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COVID-19: Outbreak, Advancements and Possibilities

Fahad Asim[1], Muhammad Sameer Ashaq[1*], Humayun Riaz[2], Syed Atif Raza[3], Abdul Raheem Malik[1], Umer Farooq[4], Rana Khalid Mehmood[4], Syed Ali Faran[4], Muzammil Raza[5]

[1]*Department of Pharmacology, Rashid Latif College of Pharmacy, Lahore, Pakistan*

[2]*Rashid Latif College of Pharmacy, Lahore, Pakistan*

[3]*Department of Pharmaceutics, Punjab University College of Pharmacy, Pakistan*

[4]*Department of Pharmaceutics, Rashid Latif College of Pharmacy, Lahore, Pakistan*

[5]*Department of Pharmaceutical Chemistry, Rashid Latif College of Pharmacy, Lahore, Pakistan*

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Abstract

Coronaviruses are diverse, positive-natured viruses containing RNA, which belong to a family *Coronaviridae,* that cause various diseases in humans, birds and several other wild animals, causing gastrointestinal, nervous system and respiratory tract infections. COVID-19 pandemic started from Wuhan in December 2019. It advanced to many other countries in a couple of weeks. Coronaviruses are RNA-containing viruses that vary in size from 27 to 32 kb. They are grouped into four genera, namely, alpha, beta, gamma and delta coronavirus targeting different hosts. Previously, six types of coronaviruses were identified to affect humans and produce respiratory tract infections, i.e., HCoV-229E, HCoV-NL63, HCoV-OC43, and HKU1 that affect upper respiratory tract with mild infection while SARS-CoV and MERS-CoV affecting lower respiratory tract with severe infection, were identified leading to morbidity and mortality. The causative agent of COVID-19 is SARS-COV2. The virion is an enveloped particle. It contains a single RNA strand with 30,000 nucleotides. The most common clinical features of COVID-19 are respiratory, gastrointestinal, neurological, cardiovascular and hematological manifestations. Numerous laboratory tests have been developed for the significant diagnosis of COVID-19, such as RT-PCR, Serology, Radiography, and CT- imaging. This review also describes available treatment strategies to counter COVID-19. The previous literature was thoroughly analyzed to design this review. To deal with this pandemic, further investigation about its treatment and genera is mandatory.

* **Corresponding Author:** Muhammad Sameer Ashaq ✉ sameer.ashaq@rlmc.edu.pk

Introduction

Coronaviruses are diverse, positive-natured viruses containing RNA, which belong to a family *Coronaviridae,* that cause various diseases in humans, birds and several other wild animals, causing gastrointestinal, nervous system and respiratory tract infections (Rodriguez-Morales *et al.*, 2020; Stewart *et al.,* 2020). There are four genera of coronavirus, namely, alpha, beta, gamma and delta. Among these, alpha and beta-type transmit disease to mammals, whereas the other two types infect birds and fish (Chen *et al.* 2020; Cui *et al.* 2019). Earlier, six strains of coronaviruses were investigated to affect mankind and cause respiratory tract infections. Out of these six, HCoV-229E, HCoV-NL63, HCoV-OC43, and HKU1 affect only upper respiratory tract infections (URTI) with mild symptoms while SARS-CoV and MERS-CoV affect the lower respiratory tract infections (LRTI) with severe symptoms, leading to morbidity and mortality (Su *et al.* 2016).

In recent years emergence of various viral diseases in humans has put the attention of researchers, especially virologists, on understanding and investigating the inception of these diseases. One of such viral diseases caused by a novel strain of coronavirus is a severe acute respiratory syndrome (SARS). It resembles viral pneumonia, causes LRTI and produces clinical signs like febrility, pertussis, difficult breathing and headache (Shaila 2003). The outbreak started in February 2002 in Guangdong, Province of China and was estimated to be spread from some animal reservoir, maybe bats or other wild animals and then first vitiate humans. More than 8000 people were affected and about 774 patients died. In less than a few months, it overspread to 26 states, emerging as the first pandemic in 21stcentury (Peiris *et al.* 2004).

Back in 2012, an outbreak reported by WHO was the Middle East respiratory syndrome coronavirus (MERS-CoV) (Assiri *et al.,* 2013). The Middle East respiratory syndrome (MERS) is a fatal disease caused by a beta coronavirus (One of the coronaviruses discussed earlier (Stewart *et al.* 2020), altering the respiratory tract system, especially of those having certain comorbidities. The initial incidence of MERS was documented in June 2012 in Jeddah, the port city of Saudi Arabia. The virus was identified to be the same as SARS-CoV; however, the mortality rate in MERS is seen less as compared to SARS. As in 2013 and 2014, little to no case with MERS was reported and in May 2015 the death rate of patients died by MERS was 40% (Zumla *et al.* 2015).

