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Review Article

COVID-19: A Global Pandemic of 21st Century

Prabhakar Budholiya*, Abdul Wajid Ali, Deepshikha Gunwan, Sana Sahil, C.K. Tyagi, Hemant Sharma

College of Pharmacy Sri Satya Sai University of Technology and Medical Sciences, Sehore (M.P.), India

ABSTRACT

In last of 2019, the Centers for Disease Control and Prevention started monitoring the outbreak of a new corona virus, SARS-CoV-2, which causes the respiratory illness now known as COVID-19. Authorities first identified the virus in Wuhan, China. More than 82542 case of Corona virus in China at 31 March 2020. Health authorities have identified many other people with COVID-19 around the world. On 31 March 2020, the virus spread more than 750890 People in the World. The World Health Organization (WHO) has declared a public health emergency relating to COVID-19. Since then, this strain has been diagnosed in several residents of world. The CDC have advised that it is likely to spread to more people. COVID-19 has affected at least 213 countries or territories or areas. The first people with COVID-19 had links to an animal and seafood market. This fact suggested that animals initially transmitted the virus to humans. However, people with a more recent diagnosis had no connections with or exposure to the market, confirming that humans can pass the virus to each other. Corona viruses will infect most people at some time during their lifetime. Corona viruses can mutate effectively, which makes them so contagious. Information on the virus is scarce at present. In the past, respiratory conditions that develop from corona viruses, such as SARS and MERS, have spread through close contacts. On 17 February 2020, the Director-General of the WHO presented at a media briefing the following updates on how often the symptoms of COVID-19.However, while some viruses are highly contagious, it is less clear how rapidly corona viruses will spread. Symptoms vary from person-to-person with COVID-19. It may produce few or no symptoms. However, it can also lead to severe illness and may be fatal. On 11 March 2020, WHO declared Novel Corona virus Disease (COVID-19) outbreak as a Pandemic.

Keywords: WHO, ICMR, SARS-CoV-2, Bats, Wuhan City, Pneumonia, Respiratory Infection, Pandemic

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***Address for Correspondence:**

Prabhakar Budholiya, College of Pharmacy Sri Satya Sai University of Technology and Medical Sciences, Sehore (M.P.), India

Introduction

In end of November and Starting of December 2019, few case of unknown Respiratory Infection was reported in Wuhan and Hubei, China. Its clinical characteristics are very similar to those of viral pneumonia. After analysis on respiratory samples, PRC Centers for Disease Control experts declared that the pneumonia, later known as novel corona virus pneumonia, was caused by novel corona virus[1]. WHO officially named the disease COVID-19. COVID-19 is a disease caused by a new strain of corona virus. 'CO' stands for corona, 'VI' for virus, and 'D' for disease. Formerly, this disease was referred to as '2019 novel corona virus' or '2019-nCoV.'The COVID-19 virus is a new virus linked to the same family of viruses as Severe Acute Respiratory Syndrome (SARS) and some types of common cold. International Committee on Taxonomy of Viruses (ICTV) named the virus severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). On 11 March 2020, WHO declared Novel Corona virus Disease (COVID-19) outbreak as a pandemic and reiterated the call for countries to take immediate actions and scale up response to treat, detect and reduce transmission to save people's lives. This virus belongs to β–corona virus, a large class of viruses prevalent in nature. Similar to other viruses, SARS-CoV-2 has many potential natural host, Intermediate host and final host. This poses great challenges to prevention and treatment of virus infection. this virus has high transmissibility and infectivity, but low mortality rate Compared with SARS and MERS,[2]. Genome analysis of novel corona virus sequences revealed that the complete genome sequence recognition rates of SARS-CoV and bat SARS corona virus (SARSr-CoV-RaTG13) were 79.5% and 96% respectively[3]. It implies that the corona virus might originate from bat. On 29 February 2020, data published by World Health Organization showed that, since 31 March 2020 when the first case was reported, 750890 cases were Globally confirmed to be infected by novel corona virus and 36405 individuals were deaths in total[4]. In the meantime, 1071 cases were confirmed, 29 were died in India[4,5]. It posed a great threat to global public health. This report reviews the genetic structure, infection source, transmission route, pathogenesis, clinical characteristics, and treatment and prevention of the SARS-CoV-2, so that it can provide references for follow-up research, prevention and

treatment, and may help readers to have the latest understanding of this new infectious disease.

History

The history of human corona viruses began in 1965 when Tyrrell and Bynoe[6] found that they could passage a virus named B-814. 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 in tranasally 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[7] 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[8] 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[9] 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.

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.[10,11] 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.[12]

Ongoing research using serologic techniques has resulted in a considerable amount of information regarding the epidemiology of the human respiratory corona viruses. It was found that in temperate climates, respiratory corona virus infections occur more often in the winter and spring than in the summer and fall. Data revealed that corona virus infections contribute as much as 35% of the total respiratory viral activity during epidemics. Overall, he proportion of adult colds produced by corona viruses was estimated at 15%.[13]

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.[14] 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.[15] Infection could occur at any age, but it was most common in children.

