidemic. 5,388 (3.78%) cases have been fatal.

In china, 81,021 (57%) cases confirmed clinically and, in the laboratory, and 3,173 deaths are reported. In addition to China, there are 61,299 confirmed cases in 129 other countries. The countries with most cases are Italy (17,660) and the Islamic Republic of Iran (11,364). The epidemiological scenario, therefore, has drastically changed, as on March 3 about 92% (79,968) of the confirmed cases were recorded in China, where almost all the deaths were also recorded (2,873, 96.5%). Of note, the "confirmed" cases reported between February 13, 2020, and February 19, 2020, include both laboratory-confirmed and clinically diagnosed patients from the Hubei province.

The most up-to-date source for the epidemiology of this emerging pandemic can be found at the following sources:

- The WHO Novel Coronavirus (COVID-19) Situation Board
- The Johns Hopkins Centre for Systems Science and Engineering site for Coronavirus Global Cases COVID-19, which uses openly public sources to track the spread of the epidemic.

Sex differences

The impact of the pandemic and its mortality rate are different for men and women. Mortality is higher in men in studies conducted in China and Italy. The highest risk for men is in their 50s, with the gap between men and women closing only at 90. In China, the death rate was 2.8 percent for men

and 1.7 percent for women. The exact reasons for this sex-difference are not known, but genetic and behavioral factors could be a reason. Sex-based immunological differences, a lower prevalence of smoking in women, and men developing co-morbid conditions such as hypertension at a younger age than women could have contributed to the higher mortality in men. In Europe, of those infected with COVID-19, 57% were men; of those infected with COVID-19 who also died, 72% were men. As of April 2020, the U.S. government is not tracking sex-related data of COVID-19 infections. Research has shown that viral illnesses like Ebola, HIV, influenza, and SARS affect men and women differently. A higher percentage of health workers, particularly nurses, are women, and they have a higher chance of being exposed to the virus.

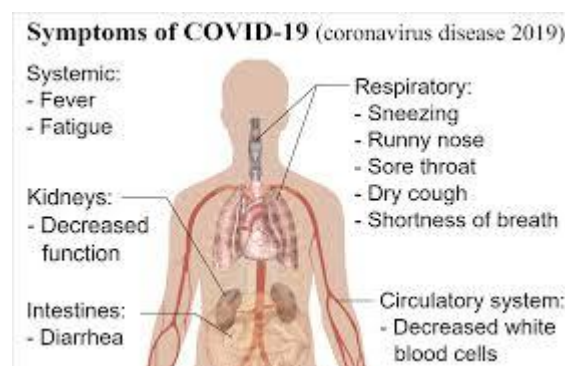
PATHOGENESIS

ACE2, found in the lower respiratory tract of humans, is known as cell receptor for SARS-CoV and regulates both the cross-species and human-to-human transmission. The virion S-glycoprotein on the surface of coronavirus can attach to the receptor, ACE2 on the surface of human cells. S glycoprotein includes two subunits, S1 and S2. S1 determines the virus-host range and cellular tropism with the key function domain – RBD, while S2 mediates virus-cell membrane fusion by

two tandem domains, heptad repeats (HR1) and HR2. After membrane fusion, the viral genome RNA is released into the cytoplasm, and the uncoated RNA translates two polyproteins, pp1a and pp1ab, which encode non-structural proteins, and form replication-transcription complex (RTC) in double-membrane vesicle. Lastly, the virion-containing vesicles fuse with the plasma membrane to release the virus.

SIGNS AND SYMPTOMS

The most common symptoms of COVID-19 are fever, dry cough, and tiredness. Some patients may have aches and pains, nasal congestion, sore throat or diarrhea. These symptoms are usually mild and begin gradually. Some people become infected but only have very mild symptoms. Most people (about 80%) recover from the disease without needing hospital treatment. Around 1 out of every 5 people who gets COVID-19 becomes seriously ill and develops difficulty breathing. Older people, and those with underlying medical problems like high blood pressure, heart and lung problems, diabetes, or cancer, are at higher risk of developing serious illness. However, anyone can catch COVID-19 and become seriously ill. Even people with very mild symptoms of COVID-19 can transmit the virus. People of all ages who experience fever, cough and difficulty breathing should seek medical attention.



TRANSMISSION

People can catch COVID-19 from others who have the virus. The disease spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. These

droplets are relatively heavy, do not travel far and quickly sink to the ground. People can catch COVID-19 if they breathe in these droplets from a person infected with the virus. This is why it is important to stay at least 1 meter (3 feet) away from others. These droplets can land on objects and

surfaces around the person such as tables, doorknobs and handrails. People can become infected by touching these objects or surfaces, then touching their eyes, nose or mouth. This is why it is

important to wash your hands regularly with soap and water or clean with alcohol-based hand rub [1-4].