Since the pandemic of SARS, so many new coronaviruses related to SARS, have been located, considering that they belong to some zoonotic origin, i.e., bats are considered as their natural hosts (Zhou *et al.* 2020b). Recently a new outbreak of pneumonia, the cause of which was unknown initially, occurred in December 2019 in China city, Wuhan. This outbreak was initially called 2019-nCoV and the COVID-19 by the (WHO)(Rothan and Byrareddy 2020; Xu *et al.* 2020b). The COVID-19 virus is thought to be the same as SARS-related coronaviruses as they both enter the human via the same receptor site, i.e., Angiotensin-converting enzyme 2 (ACE-2).

The typical presentation of the disease includes febrile episodes, difficult breathing, fatigue, headache as well as productive cough (Huang *et al.* 2020). From January 22 to February 17, 2020 the virus spread in every single city of China, including other 27 countries, causing infection in about 70,000 people and becoming a worldwide pandemic (Dong *et al.* 2020a). Death cases appeared mostly in patients aged >70 years old with a weakened immune system. Based on various investigations and the growing number of disease victims, it is identified that the mode of transmission among humans is either by direct touching or indirect, i.e., by coughing and sneezing. On the other side, the rapid increase in this pandemic has created so much fear among people worldwide as it is spreading in an unsurpassed manner that anyone can be affected. It can be seen in the case of COVID-19 now, as compared to previous pandemics, because it escalated the psychological response of people towards the epidemic threat resulting in various mental diseases (Ho *et al.* 2020).

So many efforts have been made by different Health organizations, medical institutes and especially telehealth services for the implementation of precautionary measures for the stability of physical and mental health among people to reduce the transmission and to command the trend pandemic (Ohannessian *et al.* 2020; Rothan and Byrareddy 2020).

Epidemiology

COVID-19 pandemic started Wuhan in December, 2019. It advanced to many other countries in a couple of weeks. Investigations have proved the beginning of the virus from the wet market located in Wuhan, where different wild animals are vended. However, the main natural origin of the virus is a bat, i.e., the virus is of zoonotic origin (Bogoch *et al.* 2020; Huang *et al.* 2020; Zhou *et al.* 2020b). From December 18 to December 29, five patients were admitted to the Jin Yin-tan hospital in Wuhan with symptoms of difficulty breathing, cough and obvious fever. Chest radiography revealed small patches in the chest of all of these patients. All the nucleotide and Amino acid sequences from these patients revealed a resemblance with that of the previous SARS-CoV (Kalil and Sun 2011; Rothan and Byrareddy 2020). On January 02, 2020, 41 new confirmed cases with COVID-19 were reported. All the patients were identified with little to no underlying comorbidities. However, complications showed resemblance with acute respiratory distress syndrome (ARDS). From January 22 to February 17 2020, as discussed earlier, all the provinces of China and other 27 countries were enfolded by this pandemic and about 70,000 people got infected. In just a few weeks and months, it spreads everywhere and becomes a pandemic worldwide (Dong *et al.* 2020a).

In Pakistan, the first victim of COVID-19 was reported on February 26 2020 in Karachi. On February 26 2020, the first laboratory-confirmed positive case with COVID-19 was reported in Karachi City, Pakistan. On the very day, the ministry of health reported one more victim in Islamabad and within 15 days, the number of cases started increasing, showing the highest number of cases in Sindh, province of Pakistan as there is no vaccine or any antiviral treatment yet approved for treating COVID-19. Owed to the increasing number of cases and to tackle the situation, it was decided to enforce a complete lockdown on March 23 the Government of Pakistan. On March 27, about 13,328 positive COVID-19 cases were reported, with 281 deaths all over the country. On April 06, 2020, out of 3277 reported cases, about 50 patients died of COVID-19 (Salman *et al.* 2020; Waris *et al.* 2020). Currently, the number of cases is increasing day by day and the pandemic has gone worse now. With the growing pandemic, it is noted that most of the reported cases were of people aged above 60 years old with risk factors related to smoking. However, cases with children were also reported but less as compared to elderly patients with some underlying diseases.

The incubation time period for the virus is about 5 to 6 days and it leads to further comorbidities (Wu and McGoogan 2020; Yuki *et al.* 2020). Investigations showed that people who died with COVID-19 infection experienced respiratory failure and ARDS (Yuki *et al.* 2020). Some of the individuals infected with COVID-19 remain asymptomatic, i.e., no symptoms until the condition gets severe with it, while symptomatic patients are shown to have symptoms like dyspnea, fever, cough and other upper and lower respiratory tract infections (Velavan and Meyer 2020). Besides these physical symptoms, the growing pandemic has also had its effect on the mental condition of people causing various problems including anxiety, depression and other psychological issues even among those having no previous history of mental illness. One of the major reasons for all these mental conditions is substantial coverage of the pandemic by the media that has a great influence on the psychological response of people towards the disease as not all but many social media channels are used to spread the fake news about the infectious disease. Another reason is that many people lost their loved ones and still, the pandemic is growing in an uncontrollable manner in that it can affect anyone (Ho *et al.* 2020; Rajkumar 2020). In order to tackle

the growing situation, the Government of Pakistan took various steps in order to prevent the transmission of disease among persons. For this purpose, various systems were developed to screen the passengers who had a traveled history from the infected areas or countries. Public awareness campaigns launched by the National Institute of Health (NIH) provide information related to disease prevention and utilization of the face mask as well as adopting proper hygienic measures (Saqlain *et al.* 2020).

