Summary of the clinical manifestations, infection mechanisms and current drug treatment of SARS-CoV-2 infection

Furong Qin[1], Weiqi Hong[1], Yuan Cheng[1], Xian Li[1], Yang Wang[1], Jian Liu[1], and Xiawei Wei[1]

[1]Affiliation not available

September 10, 2020

Abstract

The recent outbreak of the novel coronavirus disease (COVID-19) and rapid spread have continued to negatively affect the public health and global economy. It has been reported that the commonest symptoms of COVID-19 include fever, cough, fatigue, sputum production, and shortness of breath. SARS-CoV-2, a novel enveloped RNA β-coronavirus, enters the host cell with the aid of SARS-CoV receptor ACE2 and the spike protein of SARS-CoV-2, primed by TMPRSS2. Currently, the most effective method that lowers the risk of exposure to virus is isolation because the virus is transmitted person-to-person. Several studies have been conducted to determine drugs and vaccines likely to be effective against COVID-19. However, no specific medicine is reported for the prevention or treatment for SARS-CoV-2. This article not only reviews the clinical manifestations, epidemiology of COVID-19 and the infection mechanisms of SARS-CoV-2, but also discusses potential treatments for COVID-19, including drug therapy, immune therapy (i.e., immunomodulator, neutralizing antibody therapy and convalescent plasma therapy) and vaccines. Our aim is to provide knowledge about SARS-CoV-2 and promotes research through which more effective treatments and preventive measures can be developed.

Introduction

A novel coronavirus, recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the pathogen resulting in the 2019-2020 viral pneumonia outbreak of coronavirus disease 2019 (COVID-19) (Q. Li et al., 2020; F. Wu et al., 2020; P. Zhou et al., 2020; N. Zhu et al., 2020). Since then, the novel coronavirus (COVID-19) has been spread around the world and has continued to negatively affect the global public health and economies. COVID-19 is a brand-new respiratory disease triggered by SARS-CoV-2, a novel enveloped RNA β-coronavirus (N. Zhu et al., 2020). Coronavirus is a lipid enveloped, positive-sense and single-stranded RNA virus. Under the electron microscope, the virus has protrusions that resemble the corona, and looks like a crown, so it is called coronavirus. The clinical manifestations of SARS-CoV-2 are mainly fever, cough, occasional dyspnea, invasive bilateral lung pneumonic infiltrates, and other severe complications(C. Huang et al., 2020). Acute respiratory distress syndrome (ARDS) is a common complication of severe viral pneumonia, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (Channappanavar & Perlman, 2017), which are the fatal coronavirus infections that have occurred over the past two decades. A high sequence identity between SARS-CoV-2 and SARS-CoV is known by gene sequence (Xiaolong Tian et al., 2020). The genome of SARS-CoV-2 partially resembles SARS-CoV (82%) and MERS-CoV (50%) (Chan et al., 2020), both of which are of bat origin. Therefore, bats are thought to be the most probable animal hosts of SARS-CoV-2. However, due to the existence of natural ecological isolation, the probability of bat coronovirus ((BatCoV)-ZC45, BatCoV-RmYN02, and BatCoV-RaTG13) infecting directly to humans is very low, so there may exist other mammalian species act as intermediate hosts. Pangolins is reported as the possible intermediate hosts due to approximately 85.5%–92.4% similarity in their genome with COVID-19 (Lam et al., 2020).

This review summarizes the clinical manifestations, epidemiology, and the infection mechanism of SARS-CoV-2. We found that hACE2 plays an important role in the infection process, which also provides new research directions for potential therapeutic targets. This study highlights the treatment of COVID-19. There is no vaccine or effective antiviral treatment against COVID-19 presently. Novel therapeutics continue to be developed with the emergence of viruses. This article introduces potential drug therapy (i.e. remdesivir, ribavirin, Lopinavir/ritonavir, chloroquine, chloroquine phosphate, Arbidol, and traditional Chinese medicine) and immunotherapy (i.e. IL-6 or vaccines) for the treatment of COVID-19.