IMMUNOPATHOLOGY

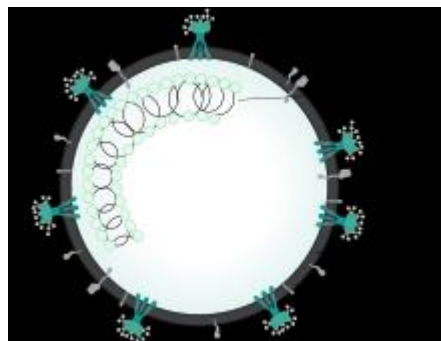
Although SARS-CoV-2 has a tropism for ACE2-expressing epithelial cells of the respiratory tract, patients with severe COVID-19 have symptoms of systemic hyper-inflammation. Clinical laboratory findings of elevated IL-2, IL-7, IL-6, granulocyte macrophage colony stimulating factor (GM-CSF), interferon inducible protein (IP-10), monocyte chemo attractant protein (MCP-1), macrophage inflammatory protein (MIP-1 α), and tumor necrosis factor (TNF- α) indicative of (CRS) suggest an underlying immunopathology.

Additionally, people with 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

Virology

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus, first isolated from three people with pneumonia connected to the cluster of acute respiratory illness cases in Wuhan. All features of the novel SARS-CoV-2 virus occur in related coronaviruses in nature.

SARS-CoV-2 is closely related to SARS-CoV, and is thought to have a zoonotic origin. SARS-CoV-2 genetically clusters with the genus beta coronavirus, and is 96 per cent identical at the whole genome level to other bat coronavirus samples and 92 per cent identical to pangolin coronavirus



DIAGNOSIS

Viral testing

The standard test for current infection with SARS-CoV-2 uses RNA testing of respiratory secretions collected using a nasopharyngeal swab,

though it is possible to test other samples. This test uses real-time RT-PCR which detects presence of viral RNA fragments. A number of laboratories and companies are developing serological tests, which detect antibodies produced by the body in response to infection.

Diagnostic criteria

The viral research institution in China has conducted preliminary identification of the SARS-CoV-2 through the classical Koch's postulates and observing its morphology through electron microscopy. So far, the golden clinical diagnosis method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract samplings by real-time PCR and further confirmed by next-generation sequencing.

In laboratory examination results, most patients had normal or decreased white blood cell counts, and lymphocytopenia. But in the severe patients, the neutrophil count, D-dimer, blood urea, and creatinine levels were higher significantly, and the lymphocyte counts continued to decrease. Additionally, inflammatory factors (interleukin (IL)-6, IL-10, tumor necrosis factor- α (TNF- α) increase, indicating the immune status of patients. The data showed that ICU patients had higher plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), 10 kD interferon-gamma-induced protein (IP-10), monocyte chemo attractant protein-1 (MCP-1), macrophage inflammatory protein 1- α (MIP-1 α), and TNF- α .

Treatment of COVID-19

Current therapies

Antiviral drugs and systemic corticosteroid treatment commonly used in clinical practice previously, including neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc), ganciclovir, acyclovir, and ribavirin, as well as methylprednisolone for influenza virus, are invalid for COVID-19 and not recommended. Remdesivir has been reported to treat the first US case of COVID-19 successfully. Chloroquine is a repurposed drug with great potential to treat COVID-19. Chloroquine has been used to treat malaria for many years, with a mechanism that is not well understood against some viral infections. Chloroquine can inhibit pH-dependent steps of the replication of several viruses with a potent effect on SARS-CoV infection and spread. Moreover, Chloroquine has immunomodulatory effects, suppressing the production/release of TNF- α and IL-6. It also works as a novel class of autophagy

inhibitor, which may interfere with viral infection and replication. A combination of remdesivir and Chloroquine was proven to effectively inhibit the recently emerged SARS-CoV-2 in vitro.

Antiviral therapy

Interferon-alpha (IFN α)

IFN α is a member of the family of type I IFNs that plays an important role in host resistance to viral infection. IFN α suppresses viral infection by directly interfering with replication of the virus and by promoting both innate and adaptive immune responses. In vitro experiments showed that IFN α effectively inhibits the replication of SARS-CoV. It has also been reported that cynomolgus monkeys are protected from infection with SARS CoV by treatment with IFN α . Moreover, the therapeutic benefit of synthetic recombinant IFN α for patients with SARS was demonstrated in a pilot clinical trial. Thus, IFN α should be considered a candidate drug for COVID-19 therapy.