To cope up with the current pandemic effectively, many advanced policies were applied through the, "The National Action Plan for the COVID-19 Disease, Pakistan" to provide guidelines to all the governments of Pakistan(Javed *et al.* 2020). Not only in Pakistan, as discussed earlier, various health organizations, medical institutes and telehealth services are providing information regarding the outbreak as it will be a great help for all the people to maintain their physical as well as mental health and making efforts to reduce the transmission and stop this infectious disease worldwide (Ohannessian *et al.* 2020).

Virology

Coronaviruses are RNA-containing viruses that vary in size from 27 to 32 kb and belong to a separate family, *Coronaviridae*. They infect not only humans but also various wild animals, causing infection in the gastrointestinal, nervous system and respiratory tract systems. They are grouped into four genera, namely, alpha, beta, gamma and delta coronavirus targeting different hosts. Previously, six types of coronaviruses were identified to affect humans and produce respiratory tract infections, i.e., HCoV-229E, HCoV-NL63, HCoV-OC43, and HKU1 that affects upper respiratory tract with mild infection while SARS-CoV and MERS-CoV affecting lower respiratory tract with severe infection, were identified leading to morbidity and mortality (Lai and Cavanagh 1997; Su *et al.* 2016).

Recently a new novel coronavirus initially called 2019-nCoV and then COVID-19 by the World Health Organization, appeared in late December 2019, causing severe respiratory tract infections and spreading from human to human transmission (Lai and Cavanagh 1997; Rothan and Byrareddy 2020). Investigations have identified the COVID-19 to arise from the previous SARS-CoV as they all belong to the same zoonotic origin, i.e., bats are considered to be their natural reservoirs. Also, COVID-19 utilize the same receptor as SARS-CoV for gaining access to the host cell, i.e., angiotensin-converting enzyme receptor 2 (Zhou *et al.* 2020b). People aged above 65 years or individuals with a weakened immune system are identified to be at high risk of getting an infection with COVID-19 (Rothan and Byrareddy 2020).

The most common symptoms at the onset of infection are mild fever, dyspnea, headache and cough with uncommonly sputum production (Huang *et al.* 2020).

Definition

The Center for Disease Control (CDC), defined COVID-19 as, "A severe acute respiratory syndrome produced by a novel variety of coronaviruses with an incubation period of approximately two weeks, strikes various species like mammals, birds and reptiles. While in humans, it commonly produces less severe infections, relative to the common cold and responsible for 10–30% of URTI in adults, although more severe illness has been unusual, it can also give rise gastric as well as nervous illnesses" (Stewart *et al.,* 2020).

In accordance with WHO, the prevailing COVID-19 outbreak is caused by a coronavirus named SARS-CoV-2 that causes pulmonary diseases in humans, with symptoms ranging from the common cold to rare and serious diseases such as the Severe Acute Respiratory Syndrome and the Middle East Respiratory Syndrome (Rodriguez-Morales *et al.* 2020).

Pathogenesis of Covid-19

The causative agent of COVID-19 is SARS-COV2. The virion is an enveloped particle. It contains a single RNA strand with 30,000 nucleotides.

Life cycle

The life cycle of a virus comprises five major steps, which are binding, entry, nucleic acid synthesis, assembly and release. Firstly, the virus attaches to the host cell surface receptor then the process of endocytosis or membrane fusion occurs through which viruses enter the host cell (penetration). The viral genome is discharged within the host cytoplasm from where it enters the nucleus. At that point, new viral particles are made (maturation) and released. Coronaviruses consist of four structural proteins; Spike (S), Membrane (M), envelope (E) and nucleocapsid (N). Spike contains two useful subunits; S1 subunit is involved in attachment to the host cell receptor and S2 subunit is for the permutation of the viral and cell membranes. Angiotensin-Converting Enzymes 2 (ACE2) was recognized as a utilitarian receptor for COVID19. Basic what's more, structural and functional examination indicated that the spike for SARS-CoV-2 was too bound to ACE2. ACE2 articulation is high in the lung, heart, ileum, kidney and bladder (Yuki *et al.* 2020).

ACE2 in human physiology

ACE2 is an essential counter-regulatory enzyme to ACE by the breakdown of angiotensin-II, the focal player in the renin-angiotensin-aldosterone framework (RAAS) and the principle substrate of ACE2. Therefore, ACE2 functionally counteracts the physiological role of ACE, and ACE/ACE2 balance is responsible for the ultimate effects of RAAS activation, which determines the accessibility of different angiotensin peptides and hence the balance between pro-inflammatory and pro-fibrotic, and anti-inflammatory and anti-fibrotic pathways (Ho *et al.* 2020). Aside from its functions in RAAS, ACE2 accelerates bradykinin metabolism in the lungs by inactivating des-Arg9 bradykinin, which is an important ligand of bradykinin receptor type1 (B1), subsequently hindering effects like vasodilation and elevation of vascular permeability.