The clinicalmanifestations and epidemiology of COVID-19

The COVID-19 disease has reached pandemic status with the rapid spread worldwide. The threat of the SARS-COV-2 virus has developed rapidly since the first cluster case appeared. However, the result from phyloepidemiologic analyses suggested that the root of the SARS-COV-2 virus is not the Huanan market; they show that the virus was imported from elsewhere and then boosted in the market due to the large population (Peng Zhou et al., 2020). The epidemic curve of COVID-19 shows a mixed epidemic pattern. Because the epidemic caught up with the Spring Festival, the epidemic began in mid-to-late January. Early cases suggested that there was a continuing common source. In the South China seafood wholesale market, there may be a spillover of zoonotic diseases. Later, the increasing number of infected health care workers suggested that person-to-person transmission occurs mainly through droplet or contact transmission ("Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States," 2020; Phan et al., 2020; Rothe et al., 2020; N. Zhu et al., 2020). The latest report showed that the SARS-COV-2 virus was detected positive in the gastrointestinal tract, saliva, and urine.

Most current published data come from China, despite the severe situations around the world, and provides first-hand information on the epidemiology of COVID-19. The high-level details of patient from 72,314 cases, including patient characteristics, severity of manifestations and survival, are reported by the Chinese Center for Disease Control and Prevention; suspected (22%), clinical diagnosed (15%), asymptomatic (1%), and confirmed (62%) COVID-19 cases (Wu & McGoogan, 2020). Most of the confirmed cases (75%) were confirmed in Hubei and were predominantly identified by the degree of symptoms, most (87%) were mild, defined by no or mild pneumonia, 14% were severe with significant infiltrates or signs of dyspnea, and 5% were severe, with distinct syndromes of respiratory failure (e.g. mechanical ventilation), shock, or multiple system organ failure.

The resistance capacity of children to infection is better than adults or are rarely symptomatic. The report showed that 87% of the cases were between 30-79 years old, 8% were 20-29 years old, 3% were [?] 80 years old, 1% were 10 -19 years old, and 1% were [?] 9 years old (Wu & McGoogan, 2020). Early data from the U.S. Centers for Disease Control and Prevention showed that in 4,226 confirmed cases with symptoms or exposure, only 5% occurred in those ¡ 20 years of age (D. Wang et al., 2020; Wu & McGoogan, 2020). A study also shows that children are less susceptible to SARS-CoV-2, which may result from the maturity and function of ACE2 in children lower than that in adult (Cristiani et al., 2020). The total case fatality rate of the 44,672 confirmed cases was 2.3%, among which, there are no death cases for patients [?] 9 years old, the case fatality rate for patients aged 70 to 79 years was only 8.0%, and the case fatality rate for 80 years old and above was 14.8%. There were no reports of death in mild or severe cases, but the fatality rate of critical cases was 49.0%. Patients with hidden diseases have a high case fatality rate, of which for cardiovascular disease is 10.5%, diabetes is 7.3%, chronic respiratory disease is 6.3%, hypertension is 6.0%, and cancer is 5.6%. Therefore these conditions are risk factors for SARS-CoV-2 infection, which is consistent with the conclusions of 138 cases reported from Wuhan Central South University (Qun Li et al., 2020). Compared with SARS and MERS, the total mortality of COVID-19 is higher, which may result from its larger base. The first confirmed case of COVID-19 in the United States, which has now surpassed other countries in the absolute number of cases, was confirmed on January 20, 2020. In contrast, the United States shows the reflecting experience with COVID-19 from a few published data, which is worth learning from.

The commonest symptoms reported were fever (up to 90%), then developing into cough, fatigue, sputum production, and shortness of breath (Guan, Ni, Hu, Liang, Ou, He, Liu, Shan, Lei, Hui, Du, Li, Zeng, Yuen,

Chen, Tang, Wang, Chen, Xiang, Li, Wang, Liang, Peng, Wei, Liu, Hu, Peng, Wang, Liu, Chen, Li, Zheng, Qiu, Luo, Ye, Zhu, & Zhong, 2020). Less common symptoms, including headache, myalgia, sore throat, nausea, vomiting, and diarrhea may occur (N. Chen et al., 2020; C. Huang et al., 2020; D. Wang et al., 2020). However, only 43.8% of COVID-19 patients developed fever initially, which progressed to 87.9% after hospitalization (Guan, Ni, Hu, Liang, Ou, He, Liu, Shan, Lei, Hui, Du, Li, Zeng, Yuen, Chen, Tang, Wang, Chen, Xiang, Li, Wang, Liang, Peng, Wei, Liu, Hu, Peng, Wang, Liu, Chen, Li, Zheng, Qiu, Luo, Ye, Zhu, & Zhong, 2020). Therefore, if the surveillance method focuses on fever detection, patients with no fever or who are asymptomatic may be a hidden source of infection. A recent study (n = 214) concluded that, in addition to systemic and respiratory symptoms, of total patients with COVID-19, 36.4% develop neurological symptoms (Mao et al., 2020). The latest report from the American Association of Otolaryngology shows that anosmia and dyspepsia have been highlighted as possible symptoms of the disease. Additionally, most cases show differential results between males and females, suggesting that males are more susceptible to SARS-CoV-2 infection resulting from the innate X-chromosome, sex hormones, and adaptive immunity (Jaillon, Berthenet, & Garlanda, 2019).