Although the extensive focus placed exclusively on strains 229E and OC43, it was clear that there were other corona virus strains as well. As shown by Bradburne,[16] corona virus strain B814 was not serologically identical with either OC43 or 229E. Contributing to the various strain differences in the family of coronaviruses, McIntosh et al[17] found that 3 of the 6 strains previously identified were only distantly related to OC43 or 229E.

Epidemiologic and volunteer inoculation studies found that respiratory coronaviruses were associated with a variety of respiratory illnesses; however, their pathogenicity was considered to be low.[7,13,18,19] The predominant illness associated with infections was an upper respiratory infection with occasional cases of pneumonia in infants and young adults.[20,21] These viruses were also shown to be able to produce asthma exacerbations in children as well as chronic bronchitis in adults and the elderly.[22,23]

While research was proceeding to explore the pathogenicity and epidemiology of the human corona viruses, the number and importance of animal corona viruses were growing rapidly. Corona viruses were described that caused disease in multiple animal species, including rats, mice, chickens, turkeys, calves, dogs, cats, rabbits and pigs. Animal studies included, but were not limited to, research that focused on respiratory disorders. Study focus included disorders such as gastroenteritis, hepatitis and encephalitis in mice; pneumonitis and sialodacryoadenitis in rats; and infectious peritonitis in cats. Interest peaked particularly regarding areas of encephalitis produced by mouse hepatitis virus and peritonitis produced by infectious peritonitis virus in cats. Pathogenesis of these disease states was various and complex, demonstrating that the genus as a whole was capable of a wide variety of disease mechanisms.[25] Human and animal corona viruses were segregated into 3 broad groups based on their antigenic and genetic makeup. Group I contained virus 229E and other viruses, group II contained virus OC43 and group III was made up of avian infectious bronchitis virus and a number of related avian viruses.[26]

Types of Corona Virus

Different types of human corona viruses vary in how severe the resulting disease becomes, and how far they can spread. Physician currently recognize seven types of corona virus that can infect humans.

Common types

1. 229E (alpha coronavirus)

2. NL63 (alpha coronavirus)

3. OC43 (beta coronavirus)

4. HKU1 (beta coronavirus)

Rarer strains that cause more severe complications include MERS-CoV, which causes Middle East respiratory syndrome (MERS), and SARS-CoV, the virus responsible for severe acute respiratory syndrome (SARS). In 2019, a dangerous new strain called SARS-CoV-2 started circulating, causing the disease COVID-19[27].

Taxonomy

Corona viruses belong to the sub-family Coronavirinae in the family Coronaviridae. The scientific name for coronavirus is *Orthocoronavirinae* or *Coronavirinae.*[28,29,30] Corona viruses belong to the family of *Coronaviridae,* order *Nidovirales,* and realm *Riboviria*[31,32] They are divided into alpha corona viruses and betacoronaviruses which infect mammals – and gamma corona viruses and delta corona viruses which primarily infect birds.[33]

- Genus: ***Alphacoronavirus***

- Species: *Human coronavirus 229E*, *Human coronavirus NL63*, *Miniopterus bat coronavirus 1*, *Miniopterus bat coronavirus HKU8*, *Porcine epidemic diarrhea virus*, *Rhinolophus bat coronavirus HKU2*, *Scotophilus bat coronavirus*

- Genus ***Betacoronavirus***;[51] type species: *Murine coronavirus*

- Species: *Betacoronavirus 1* (*Bovine Coronavirus*, *Human coronavirus OC43*), *Human coronavirus HKU1*, *Murine coronavirus*, *Pipistrellus bat coronavirus HKU5*, *Rousettus bat coronavirus HKU9*, *Severe acute respiratory syndrome-related coronavirus* (*SARS-CoV*, *SARS-CoV-2*), *Tylonycteris bat coronavirus HKU4*, *Middle East respiratory syndrome-related coronavirus*, *Hedgehog coronavirus 1* (EriCoV)

- Genus ***Gammacoronavirus***; type species: *Infectious bronchitis virus*

- Species: *Beluga whale coronavirus SW1*, *Infectious bronchitis virus*

- Genus ***Deltacoronavirus***; type species: *Bulbul coronavirus HKU11*

- Species: *Bulbul coronavirus HKU11*, *Porcine coronavirus HKU15*

Outbreaks of Human Corona Virus Diseases

Severe acute respiratory syndrome (SARS)

In 2003, following the outbreak of severe acute respiratory syndrome (SARS) which had begun the prior year in Asia, and secondary cases elsewhere in the world, the World Health Organization (WHO) issued a press release stating that a novel corona virus identified by a number of laboratories was the causative agent for SARS. The virus was officially named the SARS corona virus (SARS-CoV). More than 8,000 people were infected, about ten percent of whom died.[34]

Middle East respiratory syndrome (MERS)

