Review

The Pathogenesis and Treatment of COVID-19: A System Review

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INTRODUCTION

After the outbreak of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), it was difficult to imagine the recurrence of a virus that can spread worldwide in less than two decades. However, it did. In December of 2019, this virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was associated with the emergence of pneumonia cases of unknown etiology in Wuhan, Hubei Province, China[1]. In January of 2020, successful isolation of SARS-CoV-2 was conducted using deep sequencing analysis from lower respiratory tract samples in China[2]. On February 11, 2020, this novel coronavirus disease was officially named as COVID-19 by the World Health Organization (WHO)[3]. COVID-19 was declared a Public Health Emergency of International Concern by the WHO on February 30, 2020, and was upgraded to a pandemic on March 11, 2020[4,5].

COVID-19 is caused by the SARS-CoV-2 coronavirus, which is one of a group of coronaviruses that include four major genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*[6]. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which caused epidemics and threatened the health of people around the world in the past decade, belong to the *Betacoronavirus* genus. SARS-CoV-2 is classified as a *Betacoronavirus* and is closely related to SARS-CoV (about 79%) and MERS-CoV (about 50%)[7] (This may explain why COVID-19 causes similar catastrophes). As of May 27, 2020, there were more than 200 countries involved with 5,400,000 confirmed cases and 34,000 deaths[8].

Because of the consistent spread and the ongoing study of COVID-19, it is of great significance to gain more in-depth insight. This review aims to provide an overview of the pathophysiology, symptoms, transmission, diagnosis, and prevention of COVID-19 for readers and clinicians.

THE GENERAL CHARACTERISTICS OF COVID-19

Pathophysiology

Knowledge of the structure of coronaviruses and SARS-CoV-2 is the first step to comprehending the pathophysiology of COVID-19. Coronaviruses, which belong to the family Coronaviridae, are enveloped viruses with positive-strand RNA and the largest RNA virus genome (approximately 26–32 kilobases)[9]. Its genome includes several open reading frames (ORFs), in which approximately 67% of the entire genome encode 16 non-structural proteins (nsps) that are encoded by the first ORF 1a/b at the 5′ end. The other ORFs encode structural proteins, including spike surface glycoprotein (S), a small envelope protein (E), matrix protein (M), and nucleocapsid protein (N), and accessory proteins at the 3′ end[10,11]. The nucleocapsid protein (N) forms as a helical capsid to pack the genome, and the helical capsid is wrapped with an envelope, consisting of spike surface glycoprotein (S), a small envelope protein (E), and a matrix protein (M)[6]. The spike surface glycoprotein (S) regulates the binding of receptors and virus entry into host cells, while the small envelope protein (E) and matrix protein (M) participate in the virus assembly[12]. The coronavirus spike surface glycoprotein comprises three segments—an ectodomain, a single-pass transmembrane anchor, and a short intracellular tail[6]. The ectodomain consists of a receptor-binding S1 domain and a membrane-fusion S2 domain that play a critical role in virus entry into host cells through receptor binding and membrane

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fusion[6,7,13]. Among the functional structures, the envelope plays an essential role in pathophysiology because it participates in the process of viral assembly and release.

As a new member of the *Betacoronavirus* genus, SARS-CoV-2 has a similar genome to other coronaviruses[14]. Thus, the virulence mechanism and pathophysiology of the coronaviruses, including SARS-CoV-2, are as follows.