Interaction of SARS-CoV-2 and ACE2

The binding affinity of SARS-CoV-2 with ACE2 is 10-20 folds higher than SARS-CoV-1, thus responsible for its increased transmissibility and higher susceptibility of the host. SARS-CoV-2 enters the host cell through spike proteins, then after binding to ACE2 receptor, it causes downregulation and leads toward impairment of protective effect of ACE2 and causes lungs pathologies. This downregulation of ACE2 reduces ang2 clearance and leads to amplified tissue damage (Kampf *et al.* 2020). In the lungs parenchyma, where ACE2 receptors are present, SARS-CoV-2 replicates in macrophages, pneumocytes and dendritic cells and causes infection.

ACE2 is involved in bradykinin inactivation, an important ligand of bradykinin receptor type-1 (B1). Without the action of ACE2 to inactivate bradykinin, local vascular leakage may occur in the lungs, which can lead to angioedema. Further, due to the development of antibodies against spike protein of coronavirus that binds to ACE2 receptor, this condition may be followed by a clinical exacerbation of infection that could contribute to infection by increased local immune cell reflux and pro-inflammatory cytokines to further damage. Alongside, inflammation increases the expression of B1 and ACE2 dysfunctioning continues due to the persistence of the virus leading towards worsening of infection (Bourgonje *et al.* 2020).

ACE2 is also present in alveolar type-2 Pneumocytes. Type-II Pneumocytes for the most part, produce surfactants, keep up their self-maintenance and perform immunoregulatory functions. Significantly, these cells share a similar basement membrane with firmly connected capillary endothelial cells, additionally communicating high ACE2 levels. This information shows that type-II pneumocytes along with the related capillary endothelium might be an essential site of SARS-CoV-2 passage, bringing about damage to those cells and the alveoli-capillary layer and continuous responsive hyperplasia of type-II pneumocytes. As type-II pneumocytes remain targets of virus persistently and it undergoes replication, and also due to decreased surfactants, the alveoli can collapse and this will result in impaired oxygenation leading to hypoxemia (Van De Veerdonk *et al.* 2020).

Cytokine storm

Due to the release of massive number of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, and TNF-α, TGFβ) etc. and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effectors cells in SARS-CoV infection, there is lethal uninhibited systemic inflammatory response. Due to this cytokine storm, the immune system will generate a vicious attack on the body and may lead to ARDS or any organ failure and also can cause death in case of severe condition (Li *et al.* 2020b).

Clinical presentation

There are two types of patients of COVID-19.

Asymptomatic

Symptomatic (Cascella *et al.* 2022).

The incubation time of COVID-19 is up fourteen days and the patient becomes symptomatic within 4-5 days of infection, but in some cases, the patients don't have symptoms at all. Such patients are also called "Pre-symptomatic" patients because they do have an infection but just don't have symptoms of infection(Arteaga-Livias *et al.* 2020).

The pre-symptomatic carrier of COVID-19 is able to cause transmission of the virus to other people. During the incubation period, pre-symptomatic carriers may spread the virus through direct or indirect sources from person to person. So apparently, it seems that the transmission of disease through asymptomatic and symptomatic carriers is similar to each other (Lai *et al.* 2020).

The symptomatic carrier shows signs and symptoms of infection along with the transmission of disease. Within 4-5 days, symptoms appeared.

Signs and symptoms

Symptoms of infection may vary from less severe to severe and even critical (Cascella *et al.*, 2022). There are more chances of getting an infection in immune-compromised patients (Wang *et al.* 2020b). Similarly, if the age of the patient is <70, then there are fewer chances of critical symptoms to develop as compared to patients of age >70 (Wang *et al.* 2020c). The most common symptoms in patients at the onset of the disease are high body temperature, persistent cough, tiredness, nasal congestion, sore throat, chest pain and headache. At the onset of infection, mostly URTI symptoms are seen. The least common symptoms at the onset of infection may also include gastrointestinal symptoms, which are diarrhea and gastric discomfort.

As the disease is very fast spreading worldwide, new symptoms are also appearing in the patients. These new symptoms include anosmia (sudden loss of smell) and ageusia (sudden loss of taste) (Song *et al.* 2020). Both of these symptoms appear in the patients, along with fatigue and headache. These patients don't show common URTI symptoms, including cough shortness of breath.

In South Korea, 30% of the patient also showed insomnia at the manifestation of the disease (Gautier and Ravussin 2020).

Clinical features

Respiratory manifestations

Right after the initial symptoms of COVID-19 are appeared in patients, several clinical features are also assessed by the clinician during the course of the disease. Most of the patients have fever as well as upper respiratory tract and lower respiratory tract symptoms, including nasal congestion, cough, shortness of breath (Zachariah *et al.* 2020). When the chest discomfort and the cough are worsened, patients may have pneumonia (Yang *et al.* 2020). Pneumonia is most cases develop after the second or third week of significant infection. Usual symptoms of pneumonia are characterized by low oxygen saturation deviation in blood gases. These changes are also reflected in chest x-rays and magnetic imaging techniques (Velavan and Meyer, 2020).