In September 2012, a new type of corona virus was identified, initially called Novel Corona virus 2012, and now officially named Middle East respiratory syndrome corona virus (MERS-CoV).[35,36] The World Health Organization issued a global alert soon after.[37] The WHO update on 28 September 2012 said the virus did not seem to pass easily from person to person.[38] However, on 12 May 2013, a case of human-to-human transmission in France was confirmed by the French Ministry of Social Affairs and Health.[39] In addition, cases of human-to-human transmission were reported by the Ministry of Health in Tunisia. Two confirmed cases involved people who seemed to have caught the disease from their late father, who became ill after a visit to Qatar and Saudi Arabia. Despite this, it appears the virus had trouble spreading from human to human, as most individuals who are infected do not transmit the virus.[40] By 30 October 2013, there were 124 cases and 52 deaths in Saudi Arabia.[41]

After the Dutch Erasmus Medical Centre sequenced the virus, the virus was given a new name, Human Corona virus—Erasmus Medical Centre (HCoV-EMC). The final name for the virus is Middle East respiratory syndrome corona virus (MERS-CoV). The only U.S. cases (both survived) were recorded in May 2014.[42]

In May 2015, an outbreak of MERS-CoV occurred in the Republic of Korea, when a man who had traveled to the Middle East, visited four hospitals in the Seoul area to treat his illness. This caused one of the largest outbreaks of MERS-CoV outside the Middle East.[43]As of December 2019, 2,468 cases of MERS-CoV infection had been confirmed by laboratory tests, 851 of which were fatal, a mortality rate of approximately 34.5%.[44]

Clinical Symptoms

Dry Cough, Cold, Sore Throat, High Fever (102^0C-103^0C) these symptoms usually Show in from 2–4 days after a corona virus infection. However, symptoms vary from person-to-person, and some forms of the virus can be fatal. [45,46]

Symptoms include:

1. Sneezing
2. Runny nose
3. Dry Cough
4. Watery diarrhea
5. Fever
6. Sore Throat
7. Exacerbated asthma
8, Breathlessness

It may take 2–14 days for a person to notice symptoms after infection.

Other symptoms can include:[47,48]

- Tiredness
- Aches
- Headache
- Vomiting
- Loss of smell or taste
- Fatigue
- Ongoing chest pain or pressure
- confusion
- Can't wake up fully
- Bluish lips or face

If you're infected, symptoms can show up in as few as 2 days or as many as 14. It varies from person to person. According to researchers in China, these were the most common symptoms among people who had COVID-19 [49,50]

- Fever 83%-99%
- Cough 59%-82%
- Fatigue 44%-70%
- Lack of appetite 40%-84%
- Shortness of breath 31%-40%
- Mucus/phlegm 28%-33%
- Body aches 11%-35%

Corona viruses can spread in the following ways:

Coughing and sneezing without covering the mouth can disperse droplets into the air. Touching or shaking hands with a person who has the virus can pass the virus between individuals. Making contact with a surface or object that has the virus and then touching the nose, eyes, or mouth. Some animal corona viruses, such as feline corona virus (FCoV), may spread through contact with feces. However, it is unclear whether this also applies to human corona viruses. The National Institutes of Health (NIH) suggest that several

groups of people have the highest risk of developing complications due to COVID-19.

These groups include:

1. Young children

2. People aged 65 years or older

3. Women who are pregnant

Sneezing can also help prevent transmission. It is important to dispose of any tissues after use and maintain hygiene around the home.

People can catch COVID-19 from others who have the virus. The disease can spread from person to person through small droplets from the nose or mouth which are spread when a person with COVID-19 coughs or exhales. These droplets land on objects and surfaces around the person. Other people then catch COVID-19 by touching these objects or surfaces, then touching their eyes, nose or mouth. People can also catch COVID-19 if they breathe in droplets from a person with COVID-19 who coughs out or exhales droplets. This is why it is important to stay more than 1 meter (3 feet) away from a person who is sick.[51,52]

Prevent the spread of disease

Virus spreads from person to person, it's important to limit your contact with other people as much as possible. Some people work in "essential businesses" that are vital to daily life, such as health care, law enforcement, and public utilities. Everyone else should stay home as much as you can. You might hear officials use these terms when they talk about staying home[53,54,55]:

• Social distancing or physical distancing, keeping space between yourself and other people when you have to go out

• **Quarantine** , keeping someone home and separated from other people if they might have been exposed to the virus

• **Isolation** , keeping sick people away from healthy people, including using a separate "sick" bedroom and bathroom when possible

Reduce chances of Spreading COVID-19 by taking some simple precautions:

• Regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water.

• Maintain at least 1 metre (3 feet) distance between yourself and anyone who is coughing or sneezing.When someone coughs or sneezes they spray small liquid droplets from their nose or mouth which may contain virus. If you are too close, you can breathe in the droplets, including the COVID-19 virus if the person coughing has the disease.

• Avoid touching eyes, nose and mouth, Hands touch many surfaces and can pick up viruses. Once contaminated, hands can transfer the virus to your eyes, nose or mouth. From there, the virus can enter your body and can make you sick.

• Make sure you, and the people around you, follow good respiratory hygiene. This means covering your mouth and nose with your bent elbow or tissue when you cough or sneeze. Then dispose of the used tissue immediately.

• Stay home if you feel unwell. If you have a fever, cough and difficulty breathing, seek medical attention and call in advance. Follow the directions of your local health authority.

• Keep up to date on the latest COVID-19 hotspots (cities or local areas where COVID-19 is spreading widely). If possible, avoid traveling to places – especially if you are an older person or have diabetes, heart or lung disease.