Presently, the common methods for diagnosis of SARS-CoV-2 are chest radiographs and nucleic acid detection. The chest computed tomography (CT) was abnormal in 87% of patients at the time of admission, and the typical chest CT for COVID-19 pneumonia was the initial small pleural ground glass turbidity gradually becoming larger with insane-paving pattern and consolidation. The lesions were gradually absorbed after two weeks of growth, leaving a large number of patients with turbidity and subpleural parenchyma in the recovery phase. However, the latest report suggests the complexity of disease control due to patients with normal imaging performance on initial presentation; which occurs in severe and non-severe patients.

Moreover, the common lab derangements on admission included lymphopenia, elevations in C-reactive protein (CRP), lactate dehydrogenase, liver transaminases, and D-dimer. It is worth noting that procalcitonin is rarely elevated. The considerable decrease in the total number of lymphocytes is an effective sign, which developed as an indicator for the diagnosis of SARS-CoV-2 infection; it indicates the consumption of immune cells and the impairment of cellular immune function (N. Chen et al., 2020). Another report noted elevations in other inflammatory markers, such as ferritin, interleukin (IL)-6, and erythrocyte sedimentation rate (Arentz et al., 2020; Guo et al., 2020; D. Wang et al., 2020; C. Wu et al., 2020; F. Zhou et al., 2020).

The infection mechanisms of SARS-CoV-2

A nucleocapsid protein is structured by a phosphorylated capsid protein and the single strand of RNA. This structure allows membrane protein interact with nucleocapsid protein when the virion particles are pachaged, and supports the viral genome transcription. The nucleocapsid is hidden within the phospholipid bilayers and coated by spike glycoprotein trimer (S) and probably the hemagglutinin-esterase (HE) protein. Spike protein on the lipid envelope gives SARS-CoV-2 crown-like spikes, and thus form a classic coronavirus structure. Among the spikes site the membrane (M) protein, designers of the viral envelope's shape by interacting with the nucleocapsid and by specific packaging of the viral genome into the virion, and the envelope (E) protein, viroporins that modify the host cell membranes and facilitates viruses release from the infected cells. The spike (S) protein of coronaviruses, binding to a cellular receptor through the receptor-binding domain (RBD) in the S1 subunit and followed by the fusion of the S2 subunit to the cell membrane, can facilitate viral entry into target cells. And S proteins are activated by priming cleavage between S1 and S2 and activating cleavage on S2' site by different host cell proteases, including furin, transmembrane protease serine protease-2 (TMPRSS-2), TMPRSS-4, cathepsins, trypsin, or human airway trypsin-like protease (Coutard et al., 2020). Replication of coronaviruses starts from attachment and entry (Figure 1). When the S protein interacts with its specific receptor, the virus attaches to the host cell.and then enters host cell cytosol via cleavage of S protein by a protease enzyme, bring the outcome that the viral and cellular membranes blend together. Afterward, the replicase gene is interpreted from the virion genomic RNA and then the viral replicase-transcriptase complexes are translated and assembled. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. The replication and RNA synthesis bring up the encapsidation that leads to the formation of the mature virus. Following assembly, vesicles carry virions to the cell surfaceand

release them through exocytosis. Recently, a study reported that the non-structural protein 16 (nsp16) of SARS-CoV-2 mimics cellular mRNAs by methylating the 5'-end of virally encoded mRNAs to avoid host innate immunity(Viswanathan et al., 2020).