Children and adult comparison

Children are less likely to get severe illnesses as compared to adults. Children have more upper respiratory tract symptoms than lower respiratory

tract symptoms and they play a major role in the transmission of COVID-19. Those children that are symptomatic have respiratory distress syndrome development. Children may also have co-infections. They have hypoxemia or dyspnea. Infants are more likely to have respiratory distress and severe clinical manifestations as compared to younger children (Cruz and Zeichner 2020).

Gastrointestinal manifestations

During the hospitalization phase, children and adults have gastrointestinal symptoms. Which includes diarrhea, decreased appetite, nausea, vomiting. Vomiting is most commonly seen in children whereas, and diarrhea is in both children and adults. Gastrointestinal symptoms are higher in the later than in, the earlier stage of the epidemic. The incidence of these symptoms is higher in severe patients as compared to non-severe patients (Tian *et al.* 2020).

Neurological manifestations

The neurologic manifestations are also seen in the patients during hospitalization and some of the clinical features seen in the patients include confusion, seizures, delirium and disturbed consciousness, which includes several possible mechanisms, e.g., direct infection, toxic metabolic encephalopathy and damage of parenchyma Whereas, most common neurologic symptoms include headache, anosmia, ageusia. Headache is the initial symptom of COVID-19 (Zubair *et al.* 2020).

Comorbidities

Comorbid condition in the patient of COVID-19 may lead toward critical and severe symptoms and may cause death. These comorbidities include obesity, cardiovascular disease, diabetes mellitus, hypertension, coronary heart disease. The mortality rate is greater among patients having such diseases along with COVID-19 (Wang *et al.* 2020a). Many of the older patients getting severely ill had underlying other diseases such as kidney disease, liver disease, respiratory disease and malignant tumors (Wang *et al.* 2020b).

The authors of the Chinese CDC report have further divided clinical manifestations into three types such as mild illness, critical illness, and severe illness.

Mild illness includes pneumonia or without pneumonia-like symptoms, for example, dry cough, fever and myalgia. Severe illness includes patients having difficulty in breathing and hypoxia. In contrast, critical illness includes patients that have clinical complications, including organ failure, septic shock, ARDS and many other diseases that increase the mortality rate of patients (Cascella *et al.* 2022).

Clinical complications

COVID-19 may lead the patients towards several critical diseases. These critical diseases increase the risk of mortality in patients and usually occur in older patients and patients having compromised immune systems [32].

Cardiovascular complications

One of the most important and common complications of COVID-19 is cardiovascular complications. Several heart-related complications include but are not limited to myocardial injury and myocarditis, acute myocardial infarction, acute heart failure and cardiomyopathy, dysrhythmias, venous thromboembolic events, hypotension, and hypertension. Hypotension, hypertension and arrhythmias may be caused due to drug interactions (Long *et al.* 2020).

Neurological complications

Most of the complications are associated with the central nervous system (CNS). The diseases related to the CNS include viral encephalitis, ischemic brain injury, stroke, etc. (Wu *et al.* 2020b). Common symptoms of COVID-19 associated viral encephalitis include headache, confusion, vomiting and altered consciousness. Other symptoms include disorientation, loss of consciousness, coma, paralysis and other brain dysfunction-related problems. This involves ischemic brain injury, cerebral hemorrhage and cytokine storm syndrome (Wu *et al.* 2020b).

Respiratory complications:

Another most important complication includes Acute Respiratory Distress Syndrome (ARDS). This requires ventilator criteria. The patient suffering from ARDS has serious respiratory worsening. Hypoxemia and dyspnea are also worsened. Due to decreased level of oxygen in the patient, he may have cardiac arrest (Zhou *et al.* 2020b).

Hospital-acquired pneumonia and ventilator-associated pneumonia are the two major complexities that are developed in patients after COVID-19. Both of these are life-threatening (Zhou *et al.* 2020a).

Sepsis

Clinical complications at the critical level may cause dysfunction of different organs in the body of the patient. This is the very worst stage of the disease because the mortality rate of the patients is increased because the sepsis may progress to septic shock. Among these organs, the most important are:

1) Heart
2) Liver
3) Kidney (Wang *et al.* 2020b)

After the lung infection, the virus enters the blood and from there, it enters the kidney and causes damage to the renal cells and in the end, the patient has Acute Kidney Injury (AKI) and most of the people are dead due to this renal failure (Cheng *et al.* 2020b). At the same time, liver dysfunction includes increased serum Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) levels (Feng *et al.* 2020).

Diagnosis

As currently, there is no vaccine or treatment of COVID-19, so the only way to reduce transmission of this disease is to identify and isolate the person who is contagious. Clinical suspicions and testing criteria in response to the swiftly evolving COVID-19 pandemic, countries have used special testing tactics depending on checking out potential, public health resources, and the spread of the virus inside the network (Cheng *et al.,* 2020a). The FDA released rules to permit laboratories to apply their established assays in an extra well-timed way on March 04. The CDC eliminated restrictive checking-out criteria, recommending that clinicians use their judgment to determine whether a test has to be carried out. Due to this fact, checking out capability stays suboptimal in the implementation of this advice.