Angiotensin-converting enzyme 2 (ACE2) is the crucial receptor to ensure SARS-CoV-2 enters the host cell[15]. Thus, the organs which express ACE2 are more likely to suffer SARS-CoV-2 related damage, such as lungs and gastrointestinal tract (this may explain the main symptoms of COVID-19). In the pathological findings of the lung, changes can be divided into an earlier phase and later phase of COVID-19. Early phase pathological features include: pulmonary edema, protein exudation, vascular congestion, pneumocyte hyperplasia, interstitial thickening, and inflammatory infiltration with fibrinoid material and multinucleated giant cells, accompanying some suspected viral inclusions, less neutrophil infiltration, and hyaline membrane formation[16]. Late phase pathological features include: diffuse alveolar injury with fibrous mucus-like exudates; desquamation of pneumocytes, and hyaline membrane formation [indicative of acute respiratory distress syndrome (ARDS)]; right lung pulmonary edema, and transparent membrane formation (indicative of early-stage ARDS); left lung bilateral inflammatory interstitial mononuclear infiltrates and no viral inclusions[17]. In the gastrointestinal tract, histologic staining showed no damage in the mucous epithelium of the esophagus, stomach, duodenum, and rectum. It also exhibited the infiltration of occasional lymphocytes in the esophageal squamous epithelium and the infiltration of plasma cells and lymphocytes in the lamina propria of the stomach, duodenum, and rectum[18].

Symptoms

A recent study showed that the median incubation period of COVID-19 was estimated to be 5.5 days and ranged from 2.2 days to 11.5 days (2.5%–97.5%), consistent with the recommended self-isolation period (2–14 days)[19]. The symptoms of COVID-19 are mainly fever and cough; others include nausea or vomiting, diarrhea, shortness of breath, muscle ache, headache, confusion, and chest pain[20-22]. Recent data from 1099 patients in mainland China showed the percentage of the symptoms was 43.8% on admission and 88.7% during hospitalization for fever, 67.8% for cough, 5.0% for nausea or vomiting, and 3.8% for diarrhea[23]. Therefore, it should attract our attention when fever and cough both occur in one person.

Transmission

SARS-CoV-2 exhibits strong infectivity. Initially, the confirmed cases of COVID-19 were all found to have prior exposure to the Wuhan seafood market, suggesting its common-source zoonotic characteristic[24]. In subsequent events without exposure history, the human-to-human transmission characteristic was prominent[25]. Infection was mainly through droplets and direct contact[26]. Droplet transmission means people can be infected by inhaling the droplets produced by patients with COVID-19 at a close distance who have a cough or sneeze. Direct contact transmission occurs by touching the virus contaminated surface with a hand and subsequently touching the mouth, eye, or nose with the same hand. New studies found that the coronaviruses can remain infectious on inanimate surfaces for 9 days at room temperature and students touch their faces 23 times per hour (36% involved the mouth, 31% involved the nose and 27% involved the eyes, and 6% were a combination of these regions)[27,28]. It can also be transmitted through a high concentration of aerosols in a relatively closed environment[26]. The fecal-oral route may be a potential way for spreading because of the presence of ACE2, virus nucleocapsid protein, and infectious virus particles in gastrointestinal epithelial cells and isolated fecal samples[29].

Diagnosis

The gold standard for the diagnosis of COVID-19 is high-throughput sequencing of the whole genome[30]. However, the high cost and inconvenience are the barrier to widely diagnosing COVID-19. There are two kinds of tests available for COVID-19 in the Centers for Disease Control and Prevention (CDC): viral tests and antibody tests. A viral test identifies a current infection, and an antibody test identifies a past infection. A negative viral test for COVID-19 means you were not infected at the time your sample was collected; however, you might test negative if the sample was collected early in your infection and test positive later during your illness[31]. The two tests can only be one part of the diagnosis of COVID-19. Thus, it is generally accepted to diagnose suspected cases with multiple methods, including clinical manifestations, etiological and serological tests, imaging examinations, and

laboratory tests.