Based on the sequence similarity between SARS-CoV and SARS-CoV-2, most amino acid residues essential for angiotensin-converting enzyme 2 (ACE2) binding by SARS-CoV were conserved in SARS-CoV-2. Most of these residues did not exist in the S proteins of several SARS-CoV-related viruses from bats, which had been found not to use ACE2 for entry (Ge et al., 2013). A mouse model of SARS-CoV infection revealed that the infection degree of the disease increases with the overexpression of human ACE2, which indicates that ACE2 is critical for viral entry into cells (X. H. Yang et al., 2007). Studies show that ACE2 proteins expressed on human HeLa cells, Chinese horseshoe bats, civets, and pigs, allowed host cell entry and subsequent viral replication (P. Zhou et al., 2020). SARS-CoV-2 uses the SARS-CoV receptor ACE2 entry into host cells. The affinity between ACE2 and the S protein of SARS-CoV-2 is much higher than that of the S protein of SARS-CoV. The human-to-human transmission of SARS-CoV-2 seems easier. Furthermore, serine protease TMPRSS2 prepares the S protein for SARS-CoV-2 (Hoffmann et al., 2020).

It is well established that the ACE2 receptor has been found on many cells' surface (Lukassen et al., 2020). The level of ACE2 expression has an impact on infection in different tissues. Human ACE2 is primarily expressed on type II and type I alveolar epithelial cells, suggesting that these tissues are susceptible to the virus. The risk of infection is higher than in tissues with low expression levels of ACE2. Pneumonia-associated symptoms of infected patients indicate that SARS-CoV-2 primarily infects the respiratory tract, which becomes the transmission route of the virus (Chaolin Huang et al., 2020). A previous study revealed that different tissues expressed different levels of ACE2, and the data indicated that SARS-CoV-2 may infect other human tissues (i.e., duodenum, small intestine, and heart) besides the lungs. For instance, stool from patients with SARS-CoV-2 was in favour for SARS-CoV-2, which gives a hint that the gastrointestinal tract may be infected by the virus (Smith & Turner, 2004), which is in accordance with the high-level ACE2 expression in the gastrointestinal tract (i.e. stomach, duodenum, and rectal epithelial cells) (Bao et al., 2020). Furthermore, a previous study showed that ACE2 can protect from acute lung failure except for facilitating viral entry, which suggests that the ACE2-Ang (1–7)-Mas axis can be carefully manipulated to mitigate SARS-induced tissue injuries(Imai et al., 2005; Kuba et al., 2005). In this way, it offers a potential target for therapeutic intervention.

Drug treatment for SARS-CoV-2

1 RNA polymerase- RNA dependent inhibitors

1.1 Broad-spectrum antiviral drug -Remdesivir

Currently, remdesivir is a potential drug against SARS-CoV-2 that is being tested in randomized control trials. It is approved by the USFDA for emergency medicine treatment. Remdesivir (formerly GS-5734) is a monophosphate prodrug, which is metabolized to produce active C-adenosine nucleoside triphosphate analogues. The drug was found in the process of screening antibiotics with anti-RNA virus activity. It has a low EC_{50} and its selectivity to the host polymerase of the Ebola virus has developed drugs for the treatment of Ebola infections (Siegel et al., 2017). Remdesivir is a potential therapeutic agent for COVID-19 because of its broad-spectrum of activity and effective *in vitro* antivirus activities.

According to previous data, remdesivir has a strong EC_{90}value (1.76 μM) against COVID-19 in Vero E6 cells, and remdesivir also inhibited human hepatoma cell line (human liver cancer Huh-7 cells), which is sensitive to COVID-19 (M. Wang et al., 2020). The first COVID-19 patient diagnosed in the United States has an improved clinical status after intravenous injection of remdesivir (Holshue et al., 2020). Three other hospitalized patients, with worsening clinical status, received remdesivir, which inhibits viral replication by incorporating into the nascent viral RNA and inhibiting the RNA-dependent RNA polymerase (Mulangu et al., 2019). Meanwhile, *in vitro* studies show that remdesivir inhibits SARS-CoV-2 replication in non-human cells ("Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States," 2020). There are successful case reports of remdesivir against COVID-19

infections. There are 66 ongoing clinical trials to assess the drug's safety and antiviral activity in patients with mild, moderate, or severe COVID-19 (Sanders, Monogue, Jodlowski, & Cutrell, 2020). However, among the crippling side effects of remdesivir, the commonest one is a reversible increase in transaminases, which may cause kidney damage (Sheahan et al., 2020). Therefore, its use still needs to be based on the specific clinical situation of the patient (Table 1).