Protection measures for persons who are in or have recently visited (past 14 days) areas where COVID-19 is spreading

• Follow the guidance outlined above (Protection measures for everyone)

• Self-isolate by staying at home if you begin to feel unwell, even with mild symptoms such as headache, low grade fever (37.3 C or above) and slight runny nose, until you recover. Avoiding contact with others and visits to medical facilities will allow these facilities to operate more effectively and help protect you and others from possible COVID-19 and other viruses.

• If you develop fever, cough and difficulty breathing, seek medical advice promptly as this may be due to a respiratory infection or other serious condition. Call in advance and tell your provider of any recent travel or contact with travelers.

Corona virus life cycle Steps

1. Attachment and entry

2. Replicase protein expression

3. Replication and transcription

4. Assembly and release.

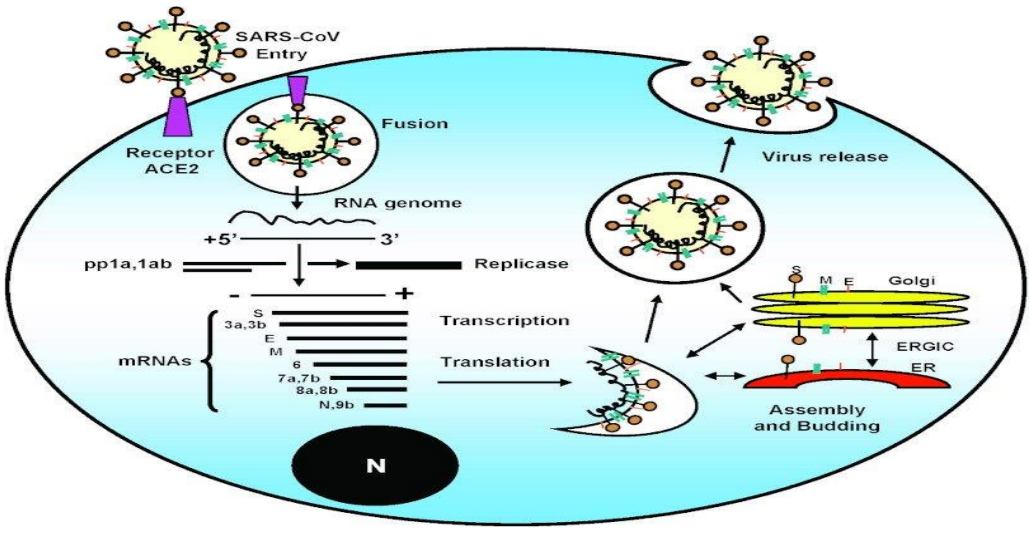

Figure 1: Life cycle of Corona virus

Genetic structure and pathogenic mechanism of SARS-CoV-2

Corona virus (COV) is a single strand RNA virus with a diameter of 80-120nm. It is divided into four types: α-corona virus (α-COV), β-corona virus (β-COV), δ-corona virus (δ-COV) and γ – corona virus (γ-COV)[56]. Six corona viruses were previously known to cause disease in humans, SARS-CoV-2 is the seventh member of the corona virus family that infects human beings after SARS-CoV and MERS-CoV[57].SARS-CoV-2, like SARS-CoV and MERS-CoV, belongs to β-corona virus. The genome sequence homology of SARS-CoV-2 and SARS is about 79%, the 2019-nCoV is closer to the SARS-like bat CoVs (MG772933) than the SARS-CoV[58], which is descended from SARS-like bat CoVs. Interestingly, for high similarity of receptor-binding domain (RBD) in Spike-protein, several analyses reveal that SARS-CoV-2 uses angiotension-converting enzyme 2 (ACE2) as receptor, just like as SARS-CoV[59]. Corona virus mainly recognizes the corresponding receptor on the target cell through the S protein on its surface and enters into the cell, then causing the occurrence of infection. A structure model analysis shows that SARS-CoV-2 binds ACE2 with above 10 folds higher affinity than SARS-CoV, but higher than the threshold required for virus infection[60]. The detailed mechanism about whether the SARS-CoV-2 would infect humans via binding of S-protein to ACE2, how strong the interaction is for risk of human transmission, and how SARS-CoV-2 causes pathological mechanisms of organs damage remains unknown, which need more studies to elaborate. These results further explains the more rapid transmission capability of the SARS-CoV-2 in humans than SARS-CoV, and the number of confirmed COVID-19 much higher than people with SARS-CoV infection. Considering the higher affinity of SARS-CoV-2 binds ACE2, soluble ACE2 might be a potential candidate for COVID-19 treatments.