National Health Commission of the People's Republic of China had published *Diagnosis and Treatment Protocols of COVID-19 Infection (7th edition)* to provide a guideline on March 4, 2020[26]. In this criteria, it specifies that a suspected patient should have two of the clinical manifestations with an epidemiological history or three of the clinical manifestations without epidemiological history. When the suspected patient has etiological and serological evidence, he/she can be recognized as a confirmed case. dEpidemiological histories include: (1) travel or residence history in a community with confirmed cases or around Wuhan city within 14 days before initial symptoms onset; (2) contact history with COVID-19 patients within 14 days before initial symptom onset; (3) contact history with patients having fever or respiratory symptoms in a community with confirmed cases or around Wuhan city within 14 days before initial symptoms onset; (4) cluster disease. Clinical manifestations include: (1) fever or respiratory symptoms; (2) typical imaging findings of COVID-19; (3) reduced/normal total white cells counts and normal/reduced lymphocyte in initial symptoms onset. Etiological and serological evidence include: (1) positive results of SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR); (2) highly homologous gene sequence with SARS-CoV-2 by viral gene sequencing; (3) positive results of SARS-CoV-2 serum specific antibodies (IgM and IgG) tests; (4) change from negative to positive of IgG or four times or more increase in titers during the recovery period compared to the acute period. Typical imaging findings include: (1) multiple small patches and interstitial changes in the early stage; (2) then ground-glass opacities and infiltrative shadow of both lungs; (3) consolidation of lungs in severe cases and rare pleural effusion.

Although this guideline can provide a reference, there are several developments and problems with diagnosis. According to the epidemiological histories of suspected cases, the guideline used in China is mainly relevant to the specific area. Therefore, the WHO modified the definition: a travel history to Wuhan or direct contact with patients from Wuhan who had a fever or respiratory symptoms within 14 days before illness onset[32]. According to clinical symptoms, there were some asymptomatic cases reported, and a small sample size study estimated that the ratio of asymptomatic cases was 30.8%[33]. According to etiological and serological tests, Ai et al.[34] and Fang et al.[35] found that the sensitivity of RT-PCR for COVID-19 infection was 59% and 71% compared to CT sensitivity of 88% and 98%; Chan JF et al.[36] reported that novel, highly sensitive, and specific real-time RT-PCR assays (targeting the RNA-dependent RNA polymerase (RdRp), envelope (E), and nucleocapsid (N) genes of SARS-CoV-2) could improve the diagnosis. Zheng et al.[37] and Yang et al.[38] presented in a supplementary that, according to CT imaging, typical characteristics include crazy-paving pattern and consolidation shadows, and emerging atypical CT manifestations include airway changes, pleural changes, fibrosis, and nodules. Thus, it is worthwhile to diagnose using multiple methods, and further studies are needed to diagnose more accurately and efficiently.

MANAGEMENT

There is no effective special anti-viral treatment for COVID-19 because it is a new pathogen that lacks extensive comprehension. Currently, it is widely accepted to use symptomatic treatment, and scientists are gritting their teeth in developing anti-viral drugs and drugs with potential clinical benefits through clinical trials and pharmacological experiments.

Symptomatic Treatment

According to symptomatic treatment, the first step is to deal with clinical manifestations of viral pneumonia, mainly including fever and cough. It is recommended to use acetaminophen (Tylenol, and others) instead of the controversial ibuprofen (Advil, Motrin, and others) as an antipyretic agent[39,40]. Empiric antibiotics are the preferred choice for the prevention of secondary infection in the setting of COVID-19[2]. Depending on the severity of the dyspnea and level of oxygen saturation, general oxygen therapy, high-flow oxygen, non-invasive ventilation, and invasive mechanical ventilation are chosen to ensure the safety of patients' lives. Extracorporeal membrane oxygenation (ECMO) is recommended to be chosen for patients unimproved by mechanical ventilation; however, the effect of reducing patient mortality rates is still unknown[41]. The outbreak of inflammatory factors is the major characteristic that causes ARDS and multiple organ dysfunction outside the lungs, leading to deterioration and even death[42]. Apremilast, a Phosphodiesterase 4 inhibitors, has anti-inflammatory properties and attenuates lung injury by inhibiting cytokine storms[43]. Tocilizumab, an IL-6 receptor antagonist of biologics, could interrupt the cytokine storm and protect the lungs by inhibiting

activation of the last hyperinflammatory phase[44]. Corticosteroids can play a protective role in ARDS and stopping or delaying the progress of pneumonia; however, it also has potential risks, such as atypical infections, a long incubation period, and extra transmission of COVID-19[45]. Thus, the use of corticosteroids should follow the principles of early, low-dose, and short-term applications, and studies are needed to determine the appropriate dosing of corticosteroids[46]. Complications, such as shock and renal insufficiency, should be managed with corresponding treatments, like circulation support and continuous renal replacement therapy.