1.2 Ribavirin

SARS-CoV-2, a single-stranded RNA beta coronavirus, reproduces itself by utilizing enzymes such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase. The potential therapy against SARS-CoV-2 may target to its virus structure. For instance, a study reported that nucleoside analogs are effective against HIV and respiratory viruses by targeting the viral RNA polymerase (Li & De Clercq, 2020). Owing to the similarity of structure between SARS-CoV-2 and HIV or respiratory virus, nucleoside analogues may have a therapeutic role by blocking RNA synthesis in SARS-CoV-2. Ribavirin, a guanine analog, showed activity against other coronaviruses, showing itself as a suitable candidate for COVID-19 treatment. A clinical study on SARS revealed that 126 SARS-CoV patients on ribavirin treatment, presented with hemolysis and anemia in up to 76% and 49% of the cases, respectively (Booth et al., 2003; Tan et al., 2004). And *in vivo*study demonstrated that the serum concentrations of ribavirin, inhibited viral replication effectively, surpassed the safe human concentration (Tan et al., 2004). *In vitro* data suggests that ribavirin monotherapy confers rapid resistance for SARS and MERS, whereas the combination therapy with Lopinavir/ritonavir or chloroquine analogs showed potential activity ("[Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]," 2020; Falzarano et al., 2013).

The therapeutic regimen of ribavirin is 500 mg twice/thrice in a day combined with Lopinavir/ritonavir or IFN-α, based on the Treatment Plan Revised Edition 5 from China (" Treatment Plan Edition 5 revision edition," 2020). Although this information may be updated as new evidence becomes available, previous experience in SARS and MERS can provide an appropriate direction for enhancing the efficacy of ribavirin. An in vitro study demonstrated antiviral activity against the WIV04 strain of SARS-CoV (M. Wang et al., 2020). There is no sufficient data on clinical trials for ribavirin, thus its efficacy may be speculated from the experience against MERS and SARS.

The most commonest adverse effect of ribavirin is hemolytic anemia, which occurred in up to 61% of the patients in a study assessing its adverse effects in the treatment of SARS (Knowles, Phillips, Dresser, & Matukas, 2003). Hemolytic anemia occurs within 3-5 days after high loading doses (> 1-2 g) against coronavirus infection (C. H. Chang, Chen, Lai, & Chan, 2002; Chu et al., 2004). Ribavirin is eliminated primarily through renal excretion; it is important to effect strict dose reductions that vary based on the indication, for patients with renal insufficiency. Ribavirin has teratogenic potential and is contraindicated in pregnancy and male partners of pregnancy (Altınbas, Holmes, & Altınbas, 2020).

The evidence from the treatment of ribavirin against other coronaviruses suggests limited efficacy and potential toxicity, which indicates that its therapy in patients with COVID-19 should be considered as combination therapy for enhancing the clinical efficacy.

2 Viral protease inhibitors

2.1 Lopinavir/Ritonavir

Lopinavir/ritonavir (Kaletra), an orally administered co-formulated ritonavir-boosted protease inhibitor (PI), can be coalesced into another antiretroviral drugs for the treatment of HIV-1 infection in adults, adolescents and children (Croxtall & Perry, 2010). For good tolerability, the co-administration of lopinavir with a low boosting dose of ritonavir can increases its bioavailability by reducing its hepatic clearance, therefore allowing for lower therapeutic dosages (Scott, 2005). Lopinavir functions by inhibiting the activity of HIV protease enzymes, which prevents the cleavage of polyproteins, leading to the result of immature, non-infectious HIV particles. Meanwhile, ritonavir inhibits CYP3A metabolism and increases the half-life of lopinavir when used in combination, which results in elevated levels, boosting its inhibition of HIV protease

(Porche, 2001). Previous studies show that Lopinavir/ritonavir can inhibit the replication of coronavirus to a certain extent (Chu et al., 2004; Götz et al., 2016). Chinese scholars found that the combination of Lopinavir/ritonavir and interferon-β for the treatment of MERS-CoV is better than the control in an infectious marmoset animal model (Chan et al., 2015). During the SARS epidemic in 2003, studies found that 41 SARS patients, who took the treatment of the Lopinavir/ritonavir - ribavirin combination, had reduced ARDS or a lower risk of death compared with 111 SARS patients treated with ribavirin (Chu et al., 2004). In 2016, King Abdullah International Medical Research Center launched a placebo-controlled clinical trial (NCT02845843), the regimen as follows: Lopinavir /Ritonavir (400mg +100 mg/ml) twice a day for 14 days and Interferon β -1b (0.25 mg) subcutaneous once every other day for 14 days. The result showed that the combination of Lopinavir/ritonavir and interferon-β can ameliorate the patients' condition with MERS-CoV. A clinical randomized controlled study on the efficacy and safety of Lopinavir/ritonavir combined with interferon-β (ChiCTR2000029308) in patients with COVID-19 infection is currently underway.