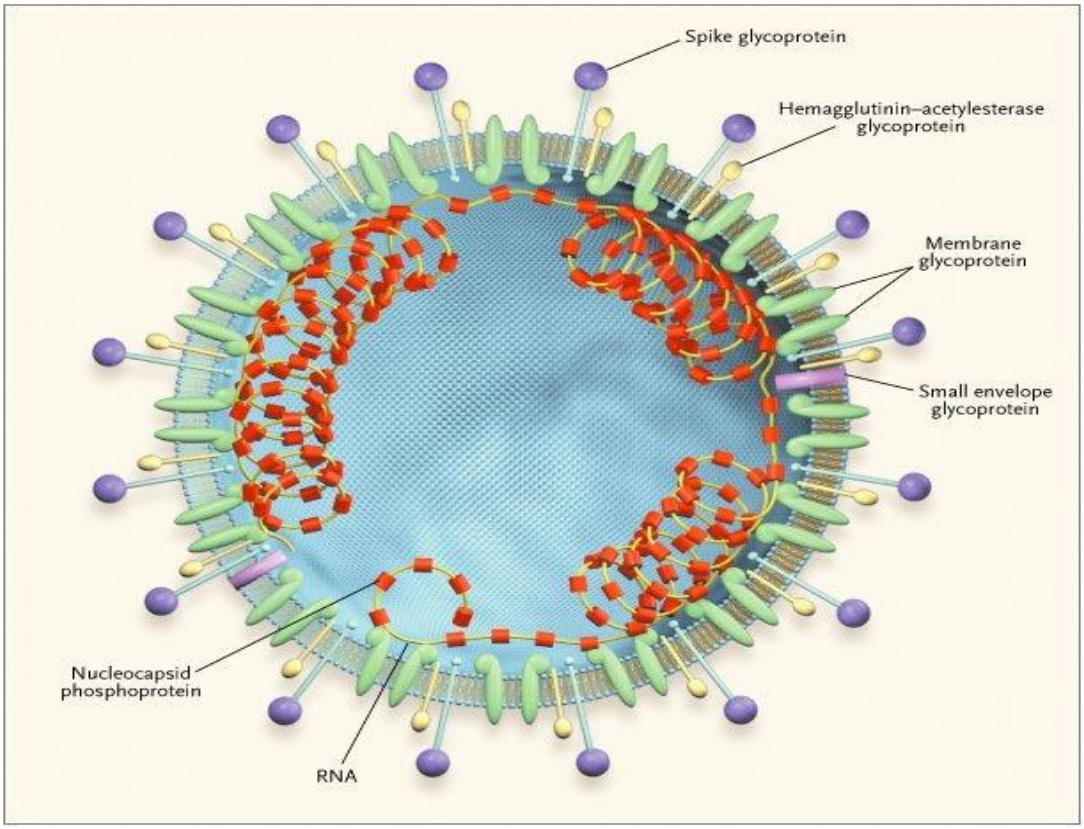

Figure 2: Genetic structure of corona Virus

Prevalence of SARS-CoV-2

Basic Reproduction Number (R_0) refers to the average amount of secondary infection that patients may produce in completely susceptible population without intervention[61]. The estimation of R_0 varies among different research teams and is updated as more information is exposed. Wu, JT, Leung et al. of York University estimated the R_0 of novel corona virus to be 2.47-2.86[62] using the SEIR model. Majumder of Boston Children's Hospital and his colleagues adjusted R_0 to be 2.0-3.3 using the IDEA model[63]. The R_0 value of other viruses of β – corona virus, such as SARS-CoV, is estimated to be 2.2-3.6[64]. The R_0 value of MERS-CoV is estimated to be 2.0-6.7[65]. These indicate that SARS-CoV-2 has relatively high transmissibility. Population is generally susceptible to SARS-CoV-2, the median age was 47.0 years (IQR, 35.0 to 58.0), 87% case patients were 30 to 79 years of age, and 3% were age 80 years or older, and the number of female patients was 41.9%[66,67]. Most cases were diagnosed in Hubei Province, China (75%). 81% cases were classified as mild, 14% cases were severe, and 5% were critical. The overall case-fatality rate (CFR) was 2.3%, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR[68]. This implies that elderly male citizens are more susceptible to this corona virus as compared with other groups, and this virus is more likely to affect elderly male citizens with chronic underlying diseases.[69] In summary, COVID-19 is high in prevalence and population is generally susceptible to such virus, and COVID-19 rapidly spread from a single Wuhan city to the entire country in just 30 days. So that prompt measures should be taken to control the spread of the disease.