The CDC nonetheless recommends priority for testing three groups, hospitalized sufferers with displays well suited with COVID-19, other symptomatic people at danger for infection, and folks who had close contact with a person with suspected or confirmed COVID-19 within 14 days of infection onset or have a history of the journey in an affected location.

Laboratory testing: Suspects who meet the testing criteria mentioned above have to undergo testing for SARS-CoV-2 (McIntosh *et al.*, 2020).

RT-PCR: RT-PCR is a diagnostic procedure; it uses nasal swab, tracheal aspirate, or bronchoalveolar lavage (bal) specimens. The primary and desired method for prognosis is the gathering of upper respiratory samples through nasopharyngeal and oropharyngeal swabs. The usage of bronchoscopy as a diagnostic approach for COVID -19 is not endorsed as the aerosol that is generated poses a substantial risk for each patient and healthcare workforce. Bronchoscopy may be taken into consideration simplest for intubated patients whilst higher respiratory samples are terrible and different diagnostic gear might considerably exchange the medical management. But, bronchoscopy can be indicated whilst medical and safety criteria are met and in the case of unsure analysis instead, tracheal aspiration and non-bronchoscopical can be used to gather respiration specimens in intubated patients (Pascarella *et al.* 2020). The specificity of the RT-PCR test seems to be very excessive, although there can be false-positive results because of swab contamination, specifically in asymptomatic patients.

The sensitivity rate isn't always clear but is envisioned to be around 66–80% (Yang and Yan 2020).

Serology: Serologic methods that test antibodies (IgA, IgM and IgG) to SARS-CoV-2 from medical specimens (along with blood or saliva), consisting of enzyme-linked immunosorbent assays, can be much less complex than molecular checks and feature the capability for use for analysis in some conditions. Antibody responses to contamination take days to weeks to be reliably detectable negative results would now not eliminate SARS-CoV-2 infection, especially among those with recent exposure to the virus. Cross-reactivity of antibodies to non–SARS-CoV-2 coronavirus proteins is also a capability hassle, whereby positive result may be the end result of past or present infection with other human coronaviruses (Guo *et al.* 2020).

Radiographic tests: Many centers have evaluated the utility of chest imaging for prognosis. On chest radiography, bilateral pneumonia is the maximum often reported feature (variety, 11.8% to 100%) and is more not unusual than a unilateral cognizance (Chung *et al.* 2020). Computed tomography has appeared as more useful than radiography, with several cohort research reporting that most patients (77.8% to 100%) had floor glass opacities. Different capabilities generally reported with COVID-19 on chest computed tomography encompass peripheral distribution, quality reticular opacities, and vascular thickening. Compared with serial nasopharyngeal sampling, chest computed tomography can be more sensitive than RT-PCR test at a time for the prognosis of COVID-19 (Li *et al.* 2020a).

CT-imaging: The imaging findings vary with the affected person's age, immunity frame, ailment stage on the time of scanning, underlying illnesses, and drug interventions. The imaging functions of lesions display: (1) dominant distribution (particularly sub-pleural, alongside the bronchial vascular bundles); (2) amount (frequently greater than 3 or greater lesions, occasional single or double lesions); (3) shape (patchy, big block, nodular, lumpy, honeycomb-like or grid-like, cord-like, etc.); (4) density (typically uneven, a paving stones-like exchange mixed with floor glass density) and interlobular septal thickening, consolidation and thickened bronchial wall, and so and concomitant signs and symptoms range (air-bronchogram, rare pleural effusion and mediastinal lymph nodes growth) and so forth (Li *et al.* 2020a).

Laboratory findings: The maximum common laboratory abnormalities pronounced on admission among hospitalized patients with pneumonia covered leucopenia (9–25%) or leukocytosis (24–30%), lymphopenia (63%) and increased levels of alanine aminotransferase and aspartate aminotransferase (37%) (Zhou *et al.* 2020b). Increased inflammation indices, usually including reduced procalcitonin and increased C-reactive protein (CRP) levels, are associated with clinical severity (Pascarella *et al.* 2020).

Treatment

In relation to the COVID-19 pandemic, we call on the WHO to focus on the following areas of work and to be held accountable. First, provide regularly updated recommendations regarding preventive strategies and potential treatments for COVID-19 from independent expert committees. Second, suggest universal and standardized methods to capture and monitor country-specific epidemiological evidence. Third, speed up the diagnostic examination evaluation, collection, and procurement. Fourth, collect knowledge on the success of COVID-19 vaccine development and collaborate with collaborators directly to ensure proper distribution and availability to therapeutics and vaccines when they are available. Fifth, facilitate the logistical coordination and availability of reagents, personal protective equipment, and potential treatments. Finally, supporting countries with fragile health systems in maintaining the standards of routine health care, especially for chronic diseases, and primary health care (Nay 2020).