Lopinavir/ritonavir (Kaletra)

Lopinavir/ritonavir was first known as a protease inhibitor that interferes with the replication and synthesis of human immunodeficiency virus (HIV), leading to the production of immature, non-infectious virus particles. It has been reported that ritonavir and lopinavir can bind to the endopeptidase C30 of SARS-CoV-2 protease as evaluated by molecular models. This suggests that lopinavir/ritonavir may exert an antiviral effect by inhibiting protein synthesis of SARS-CoV-2. In addition, several lines of evidence showed that treatment with lopinavir/ritonavir alone or in combination with other antiviral drugs was shown to improve the outcome of severe patients with SARS or MERS by ameliorating ARDS. SARS-CoV-2 is similar to these two viruses, may have a beneficial effect on COVID-19.

Ribavirin

Ribavirin is a nucleoside analogue with broad antiviral activity. It can prevent the replication of RNA and DNA viruses by suppressing the activity of inosine monophosphate dehydrogenase, which is required for the synthesis of guanosine triphosphate (GTP). Ribavirin was widely used to treat SARS patients with or without concomitant use of steroids

during the outbreak of SARS in Hong Kong. Thus, ribavirin could be considered as a treatment option for COVID-19 patients.

Chloroquine

Chloroquine is a widely used antimalarial and autoimmune disease drug. Recently, Chloroquine has been reported as a potential broad-spectrum antiviral drug. Research found that Chloroquine effectively suppresses the recently emerged novel CoV (SARS-CoV-2) in vitro. Chloroquine is a cheap and safe drug that has been used for more than 70 years and thus it is potentially clinically applicable against COVID-19.

Arbidol (umifenovir)

Arbidol is an antiviral drug against influenza infection that is widely used in Russia and China. Arbidol and arbidol mesylate were shown to have a potent inhibitory effect in reducing the reproduction of SARS-CoV in vitro. Case reports and case series revealed that arbidol alone or combined with antiviral drugs produced certain benefits in the treatment of COVID-19 pneumonia. Currently, many randomized clinical controlled trials are being carried out

Remdesivir

The nucleoside analogue remdesivir (GS-5734) was reported to inhibit SARS-CoV and MERS-CoV in vivo. More recently, an in vitro study showed that remdesivir potentially blocked SARS-CoV-2 infection at low-micro molar concentrations and showed a high selectivity index. In addition, the first case of SARS-CoV-2 infection in the USA was treated with intravenous remdesivir when the patient's condition deteriorated. Although remdesivir has some benefits for the treatment of COVID-19 pneumonia, randomized controlled trials are still required to determine its efficacy and safety.

Taken together, these antiviral drugs may be promising treatment options for the treatment of COVID-19. However, there are also a few points worth noting here:

- The potential interaction of these antiviral drugs with other therapeutic drugs should be considered;
- Adverse reactions caused by lopinavir/ritonavir, such as diarrhea, nausea, vomiting and liver damage, should be also considered;

- It is not recommended to use three or more antiviral drugs at the same time, and the use of related drugs should be stopped when there are intolerable side effects; and
- Further evaluation of the efficacy of current antiviral drugs in clinical applications is needed.

Management

People are managed with supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs. The CDC recommends that those who suspect they carry the virus wear a simple face mask. Extracorporeal membrane oxygenation (ECMO) has been used to address the issue of respiratory failure, but its benefits are still under consideration. Personal hygiene and a healthy lifestyle and diet have been recommended to improve immunity. Supportive treatments may be useful in those with mild symptoms at the early stage of infection.

The WHO, the Chinese national organization, and the United States' national institute of health have published recommendations for taking care of people who are hospitalized with COVID-19.

Prevention

Preventive measures are the current strategy to limit the spread of cases. Because an epidemic will increase as long as R_0 is greater than 1 (COVID-19 is 2.2), control measures must focus on reducing the value to less than 1.