Additionally, coagulation disorder is not uncommon in COVID-19 patients. The treatment for this problem should be taken into consideration. In two large retrospective studies, D-dimer levels were found to increase more than 40%, and there was a correlation between coagulation disorder and adverse clinical outcomes among severe COVID -19 patients[23,47]. It is accepted by the International Society of Thrombosis and Haemostasis (ISTH) that low-molecular-weight heparin should be used in severe COVID-19 patients[48]. However, clinical attention to the adverse effect of low-molecular-weight heparin, heparin-induced thrombocytopenia, is necessary, during which anticoagulation should be changed to other options, including fondaparinux or direct thrombin inhibitors[49].

Therefore, the key point of symptomatic treatment is to keep patients in a stable condition to prevent disease progression and prepared for further treatment.

Pharmaceutical Treatment with Potential Clinical Benefits

Convalescent Plasma Convalescent plasma (CP) is a treatment to prevent and treat infectious diseases, which has a long history dating back to over a century ago. CP is widely recognized to carry a relatively high level of antibodies against the pathogen in the blood that provides some degree of protection, allowing for pathogen elimination or reduction of severe damage caused by acute viral infections[50,51]. The initial use of CP dates back to the Spanish influenza pandemic period of 1918 to 1920[52]. Meanwhile, the use of CP for 80 cases with SARS in Hong Kong, China indicated that patients treated with CP had a higher day-22 discharge rate within 14 days of illness[53]. For MERS, although there was a lack of potential donors with sufficiently high antibody titers, it provided the clinical evidence to prove the feasibility of CP[54]. Since SARS-CoV-2, SARS-CoV, and MERS-CoV are all members of *Betacoronavirus* and have a high level of virological homology, CP could be a potential COVID-19 treatment.

There were three COVID-19 related studies conducted that suggested that CP is an available treatment for severe patients[55-57]. Zhang et al.[55] collected the information of four patients with CP, which showed that all four patients (including a pregnant woman) were eventually discharged after at least 200 mL of CP. In 10 cases of severe COVID-19 patients managed with CP, Duan et al.[56] found that patients showed improvement in clinical symptoms and laboratory parameters within 3 days after CP transfusion with neutralizing antibody titers above 1:640, and no severe adverse effects were observed. The study of Shen et al.[57] consisted of five critically ill patients with ARDS. Following plasma transfusion, four of five patients' body temperatures recovered within 3 days; viral loads decreased and became negative in all five patients within 12 days, and four of five patients recovered from ARDS within 12 days.

Though these findings provided some evidence of CP's benefits, some limitations and problems exist. First, patients were often treated with multiple methods, and we can not attribute all benefits to CP. Besides, the mechanism of CP is artificially acquired passive immunity, and it is not clear whether there is any interaction between CP and corticosteroids, which is widely used in severely ill patients. Second, there is still a supply shortage of CP, and critically ill patients require a high concentration of antibodies. Third, all the reports are of small case series with no controls and large scale, multi-center randomized controlled clinical trials are necessary.

Vitamins Vitamin C is a simple low-molecular-weight carbohydrate with an ene-diol structure and is mainly considered to protect against scurvy[58]. Currently, researchers found that vitamin C could enhance differentiation and proliferation of B- and T-cells, and vitamin C deficiency results in impaired immunity and higher susceptibility to infections[59,60]. When the degree of infection deepens, vitamin C gradually depletes, and the demand for vitamin C increases[61]. Vitamin C can also reduce the duration of injection caused by respiratory viruses[62]. The high proportion of COVID-19 patients with ARDS in ICU is a major feature and focus and is also the cause of death[21]. Two meta-analysis studies showed that vitamin C could reduce the length of ICU stay on average by 7.8% and shorten the duration of mechanical ventilation[63,64]. Meanwhile, Zhongnan Hospital conducted a new randomized controlled