Clinical characteristics of SARS-CoV-2 infection

COVID-19 produces an acute viral infection in humans with median incubation period was 3.0 days [66], which is similar to the SRAS with an incubation period ranging from 2–10 days[82]. The presenting features of COVID-19 infection in adults are pronounced. The presenting features in adults are pronounced. The most common clinical symptoms of SARS-CoV-2 infection were fever (87.9%), cough (67.7%), fatigue (38.1%), whereas diarrhea (3.7%) and vomiting (5.0%) were rare[66,83] which were similar to others corona virus. Most patients had some degree of dyspnoea at presentation, because the time from onset of symptoms to the development of acute respiratory distress syndrome (ARDS) was only 9 days among the initial patients with COVID-19 infection[1]. Moreover, severe patients are prone to a variety of complications, including acute respiratory distress syndrome, acute heart injury and secondary infection[67]. There are already some evidences that COVID-19 can cause damage to tissues and organs other than the lung. In a study of 214 COVID-19 patients,[69] (36.4%) patients had neurological manifestations[84]. In addition, there is already evidence of ocular surface infection in patients with COVID-19, and SARS-CoV-2 RNA was detected in eye secretions of patient[85]. Some COVID-19 patients have arrhythmia, acute heart injury, impaired renal function, and abnormal liver function (50.7%) at admission[1,86,87]. A case report of the pathological manifestations of a patient with pneumonia showed moderate microvesicular steatosis in his liver tissue[88]. Besides, tissue samples of stomach, duodenum, and rectal mucosa were confirmed positive for SARS-CoV-2 RNA[90]. In general, the radiographical features of corona virus are similar to those found in community-acquired pneumonia caused by other organisms[90]. Chest CT scan is important tool to diagnose this pneumonia. Nevertheless, several typical imaging features are frequently observed in COVID-19 pneumonia, including the predominant groundglass opacity (65%), consolidations (50%), smooth or irregular interlobular septal thickening (35%), air bronchogram (47%), and thickening of the adjacent pleura (32%), with predominantly peripheral and lower lobe involvement[91]. A recent study reported that most patients (90%) had bilateral chest CT findings and the sensitivity of chest CT to suggest COVID-19 was 97%[85]. Combining chest CT imaging features with clinical symptom and laboratory test could facilitate early diagnosis of COVID-19 pneumonia.

Laboratory examination revealed that 82.1% of patients was lymphopenia and 36.2% of patients was thrombocytopenia. Most patients had normal leukocytes, but leukopenia was observed in 33.7% of patients. In addition, most patients demonstrated elevated levels of C-reactive protein（CRP）, lactate dehydrogenase (LDH）and creatinine kinase（CK）, but minority of patients had elevated transaminase, abnormal myocardial enzyme spectrum, or elevated serum creatinine[1,75]. As compared with bacterial pneumonia, patients with SARS-CoV-2 showed lower oxygenation index. Cytokine release syndrome is a vital factor that aggravates disease progression. A higher levels of IL-6 and IL-10, and lower levels of CD4+T and CD8+T are observed in COVID-19 patients parallel with the severity of the disease [92].

Treatment of SARS-CoV-2

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.

On 28 January 2020, the WHO released a document summarizing WHO guidelines and scientific evidence derived from the treatment of previous epidemics from HCoVs. This document addresses measures for recognizing and sorting patients with severe acute respiratory disease; strategies for infection prevention and control; early supportive therapy and monitoring; a guideline for laboratory diagnosis; management of respiratory failure and ARDS; management of septic shock; prevention of complications; treatments; and considerations for pregnant patients.

(A) Antiviral Allopathic treatment

At present, the treatments of patients with SARS-CoV-2 infection are mainly symptomatic treatments. Remdesivir was recently reported as a promising antiviral drug against a wide array of RNA viruses. Holshue et al. for the first time reported that treatment of a patient with COVID-19 used remdesivir and achieved good results[97]. Then, Xiao *et al.* findings reveal that remdesivir effectively in the control of 2019-nCoV infection in vitro. Meanwhile, also found that chloroquine has an immune-modulating activity and could effectively inhibit in this virus in vitro[98] . Clinical controlled trials have shown that Chloroquine was proved to be effective in the treatment of patients with COVID-19[99]. Remdesivir is undergoing a large number of clinical trials in several hospitals, and the final efficacy of the drug is uncertain. Arbidol, a small indole derivative molecule, was found to block viral fusion against influenza A and B viruses and hepatitis C viruses[100] and confirmed to have antiviral effect on SARS-CoV in cell experiment[101], so that it might be a choice for COVID-19 treatment. The randomized controlled study on treatment of novel corona virus by Arbidol and Kaletra undertaken at present showed that Arbidol had better therapeutic effect than Kaletra did and could significantly reduce the incidence of severe cases. Apart from the above, lopinavir/ritonavir, nucleoside analogues, neuraminidase inhibitors, remdesivir, and peptide EK1 could also be the choices of antiviral drugs for COVID-19 treatment[103]

(B) Ayurvedic Treatment

The Treatment of patients Show SARS-CoV-2 mild Symptom. Formulations like *Lakshmi Vilas Rasa*[104]*, Pippali rasayana*[105]*, Sanjeevani vati, Chitrakadi vati, Go jihvaadi Kashaya, Vyaghri haritaki, Kantakaari Avaleha, Dashamul kwath, Sitopaladi*[106]*, Talishadi,* and *Yashtimadhu* may be the most suitable drugs to be used at this stage in an integrative model. Population where the moderate to severe symptoms are present and the patients also belong to high risk . These patients require tertiary care from the beginning itself but can also be co-prescribed with Ayurveda medicines in order to reduce the impact of the pathology and to buy more time to have intensive management[107]. Recommended formulations here may include *Pippali rasayana*[105]*, Laghu Vasant Malati, Sanjeevani vati, Tribhuvan keerti rasa*[108]*, Brihata Vata Chintamni rasa, Mrityunjaya rasa,* and *Siddha makardhvaja rasa*. The key criterion for choosing *rasa aushadhi* in category 3 and 4 as noted above is the urgency of initiation of therapeutic actions. *Rasaaushadi* are shown to have better bioavailability and absorption through sublingual and oral route accounting to the nano size of their particles[109]. For example, *suvarna bhasma* has been found to get absorbed well through sublingual administration when mixed with black pepper powder and ghee[110].