Preventive strategies are focused on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient. For instance, droplet, contact, and airborne precautions should be adopted during specimen collection, and sputum induction should be avoided. The WHO and other organizations have issued the following general recommendations:

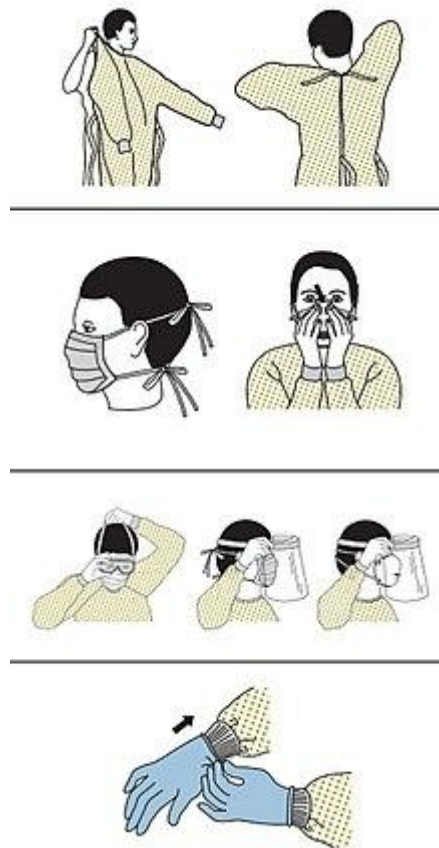
- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.

- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen, in particular, in emergency medicine departments, the application of strict hygiene measures for the prevention and control of infections.
- Individuals that are immune compromised should avoid public gatherings.

The most important strategy for the people to undertake is to frequently wash their hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment.

Healthcare workers caring for infected individuals should utilize contact and airborne precautions to include PPE such as N95 or FFP3 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.

Meanwhile, scientific research is growing to develop a coronavirus vaccine. In recent days, China has announced the first animal tests, and researchers from the University of Queensland in Australia have also announced that, after completing the three-week in vitro study, they are moving on to animal testing. Furthermore, in the U.S., the National Institute for Allergy and Infectious Diseases (NIAID) has announced that a phase 1 trial has begun for a novel coronavirus immunization.



CONCLUSION

Conclusion and perspective

The novel coronavirus originated from the Hunan seafood market at Wuhan, China where bats, snakes, raccoon dogs, palm civets, and other animals are sold, and rapidly spread up to 109 countries. The zoonotic source of SARS-CoV-2 is

not confirmed, however, sequence-based analysis suggested bats as the key reservoir. DNA recombination was found to be involved at spike glycoprotein which assorted SARS-CoV (CoVZXC21 or CoVZC45) with the RBD of another Beta CoV, thus could be the reason for cross-species transmission and rapid infection. According to phylogenetic trees, SARS-CoV is

closer to SARS-like bat CoVs. Until now, no promising clinical treatments or prevention strategies have been developed against human coronaviruses. However, the researchers are working to develop efficient therapeutic strategies to cope with the novel coronaviruses. Various broad-spectrum antivirals previously used against influenza, SARS and MERS coronaviruses have been evaluated either alone or in combinations to treat COVID-19 patients, mice models, and clinical isolates. Remdesivir, Lopinavir, Ritonavir, and Oseltamivir significantly blocked the COVID-19 infection in infected patients. It can be concluded that the homologous recombination event at the S protein of RBD region enhanced the transmission ability of the virus. While the decision of bring back the nationals from infected area by various countries and poor screening of passengers, become the leading cause of spreading virus in others countries.

Most importantly, human coronaviruses targeting vaccines and antiviral drugs should be designed that could be used against the current as well as future epidemics. There are many companies working for the development of effective SARS-CoV-2 vaccines, such as Modern Therapeutics, Innova Pharmaceuticals, Novavax, Vir Biotechnology, Stermirna Therapeutics,

Johnson & Johnson, VIDO-InterVac, GeoVax-BravoVax, Clover Biopharmaceuticals, CureVac, and Codagenix. But there is a need for rapid human and animal-based trails as these vaccines still require 3–10 months for commercialization. There must be a complete ban on utilizing wild animals and birds as a source of food. Beside the development of most efficient drug, a strategy to rapidly diagnose SARS-CoV-2 in suspected patient is also required. The signs and symptoms of SARS-CoV-2 induced COVID-19 are a bit similar to influenza and seasonal allergies (pollen allergies). Person suffering from influenza or seasonal allergy may also exhibit temperature which can be detected by thermo-scanners; hence the person will become suspected. Therefore, an accurate and rapid diagnostic kit or meter for detection of SARS-CoV-2 in suspected patients is required, as the PCR based testing is expensive and time consuming. Different teams of Chinese doctors should immediately sent to European and other countries, especially Spain and Italy to control the over spread of COVID-19, because Chinese doctors have efficiently controlled the outbreak in china and limited the mortality rate to less than 3% only. The therapeutic strategies used by Chinese, should also be followed by other countries.

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