trial (Identifier: NCT04264533) that aimed to evaluate whether vitamin C could confer protection against COVID-19. This prospective randomized clinical trial included an infusion of 12 g vitamin C twice a day for seven days in the treatment group and ventilation-free days as primary outcome measures. The trial is estimated to be completed on September 30, 2020. Although the findings may be a little late for the pandemic, it can provide a reference of vitamin C's effects in viral outbreaks.

The effects of Vitamin D against viral injection have drawn much attention. Vitamin D can activate antimicrobial peptide LL-37 to contribute to innate and adaptive immunity by recruiting neutrophils, monocytes, and T cells to sites of microbial invasion[65,66]. Vitamin D can also confer protection against acute respiratory tract infection and reduce the risk of t acute respiratory tract infection[67]. Vitamin D protects against COVID-19 by reducing the cytokine storm, thereby: (1) reducing the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor α and interferon γ; (2) and inhibiting the inflammatory response by regulating the homing of cells to the lymph nodes[68,69]. Besides, treatment with vitamin D can reduce lung permeability by modulating ACE2 expression and renin-angiotensin system activity, which has protected against ARDS in animal models[70]. Meanwhile, a recent study found that vitamin D tends to decrease with age, and vitamin D deficient countries have a higher mortality rate, which may explain the difference of COVID-19 mortality rate in age and geography[71,72].

Because the use of vitamins is a convenient and inexpensive treatment, vitamin supplementation is encouraged in the management of COVID-19.

Traditional Chinese Medicine When it comes to viral reduction, traditional Chinese medicine seems to be beneficial. During the SARS epidemic, from May 5 to May 20, the case fatality rate for Beijing decreased from 52% to 4%–1%, indicating the apparent relationship between the use of traditional Chinese medicine and reduction in case fatality rate[73]. The study published in The *Lancet* reported that glycyrrhizin, an active component of licorice roots, played a crucial role in inhibiting the replication of the SARS-associated virus[74]. The mechanism of the anti-SARS-CoV effect mainly includes three aspects: (1) the extracts of *Rhubarb*, *Houttuynia cordata*, and *Isatis indigotica* could inhibit the enzymatic activity of SARS 3-chymotrypsin-like protease, which is a replication participant of the virus[75-77]; (2) *myricetin* and *scutellarein* potently could affect the ATPase activity to inhibit the SARS-CoV helicase protein, which is essential to viral genome replication[78]; (3) *kaempferol glycosides* and *emodin* could inhibit 3a channel proteins of SARS, which is the key point of virus release[79,80]. Thus, traditional Chinese medicine demonstrates a strong potential ability for treating COVID-19.

In the guideline of Diagnosis and Treatment Protocols of COVID-19 Infection (7th edition) published by the National Health Commission of the People's Republic of China[26], it describes *Qing Fei Pai Du Tang,* and other herbal medications that adapted to different clinical types of COVID-19. On February 17, 2020, the National Administration of Traditional Chinese Medicine reported the effect of traditional Chinese medicine[81]. Among 351 cases of COVID-19, there were 112 patients with body temperature over 37.3 °C and 214 patients with cough. One day after managing with *Qing Fei Pai Du Tang*, 51.8% of patients' body temperatures recovered, and 46.7% of patients' coughs disappeared. Six days after treatment, 94.6% of patients' body temperatures recovered, and 80.6% of patients' coughs disappeared. In the study on February 18, 2020, Chinese researchers found that treatment with western medicine combined with traditional Chinese medicine remarkably reduced the time of temperature recovery, symptom disappearance, and hospitalization, and decreased mortality compared with the treatment with western medicine alone[82].

Although it is encouraging that traditional Chinese medicine has a great potential to treat COVID-19, more controlled trials are needed to evaluate the efficacy and safety of traditional Chinese medicine in more centers and at larger scales.