(C) Homoeopathic Treatment

The Health advisory given by Ministry of AYUSH against corona virus infection included Homoeopathic medicine *Arsenicum album – 30* as a possible preventive for flu like illness such as coronavirus infection.[111] Scientific Advisory

Board considered that the same medicine has been advised for prevention of Influenza Like Illness[112,113]. Arsenic album as one of the constituents in a formulation has been shown to affect HT29 cells and human macrophages. Bryonia, Beryllium, Lobelia purpurescens[114] is another homoeopathic medicine helpful to patient suffer with the flu-like symptoms

(D) Unani Treatment

Unani system of medicine has its roots in ancient Greece, in the teachings of Hippocrates (460–377 BCE). The name Unani reflects its Hellenistic origin and is derived from the Yunan, the ancient name of Greece. Unani medicine flourished to its zenith during medieval ages (500–1500 CE) in the Muslim world, mostly in the Arabian peninsula, Persia, Egypt, Syria, ancient Mesopotamia, etc. Ergo it is also referred to as Greco-Arabian medicine and Persian medicine in different parts of theworld . In India, it is integrated into the national healthcare systemand officially named as Unani medicine. Unanimedicine is based on the Hippocratic concepts of mizaj (temperament) and akhlat (humors). Unani Medicines that may help in the symptomatic management of coronavirus, Drugs prescribed in Unani medicine for nazla-e-wabaiya (epidemic influenza) were Behidana,Unnab, Sapistan, Khaksi, Habb-ul-aas, Tabasheer, Tukhm-e-Kahu, Elwa, Za'fran.

Unani medicine does not mention epidemics and pandemics as separate entities, and a common term 'waba' is used for those diseases which affect a large geographical area. This is probably for two reasons, first and foremost, global communication was not possible in medieval ages like today; and second, travel over very long distances would have rarely occurred, hence the occurrence of a pandemic would have been a remote possibility, practically unlikely[115].

(E) Immuno enhancement therapy

Synthetic recombinant interferon α has proven to be effective in treatment of SARS patients in clinic trials[116]. Pulmonary X-ray abnormal remission time was reduced by 50% in the interferon-treated group compared with the glucocorticoid-treated group alone. Interferon was also found to be an effective inhibitor of MERS-CoV replication[117]. Those findings suggested that interferon could be used in the treatment of COVID-19. Intravenous immunoglobulin might be the safest immune-modulator for long-term use in all ages, and could help to inhibit the production of pro-inflammatory cytokines and increase the production of anti-inflammatory mediators[118]. Moreover, Thymosin alpha-1 (Ta1) can be an immune booster for SARS patients, effectively controlling the spread of disease[119]. Intravenous immunoglobulin and Ta1 may also be considered as therapeutics for COVID-19.

(F) Plasma therapy

When there are no sufficient vaccines and specific drugs, convalescent plasma therapy could be an effective way to alleviate the course of disease for severely infected patients[120]. In a retrospective analysis, convalescent plasma therapy is more effective than severe doses of hormonal shock in patients with severe SARS, reducing mortality and shortening hospital stays[121]. A prospective cohort study by Hung and colleagues showed that for patients with pandemic H1N1 influenza virus infection in 2009, the relative risk of death was significantly lower in patients treated with convalescent plasma[122]. Moreover, from the perspective of immunology, most of the patients recovered from COVID-19 would produce specific antibodies against the SARS-CoV-2, and their serum could be used to prevent reinfection. At the same time, antibodies can limit the virus reproduction in the acute phase of infection and help clear the virus, which is conducive to the rapid recovery of the disease[123]. Theoretically, viremia peaks during the first week of most viral infections, and it should be more effective to give recovery plasma early in the disease[123]. Therefore, the plasma of some patients recovered from COVID-19 could be collected to prepare plasma globulin specific to SARS-CoV-2. However, the safety of plasma globulin products specific to SARS-CoV-2 deserves further consideration.

(G) Auxiliary Blood purification treatment

At present, extracorporeal blood purification technology in the treatment of severe NCP patients[92] According to the latest studies[85], ACE2, the key receptor of SARS-CoV-2, is highly expressed in human kidney (nearly 100 times higher than that in lung). Kidney might be main target of attack for novel corona virus. Early continuous blood purification treatment could reduce renal workload and help to promote the recovery of renal function[125]. Most of the severe patients with novel corona virus might suffer from cytokine storm. The imbalance of pro-inflammatory factors and anti-inflammatory factors might cause immune damage. Therefore, blood purification technology could be used to remove inflammatory factors, eliminate cytokine storm, correct electrolyte imbalance, and maintain acid-base balance, to control patient's capacity load in an effective manner[126]. In this logic, the patient's symptoms could be improved and the blood oxygen saturation could be increased.

In summary, the drug treatment for COVID-19 mainly comprised four ways, i.e., antiviral Western medicine, Chinese medicine, immune-enhancement therapy, and viral specific plasma globulin. Machines could be used as auxiliary therapy. However, randomized double-blind large sample clinical trial should be served as the standard to determine whether the antiviral drugs could be used in clinical practice.