Disease prevention and health promotion involve programs that sometimes conflict with economic priorities (Moon *et al.,* 2017). The WHO will also be willing to propose empirical and evidence-based

approaches, such as measures aimed at decreasing cigarette use, alcohol and sugar-sweetened drinks or minimizing environmental hazards, such as those associated with air pollution (Landrigan *et al.* 2018).

Treatment by off lab-label drugs

Anti-malarial drugs

Chloroquine/hydroxychloroquine: The drug was hypothesized to inhibit the effect of SARS-CoV-2 by action on the replication step of viruses which is PH-dependent (Stockman *et al.* 2006). It also was theorized to decrease the production of TNF-α and IL-6 in COVID-19 (Su *et al.* 2019). It was also thought to work at different stages of virus (i.e. entry and post-entry) and interrupt the glycosylation of cellular receptors in SARS-CoV-2 in Vero E6 cells (Chu *et al.* 2004; Savarino *et al.* 2006). The recommended dose was 500 mg (300 mg for chloroquine), 2 times per day for not more than 10 days (Dong *et al.* 2020b). One of its metabolites hydroxychloroquine is more potent than chloroquine (Yao *et al.* 2020) and its recommended dose was thought to be 200mg thrice a day for not more than 10 days (Zhao 2020). It is contraindicated in cardiovascular disease patients because it can lead to cardiac arrhythmias due to QT interval prolongation (Young *et al.,* 2020). The U.S Food and Drug Administration (FDA) revoked the further emergency use of chloroquine and hydroxychloroquine in COVID-19 patients (Coronavirus 2020).

Antiviral drugs

Lopinavir/ritonavir: It proves to be potent against SARS-CoV-2 and effectively inhibit protease and result in blockage of viral replication. Ritonavir actually enhances the effect of lopinavir by inhibiting its metabolism through CYP3A. The prescribed dose of lopinavir/ritonavir is 400 mg/100 mg for adults, 2 times/day (Dong *et al.* 2020b). The possible side effects related to it are QT prolongation, hepatitis, and anaphylaxis (Young *et al.* 2020).

Ribavirin: It inhibits the working of inosine monophosphate dehydrogenase, which causes inhibition of production of natural guanosine that leads to an increase in the destabilization of viral RNA. It also interferes with the capping mechanism of RNA and result in degradation (Graci and Cameron 2006). Ribavirin is administered through an intravenous infusion at a dose of 500 mg for adults, 2 to 3 times/ day in combination with IFN-α or lopinavir (Dong *et al.* 2020b).

Remdesivir: It is a nucleotide analog and presented in the form of pro-drug and by converting into a metabolite, it inhibits the RNA polymerase (Grein *et al.* 2020). The initial dose is 200 mg which is followed by the next 9 doses of 100mg (Dong *et al.* 2020b).

Favipiravir: It is a pro-drug that works by conversion into activated form favipiravir-RTP because it is represented as a substrate to viral RNA polymerase and results in inhibition of viral activity. Favipiravir has more potent effects than lopinavir and ritonavir and no considerable adverse effects were observed(Devaux *et al.* 2020).

Nonsteroidal anti-inflammatory drugs

Colchicine is an alkaloid soluble in lipids and is a potent anti-inflammatory agent (Cerquaglia *et al.*, 2005; Leung *et al.,* 2015). It is a polymerization inhibitor for microtubules. This attaches to unpolymerized tubulin heterodimers, creating a robust complex that effectively prevents the motion of microtubules after binding to the end of microtubules (Cerquaglia *et al.,* 2005). This is also a non-selective inhibitor of inflammatory nucleotide-binding oligomerization of the leucine-rich repeat and pyrin domain (NLRP3). Colchicine prevents inflammation on two levels: it prevents P2X7 receptor activation and ASC polymerization, thereby inhibiting association with pyrin-like domains (Marques-da-Silva *et al.* 2011; Toldo and Abbate 2018), resulting in IL-1b, IL-18 and IL-6 suppression (Martínez *et al.*, 2015; Robertson *et al.,* 2016).

Anti-hypertensive drugs The ACE inhibitors and angiotensin receptor blockers (ACEI/ARBs) upregulate angiotensin-converting enzyme 2 (ACE2)

in cell membranes. The viral S protein binds to ACE2, which supplies more membrane receptors for viral entry into cells and therefore enhances both susceptibilities to COVID-19 infection and disease intensity. Transmembrane protease serine S2 (TMPRSS2), has also been theorized as being essential for cell entry. In COVID-19 patients, such anti-hypertensive drugs are contraindicated (Curfman, 2020).

Immunomodulatory agents

Tocilizumab: It is used to normalize hyper inflammation in the severe case of COVID-19 because it acts directly on the key cytokine. It specifically binds to sIL-6R and mIL-6R and inhibits the signal transduction, which results in the inhibition of inflammatory response(Curfman 2020). It is administered in the form of IV infusion of 4-8mg/kg (400mg is recommended) in dilution with 0.9% NaCl with an infusion time of less than one hour (Zhao, 2020).