Intravenous Immunoglobulin (IVIg) Intravenous immunoglobulin (IVIg) is derived from the plasma of 1,000 to 15,000 healthy donors, consisting of highly purified immunoglobulins and is widely used as the treatment for immunodeficiency diseases, rheumatic diseases, ARDS, infectious and infection-related diseases[83]. Besides identifying and neutralizing the viral antigens as the natural antibodies, IVIg can also play an anti-inflammatory or immune-regulatory role through the interaction of Fcγ receptors and regulate the number and function of regulatory T cells, which may be the rationale for treatment with IVIG in SARS-CoV-2 infection[84]. In clinical treatment, IVIg exhibits protective effects. During the early stage of the epidemic, three patients with severe COVID-19 received high-dose IVIg at 0.3–0.5 g per kg weight

per day for five days and were clinically improved shortly[85]. In another case series, five patients with severe COVID-19 cases who failed to recover with standard treatments were also managed with high-dose IVIg at 0.3–0.5 g/kg. They all showed desirable therapeutic responses, clinical improvement, and O_2 saturation, and were discharged from the hospital in good health[86]. Meanwhile, a retrospective study with 58 cases of severe COVID-19 showed that adjuvant treatment with IVIg within 48 h of admission to the ICU could improve 28-day mortality, reduce the use of mechanical ventilation, and shorten hospital stays[87].

Although the effects of IVIg during treatment have been approved, some matters hinder the use of IVIg. Constant vigilance is necessary to avoid two potential and severe IVIg adverse effects, which may cause negative survival impact on patients with COVID-19; the transfusion (immunoglobulin)-related acute lung injury and thrombotic events related to IVIG treatment with an estimated incidence of 1%–16.9%[88]. Besides, the prohibitive cost of treatment with IVIg and a worldwide shortage of IVIg, which may be the reason for the SARS-CoV-2 pandemic and few donors, should be considered. Therefore, we recommend to treat severe cases of COVID-19 patients with IVIg, but the dose and adverse effects should be considered in advance.

Vaccination Since the SARS-CoV-2 is a new virus with high transmissibility, there is a great need to develop the most effective approach; vaccination. There is still insufficient available information to research SARS-CoV-2 vaccination; thus, it may take a long time. Although development and research are ongoing, it is normal that no vaccinations were available at the time of a viral outbreak. For example, the Ebola outbreak began in 2013, phase I clinical trials of the vaccination were conducted to assess the safety and immunogenicity in Africa and Europe in 2016[89]. On November 12, 2019, WHO announced the first prequalification of an Ebola vaccine, and the European Commission granted the vaccine marketing authorization according to the recommendation of the European Medicines Agency on November 11, 2019[90]. But the studies of vaccination in coronavirus (SARS and MERS) can provide a useful reference and shorten the development time of COVID-19. Currently, the different types of vaccinations under development include whole-cell killed and live-attenuated vaccines, subunit vaccines, mRNA vaccines, DNA vaccines, live vector vaccines, and synthetic peptide epitope vaccines[91]. Live-attenuated vaccines are developed through the collaboration of the Serum Institute of India, Ltd. and Codagenix, Inc.; subunit vaccines are developed by Chongqing Zhifei Biological Products Co., Ltd.; mRNA vaccines are researched in mice through the collaboration of Fudan University, Shanghai Jiaotong University, and Bluebird Biopharmaceutical Company; DNA vaccines are undergoing preclinical studies conducted by Inovio Pharmaceuticals; live vector vaccines are undergoing animal testing by Houston-based Greffex Inc. with Greffex Vector Platform; synthetic peptide epitope vaccines are developed through the collaboration of Generex Biotechnology and third-party groups. In these vaccines, whole-cell killed and live-attenuated vaccines, which are the earliest vaccines with mature preparatory technology, are likely to become the first COVID-19 vaccine and it is hard to find the attenuated SARS-CoV-2 variants in the large pool of infected individuals that remain asymptomatic[92]; subunit vaccines are characterized by safety and easy production, but S protein often considered as antigens may cause severe liver damage enhanced infection[93]; mRNA vaccines are the potential alternative with high potency, short production cycles, and low-cost manufacturing to traditional vaccines, but no mRNA vaccine has yet entered the market and it may spend some time undergoing safety evaluations[94]; DNA vaccines represent better stability, delivery efficiency and easier manufacture, but the efficacy remains to be verified to determine if they also prove disappointing in a variety of disease models[95]; live vector vaccines have the advantage of a combination of the strong immunogenicity of live attenuated vaccines and the safety of subunit vaccines and it is exciting that a recent dose-escalation, open-label, and non-randomised trial was conducted and found specific T-cell responses peaked at 14 days and humoral responses against SARS-CoV-2 peaked at day 28 after injection with a recombinant adenovirus type-5 vectored COVID-19 vaccine[96]; synthetic peptide epitope vaccines are more accessible in preparation and quality control, but they usually have low immunogenicity because of the low molecular weight and structural complexity[97]. Therefore, live vector vaccines and whole-cell killed and live-attenuated vaccines are more likely to be used in the clinic.