Researchers have also focused on the therapeutic effect of Lopinavir/ritonavir on COVID-19 based on related literature on Lopinavir/ritonavir for the treatment of MERS-CoV and SARS-CoV. Lopinavir/ritonavir has been proposed as a potential treatment of COVID-19 (Kim et al., 2020; Michele, Maria Anna Rachele De, & Giovanni Nicola, 2020; Nutho et al., 2020). The administration protocol for Lopinavir/Ritonavir for one treatment case was two tablets oral bid (lopinavir 200 mg/ritonavir 50 mg) starting from the early stage of the disease (day 10 of illness). Quantitative reverse transcription (RT) -PCR results showed that the coronavirus load of the patient decreased from the second day of administration, and no detectable or very small titer of coronavirus was observed thereafter (Lim et al., 2020). This case suggested that the COVID-19 may induce relatively mild symptoms and the patient can recover after an early diagnosis of pneumonia by taking Lopinavir/ritonavir (D. Chang et al., 2020; Q. Li et al., 2020; Rothe et al., 2020). Therefore, Lopinavir/ritonavir can be recommended for COVID-19 pneumonia (elderly patients or patients with underlying diseases) from the early stage. However, there should be more evidence needed from well-controlled clinical trials to demonstrate the clinical efficacy of Lopinavir/ritonavir.

An enzyme named 3-chymotrypsin-like protease (3CLpro) is is of uttermost importance in the processing of SARS-CoV-2 viral RNA. The action of 3CLpro could be inhibited by Lopinavir/ritonavir, a protease inhibitor that could thereby disrupt the the virus from replicating and releasing from the host cell (Anand, Ziebuhr, Wadhwani, Mesters, & Hilgenfeld, 2003). As a commonly-used treatment for COVID-19, patients take Lopinavir/ritonavir with food, 400 mg/100 mg twice a day, for 14 days (Cao et al., 2020; Chan et al., 2020). The commonest moderate to severe adverse reactions for the drugs are abnormal stools, diarrhea, weakness, headache, and nausea. The adverse reactions may be exacerbated due to the viral infection for patients with COVID-19. As showed in recent research, almost half of the patients who took Lopinavir/ritonavir therapy experienced a side-effect and 14% of them got so bothered by gastrointestinal adverse effects as to discontinue therapy (Cao et al., 2020). The drug interactions and potential side-effects indicated that Lopinavir/ritonavir in COVID-19 treatment need more clinical trial data and more supporting evidence.

3 Inhibitors to fusion between cell membrane and virus

3.1 Chloroquine and Chloroquine derivatives

Chloroquine (CQ) and hydroxychloroquine (HCQ), have been widely used to prevent or treat malarial or immune-mediated diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). To date, these medications are not suitable to treat viral infections and there is no evidence supported by well-controlled, prospective, randomized clinical studies that demonstrate the efficacy of their use in patients with COVID-19. Nevertheless, CQ and HCQ are being studied alone or in combination with other agents to assess their effectiveness in the treatment or prophylaxis for COVID-19 (Nicol et al., 2020). The two drugs showed positive in vitro and clinical antiviral activity against SARS-CoV-2 (Gautret et al., 2020; Liu et al., 2020; Yao et al., 2020), which suggests that CQ and HCQ can be potential treatments for COVID-19. Many studies show that the two 4-aminoquinolines drugs have in vitro activity against a range of viruses (D'Alessandro et al., 2020). Their efficacy has been attributed to different mechanisms. For instance, because they have weakly basic pH, whereas the endosome in the host cell is pH-dependent, they can inhibit viral entry to the

host cell, the autophagosome-lysosomal fusion, and glycolsyltransferase (Salata, Calistri, Parolin, Baritussio, & Palù, 2017). The antiviral mechanism associated with glycosyltransferase is achieved by inhibiting viral glycosylation (Savarino, Boelaert, Cassone, Majori, & Cauda, 2003). Besides, there are recent reports saying that CQ may be an inhibitor of quinone reductase-2, a concerned enzyme in sialic acid biosynthesis, which may impact on HIV, SARS-CoV, and orthomyxoviruses due to the presentation of sialic acid on HIV-1 glycoproteins, ACE2 receptor of SARS, and orthomyxovirus receptors (Kwiek, Haystead, & Rudolph, 2004; Savarino, Di Trani, Donatelli, Cauda, & Cassone, 2006). Thus, CQ may have an impact on SARS-CoV-2 due to ACE2 receptor.