Imitinab: It blocks the entry of viruses by inhibiting the fusion virions(Xu *et al.* 2020a). Endosomal membrane by inhibiting transmembrane type 2 serine protease enzyme and result ineffectiveness against SARS-CoV-2 (Ruan *et al.,* 2020).

Ulinastatin: It inhibits the inflammation process by inhibiting serine protease, which helps the faster recovery of serious patient of covid-19 (He *et al.,* 2020).

Monoclonal antibodies (IgG/IgM): Neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral penetration into host cells. The viral S (spike) protein binds to ACE2, which supplies further membrane receptors for viral entry into cells; neutralizing antibodies block this step (Wrapp *et al.* 2020). Monoclonal antibodies have been used for both the prevention and treatment of COVID-19 infection (Joyner *et al.* 2020). Monoclonal antibodies inhibit the development of illness. A single infusion should be adequate, despite the long half-life of most monoclonal antibodies (about 3 weeks for IgG1). A possible disadvantage of monoclonal antibodies for COVID-19 treatment is the uncertain bioavailability of actively injected IgG in disease-affected tissues, particularly the lungs, which serve as a main target of COVID-19 infection. Passive injection of monoclonal antibodies as a pre-exposure or post-exposure prophylaxis may provide effective defense against infection that can last weeks or months. New technologies that change the antibody's Fc area to prolong the half-life of monoclonal antibodies will provide potentially protective rates for months based on the concentrations of monoclonal antibodies needed (Corey *et al.,* 2020; Graham, 2020).

INF-alpha: The drug is observed very much potent against the SARS-CoV-2 because of its antiviral activity that is produced through inhibition of the reproduction step of the virus. It is administered through inhalation in the form of vapors at a dose of five million units (Stockman *et al.*, 2006).

Corticosteroids: These are the immunomodulators used for the treatment of various types of infections all over the world. The drug methylprednisolone is used among the critically ill patients of COVID-19 and results in the reduction of the rate of mortalities (Wu *et al.* 2020a; Zha *et al.* 2020). According to the treatment protocols, the recommended dose is 1-2mg/kg/day for methylprednisolone for a short duration of time (i.e., not more than 3-5 days) at a low to moderate dose (Commission and Medicine 2020). Dexamethasone is used at a low dosage to manage hospitalized adult COVID-19 patients who need oxygen treatment or ventilation that contributes to lower mortality levels. The prescribed dose of dexamethasone is 6 mg daily for up to 10 days, according to the treatment protocols (Horby *et al.* 2020).

Treatment and management of critically ill patients

Hemodynamic support

Shock and cardiac injury in COVID-19 patients: The prevalence of shock reported in adult COVID-19 patients is highly variable (i.e., 1 to 35 percent), depending on the patient population, the severity of

the disease and shock. However, the prevalence of cardiac injury can correlate with the prevalence of shock (Moreno *et al.,* 2018).

Fluid therapy: The standardized parameters contained early-goal-directed therapy elements, such as central venous pressure (CVP) and meant arterial pressure (MAP). Compared to central venous oxygen saturation (ScVO2) guided therapy, early lactate clearance-driven therapy was associated with mortality reduction, shorter ICU length of stay, and shorter mechanical ventilation duration.

A high lactate level, however, does not always indicate hypovolemia; it can also be caused by mitochondrial dysfunction, liver failure, beta-agonists, mesenteric ischemia, or epinephrine. In the ANDROMEDA-SHOCK trial, capillary refill testing (CRT) every 30 min was associated with a non-significant mortality reduction compared to serum lactate measurement every 2 hours (Hernández *et al.* 2019).

Ventilatory support

Mechanical ventilation is a potentially life-saving intervention; it can worsen lung injury and, through ventilator-induced lung injury (VILI), contribute to multi-organ failure in patients with ARDS (Slutsky and Ranieri 2014).

ECMO (extracorporeal membrane oxygenation) is a type of adapted cardiopulmonary bypass in which venous blood is taken out of the body and pumped into an artificial lung's membrane in patients with respiratory or cardiac failure(Brodie *et al.* 2019). It adds oxygen, removes carbon dioxide and returns blood to the patient, either through another vein to provide respiratory support or through a major artery to provide circulatory support. ECMO is a resource-intensive, highly specialized and expensive form of life-support with the potential for major complications, particularly hemorrhage and nosocomial infections. ECMO plays a role in the management of some COVID-19 patients who have hypoxemic refractory respiratory failure (Goligher *et al.,* 2018). Other than through systemic oxygen availability and reducing ventilator-induced lung damage, ECMO offers little clear assistance to organs other than the lungs or heart. A significant proportion of critically ill COVID-19 patients appear to have developed heart arrhythmias or shock (Wang *et al.* 2020a).

Conclusion

This review illustrates detailed information regarding outbreak, advancement, and possibilities of Covid-19 pandemic. This virus has shown revolutionary impacts in all aspects of human life over the globe. The evolution of corona virus, diagnosis and treatment strategies have been well elaborated in above sections. Unfortunatley, there is no significant treatment strategy avaibale to counter the severe damages by Covid-19. There is dire need to investigate more variants of corona virus and it,s possible vaccines to immunize the human.

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