There are still some points of caution. Older adults often have less protective responses to vaccinations because of the decline of the immune function, and it is worth formulating special vaccines for older adults with some adjuvants[98]. Additionally,

the cross-reactivity between the receptor-binding domain of SARS-CoV-2 and SARS-CoV-specific human monoclonal antibody should attract researchers' attention[99]. Finally, the close monitoring of the safety and efficiency of vaccines should be of great concern to scientists.

Anti-viral Treatments Chloroquine and its derivative, hydroxychloroquine, are used in the treatment of malaria and rheumatologic conditions[100]. Meanwhile, chloroquine and hydroxychloroquine can be considered as viral inhibitors. They could elevate the endosomal PH to intervene in the release of the infectious nucleic acid and necessary enzymes for viral replication depending on low PH and interfere with glycosylation of ACE2 cellular receptors[101,102]. Meanwhile, the protective role of chloroquine and hydroxychloroquine is reflected in controlling the cytokine storm of critical ill COVID-19[103]. In vitro, chloroquine can have anti-viral effects at both entry and post-entry stages of the COVID-19 infection[101]. In clinical trials, a small open-label and non-randomized study in France showed hydroxychloroquine could significantly reduce the viral load, and the effects could be enhanced with azithromycin[104]. However, Molina et al.[105] found there were no effects of anti-viral clearance or clinical benefit in severely ill patients with COVID-19. Thus, larger, multiple centers and randomized controlled trials are in great demand.

Remdesivir is a 1'-cyano-substituted adenosine nucleotide analog prodrug initially designed to treat the Ebola virus disease. Remdesivir can inhibit the viral RNA-dependent RNA polymerase by delaying chain termination to exhibit the anti-viral role[106]. In the subsequent studies, scientists found the ability of remdesivir against coronaviruses (including SRAS-CoV and MERS-CoV) both in vitro and animal models[107,108]. In the in-vitro model of primary human airway epithelial, Sheahan et al.[107] found that remdesivir could prevent the replication of SARS-CoV and MERS-CoV. In the mouse model of SARS-CoV, they found that treatment with remdesivir significantly decreased viral load in the lungs and improved lung function and ameliorated symptoms. In the rhesus monkey model of MERS-CoV, Wit et al.[108] found that remdesivir attenuated the damage caused by the disease, improved clinical signs, and reduced viral replication. Currently, remdesivir exhibited the ability to control SARA-CoV-2 injection in-vitro[101]; the first COVID-19 patient in the United States was managed with remdesivir on hospital day 7 (illness day 11) and showed improvement in clinical signs and negativity of oropharyngeal swab on hospital day 8[109]. But, a study involving 53 severely ill COVID-19 reported a total of 32 patients (60%) with adverse events, including increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension[110].