Studies have revealed that CQ has a therapeutic effect in animal infection models induced by HCoV-OC43 and has a strong antiviral effect against SARS-CoV infection in cell cultures (Keyaerts et al., 2009; Vincent et al., 2005), This indicates that CQ has therapeutic activity against viruses. CQ has shown *in vitro* activity against clinical isolates of COVID-19 at low (micromolar) concentrations. CQ was successfully used to treat >100 cases of COVID-19 leading to improved radiological findings, enhanced virus clearance; reducing disease progression (J. Gao, Tian, & Yang, 2020). Besides, Astudy in Vero E6 indicated that CQ plays a functional role in the entry and post-entry stages of SARS-CoV-2 infection and can modulates the immune response, which may synergistically enhance its in vivo antiviral effect (M. Wang et al., 2020).

A hydroxyl group makes HCQ safer than CQ. An *In vitro* study revealed that the EC_{50} values for HCQ, at 24 and 48 hours, were lower than the EC_{50} values for CQ in both treatment and prophylaxis groups. This indicates that HCQ is more effective *in vitro* than CQ for both prophylaxis and treatment (Yao et al., 2020). The *in vitro* experiments got positive outcomes, which set clinical trials in motion to explore more about the HCQ effect on COVID-19. Twenty patients were treated using HCQ and were confirmed by comparing the PCR results with 16 controls in France. HCQ was effective in viral load reduction of asymptomatic and patients with both lower and upper respiratory tract infections. The decreased viral load continued after 3, 4, 5, and 6 days of treatment (Gautret et al., 2020), which suggests that HCQ is a promising therapy for inhibiting the virus entry.

Currently, the dose of CQ against COVID-19 is 500 mg orally once or twice a day, for [?]10 days (Colson, Rolain, Lagier, Brouqui, & Raoult, 2020). However, data on the optimal dose to ensure its safety and effectiveness are not sufficient. The recommendation from pharmacokinetic modeling study suggests the optimal dose for HCQ in COVID-19 treatment, the patients can take a loading dose of 400 mg twice in the first day of treatment and then take 200 mg twice a day (Yao et al., 2020). However, both drugs have several adverse reactions, including prolonged QT interval, hypoglycemia, anaphylaxis, and retinopathy (Kalil, 2020). HCQ is relatively better tolerated than CQ, and its adverse reactions mainly include gastrointestinal reactions, skin damage, neurological symptoms, and retinopathy (Yusuf, Sharma, Luqmani, & Downes, 2017). Animal experiments show that CQ is more toxic than HCQ (P. Jordan, Brookes, Nikolic, & Le Couteur, 1999). Studies show that severe fatal arrhythmia can occur after a single intake of more than 4.0 g HCQ, which is regarded as a severe syndrome (Yanturali, Aksay, Demir, & Atilla, 2004). It is also reported that patients treated with 36g HCQ were successfully rescued (de Olano, Howland, Su, Hoffman, & Biary, 2019). Some elderly patients who have died from COVID-19 had cardiovascular comorbidities; the use of HCQ and CQ may increase the risk of cardiac death (Wu & McGoogan, 2020; Young et al., 2020). Hepatitis and neutropenia are clinical manifestations of COVID-19, and both hepatic and bone marrow dysfunctions could be worsened in the off-label use of these drugs. Besides the antiviral effect of CQ and HCQ, their affordability and safety make them more suitable for clinical use against COVID-19 infections. Further studies are needed to determine the optimal dose for COVID-19 and physicians should pay more attention to the adverse reactions when treating COVID-19 patients with CQ and HCQ.