(I) Corona virus Vaccine

There's no vaccine, but intense research has been underway around the world since scientists shared the virus' genetic makeup in January 2020. Vaccine testing in humans started with record speed. UK government formed a COVID-19 vaccine taskforce to stimulate British efforts for rapidly developing a vaccine through collaborations of industry, universities, and government agencies across the vaccine development pipeline, including for clinical trial placement at UK hospitals, regulations for approval, and eventual manufacturing.[127] The vaccine development initiatives at the University of Oxford and Imperial College of London.[128,129]

France, CEPI announced a US$4.9 million investment in a COVID-19 vaccine research consortium involving the Institut Pasteur, Themis Bioscience (Vienna, Austria), and the University of Pittsburgh, bringing CEPI's total investment in COVID-19 vaccine development to US$480 million in May.[130,131] In March, the European Commission provided an €80 million investment in CureVac, a German biotechnology company, to develop a mRNA vaccine.[132] Belgium, Norway, Switzerland, Germany, and the Netherlands have been major contributors to the CEPI effort for COVID-19 vaccine research in Europe.[133] U.S. Biomedical Advanced Research and Development Authority (BARDA) a federal agency that funds disease-fighting technology, announced investments of nearly US$1 billion to support American COVID-19 vaccine development, and preparation for manufacturing the most promising candidates. BARDA made a US$483 million investment in the vaccine developer, Moderna and its partner, Johnson & Johnson.[133,134] BARDA has an additional US$4 billion to spend on vaccine development, and will have roles in other American investment for development of six to eight vaccine candidates to be in clinical studies over 2020-21 by companies, such as Sanofi Pasteur and Regeneron.[135] Nine Chinese COVID-19 vaccines in development, involving

1,000 scientists and Chinese research institutes and military hospitals.[136] Three Chinese vaccine companies and research institutes are supported by the government for financing research, conducting clinical trials, and manufacturing the most promising vaccine candidates, while prioritizing rapid evidence of efficacy over safety.[137]

(H) Monoclonal Antibodies

Chunyan Wang et al. were first to report that 47D11 (human) monoclonal antibody that neutralizes SARS-CoV-2. Research reports declaring that the 47D11 binds a conserved epitope on the spike receptor-binding domain and cross-neutralize SARSCoV-2. The cross-reactive nature of 47D11 shows that the antibody is more possible to target the conserved core structure of the S1B receptor binding domain. Hence these neutralizing antibodies can reduce the course of virus action inthe host or defend an uninfected host that is exposed to the virus[138] . Tian et al. reported that the RBD of SARS-Cov-2 differs largely from the SARS-CoV at the C-terminus residues. Their results implied that SARS-CoV specific neutralizing antibodies such as m396, CR3014 that target the receptor-binding domain of SARS-CoV ineffective to bind SARS-Cov-2 spike protein. Their research report stating that the antibody CR3022 completely neutralized both the wild-type SARS-CoV and SARS-Cov-2 at a concentration of 23.5 μg/ml. Tian et al. suggested that CR3022 can be used as a potential therapeutics, alone or in combination with other neutralizing antibodies, for the prevention and treatment of SARS-Cov-2 infections [139].

Monoclonal antibodies could provide a strategy for emergency prophylaxis and SARS-CoV-2 therapy, while alternative and more time consuming development of vaccines and new drugs are underway. As a result, SARS-CoV-2 neutralizing antibodies may be used to prevent infection in people exposed to SARS-CoV-2, such as hospital staff caring for suspected SARS-CoV-2 patients, and may also be used for early treatment of infected individuals to prevent the onset of serious SARS-CoV-2 disease and to reduce the chance of spreading the virus to exposed individuals.

Conclusion

Human history is observing a very strange time fighting an invisible enemy, Over the past 50 years the emergence of many different corona viruses that cause a wide variety of human diseases has occurred. It is likely that these viruses will continue to emerge and to evolve and cause human outbreaks owing to their ability to recombine, mutate, and infect multiple species and cell types. WHO declared Novel Corona virus Disease (COVID-19) outbreak as a pandemic on 11 March 2020. Future research on corona viruses will continue to investigate many aspects of viral Symptom, Spread, Life cycle, replication and pathogenesis. This review provides an insight into the COVID-19 current situation and represents a picture of the current state of the art in terms of public health impact, pathophysiology and clinical manifestations, diagnosis, case management, emergency response and preparedness. Understanding the propensity of these viruses to jump between species, to establish infection in a new host and to identify significant reservoirs of corona viruses will dramatically aid in our ability to predict when and where potential epidemics may occur. As bats seem to be a significant reservoir for these viruses, it will be interesting to determine how they seem to avoid clinically evident disease and become persistently infected. Many of the non-structural and accessory proteins encoded by these viruses remain uncharacterized with no known function, and it will be important to identify mechanisms of action for these proteins as well as defining their role in viral replication and pathogenesis. These article helpful for Identification of corona patient on the basis of Symptom and the best practice for the management and treatment of symptomatic cases & stop Spreading of COVID-19.

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