Lopinavir/ritonavir is a combination medication used to treat human immunodeficiency virus (HIV). Scientists found that lopinavir can interfere with the replication of coronaviruses through inhibiting 3C-like protease, and the effect can be enhanced by ritonavir[111]. After 48 hours of the combined treatment, lopinavir/ritonavir significantly decreased the viral load SARS-COV and reduced adverse clinical outcomes (ARDS or death)[112]. For the SARS-CoV-2, there were some incongruent findings. In the observation of four cases with COVID-19, lopinavir/ritonavir remarkably improved the clinical signs of the disease[113]. But in a randomized, controlled, open-label trial, the only clinical improvement in the median time (median, 15 days *vs*. 16 days) was significant, albeit modest, and the clinical trial concluded that there was no benefit in treatment with lopinavir/ritonavir beyond standard care[114]. Thus, clinical trials are still in progress.

Prevention

The best practice to stop the spread of infectious disease is prevention. Since vaccinations are under development, the most available approach is to avoid being exposed to this virus. *Coronavirus disease (COVID-19) advice for the public* published by the WHO provides some suggestions, including: (1) Regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water; (2) Maintain at least 1 meter (3 feet) distance between yourself and others; (3) Avoid going to crowded places; (4) Avoid touching eyes, nose and mouth; (5) Make sure you, and the people around you, follow good respiratory hygiene; (6) Stay home and self-isolate even with minor symptoms such as cough, headache, mild fever, until you recover, and have someone bring you supplies. If you need to leave your house, wear a mask to avoid infecting others. (7) If you have a fever, cough, and difficulty breathing, seek medical attention, but call by telephone in advance if possible and follow the directions of your local health authority; (8) Keep up to date on the latest information from trusted sources, such as the WHO or your local and national health authorities[115]. Regarding face coverings, CDC recommends that people in public settings, such as grocery stores and pharmacies, should wear cloth

face coverings (fashioned with additional household items or made at home from common materials). Surgical masks or N-95 respirators are not recommended as they are critical equipment that should be provided to healthcare workers and other medical first responders[116]. Because of the rapid developments in the field of computational techniques and information and communication technologies (ICTs), Big Data could play a huge role in time-scale: (1) Big Data can rapidly identify an ongoing outbreak and diagnose and predict cases of COVID-19 in short-term (weeks); Big Data can identify a potential therapeutic option in medium-term (months); Big Data can enhance cities and favor the development of healthy, smart, resilient cities in long-term (decades)[117]. After all, prevention not only blocks disease progression in terms of sources, but also reduces the economic burden of society.

CONCLUSIONS AND PERSPECTIVE

In summary, SARS-CoV-2 is a new member of the *Betacoronavirus* genus and has a high level of virological homology with SARS-CoV and MERS-CoV. The pathogenesis of SARS-CoV-2 is not well understood and is partly related to the spike surface glycoprotein and ACE2. The main clinical symptoms include fever and cough, while the median incubation period of COVID-19 is estimated to be 5.5 days and ranges from 2.2 days to 11.5 days (2.5%–97.5%). The main methods of spreading SARS-CoV-2 include droplets and direct contact, which points to a mode of prevention. There is no clear beneficial vaccine, the management is symptomatic, and treatment is with existing anti-viral drugs. It is so exciting that several studies of potential drugs are in progress, and it is hopeful that a vaccine is close to being developed.

Since the outbreak of COVID-19 approximately half a year ago, knowledge of SARS-Cov-2 has deepened. But we still need to be vigilant for increased asymptomatic cases, and the spread of the virus is not under complete control[33]. Zhang Wenhong, director of the infection department, Huashan Hospital affiliated to Fudan University, said SARS-CoV-2 might last two years. This review details the development of COVID-19 and introduces the corresponding measures of prevention and treatment. When the pandemic ends, people will be able to evaluate the influence of the infective disease on health, social interactions, and the economy, and we can gain a deeper insight to use in response to any future pandemic that affects global public health.

Author Contributions

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Competing Interests

None of the authors have competing interests to declare.

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