Chloroquine phosphate is a derivative of CQ and is also an antimalarial drug. The drug also inhibits SARS-CoV replication *in vitro* , mainly by reducing the terminal glycosylation of the ACE2 on the surface of Vero E6 cells, therefore, interfering with the combination of SARS-CoV and ACE2 (Q. Gao, 2020). The cases of lung imaging in a study show an effective response in > 100 patients: the exacerbation of pneumonia is inhibited, with a virus-negative conversion put forward and a shortened disease course. No obvious serious adverse

reactions could be found among the patients (J. Gao et al., 2020). The adverse reactions of chloroquine phosphate are usually mild and reversible after withdrawal (Y. J. Duan et al., 2020). However, its acute poisoning and accumulated toxicity require attention in the case of large-dose and long-term treatment. It is recommended to include chloroquine phosphate in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China, to treat a wide range of COVID-19 infections.

3.2 Arbidol

Arbidol, a drug used for prophylaxis and treatment of influenza and respiratory viral infections in Russia and China, targeted ACE2 S protein interaction and blocked viral fusion to the target cell membrane (Kadam & Wilson, 2017). This drug has demonstrated activity against several viruses including SARS (P. C. Jordan, Stevens, & Deval, 2018). A study showed that arbidol and arbidol mesylate can inhibit the reproduction of SARS-CoV *in vitro* (Khamitov et al., 2008). Several lines of evidence revealed that single use of arbidol or combination with antiviral drugs may provide beneficial effects in patients with COVID-19 pneumonia (Wang, Chen, Lu, Chen, & Zhang, 2020; X. W. Xu et al., 2020; J. Zhang et al., 2020). Data from a small number of patients treated with arbidol combined with Lopinavir/ritonavir showed that these drugs delayed the progression of lung lesions and lowered the possibility of respiratory and gastrointestinal transmission thereby decreased the viral load of COVID-19 (Deng et al., 2020). Currently, many randomized clinical controlled trials are in progress to investigate how efficacious arbidol is for COVID-19 pneumonia in China.

4 Immunomodulator

4.1 IL-6 inhibitor

Coordinated cytokine response is a necessary condition for host immune response. Nevertheless, uncoordinated response results in excessive inflammation in some patients infected with COVID-19. The concentration of cytokines, granulocyte-macrophage colony stimulating factor and interleukin-6 in plasma are higher than in non-infected people. This not only suggests that cytokine secretion is related to the severity of the disease, but also indicates that inhibition of excessive inflammatory response may be an adjuvant therapy for COVID-19 (Guan, Ni, Hu, Liang, Ou, He, Liu, Shan, Lei, Hui, Du, Li, Zeng, Yuen, Chen, Tang, Wang, Chen, Xiang, Li, Wang, Liang, Peng, Wei, Liu, Hu, Peng, Wang, Liu, Chen, Li, Zheng, Qiu, Luo, Ye, Zhu, Zhong, et al., 2020). A clinical result from Chinese research reveals that IL-6 may probably be a key to this inflammation (F. Zhou et al., 2020). Therefore, it may reverse this process and improve clinical conditions to direct monoclonal antibodies towards IL-6.

Tocilizumab, an interleukin-6 (IL-6) receptor blocking antibody, serves as an inhibitor to IL-6-mediated signal transduction hence control inflammation (Le et al., 2018). An early clinical report revealed that 91% of 21 patients with COVID-19 showed improvement in respiratory function and decline in fever after taking tocilizumab. Preliminary data showed that tocilizumab reduced mortality. It provides immediate improvement severe cases of COVID-19. Tocilizumab treatment resolved symptoms, such as hypoxemia and CT shadow changes (X. Xu et al., 2020). Mechanistically, tocilizumab regulates IL-6 thereby promote the release of inflammatory cytokines. It is therefore an effective drug for treating patients with severe COVID-19 (Zhang, Wu, Li, Zhao, & Wang, 2020).

Currently, multiple randomized controlled trials for single or combined use of tocilizumab in patients with COVID-19 complicated with severe pneumonia are ongoing in keeping with the Chinese national treatment guidelines (Sanders et al., 2020). For example, Some administrations also study Tocilizumab with favipinavir, in order to realize the potential synergistic effect of the two drugs (NCT04310228). Furthermore, it should also be noted the potential adverse drug reactions. Tocilizumab can increase the risk of infections, especially infections of the upper airways. It can also pose risk of AST transaminases, hypertension, hematological effects, hepatotoxicity, gastrointestinal perforation, hypersensitivity reactions to the active principle (Sheppard, Laskou, Stapleton, Hadavi, & Dasgupta, 2017).

4.2 Other Inhibitors for cytokine storm

After the body is infected with the virus (e.g., respiratory syncytial virus), natural immunity (e.g., NK cells, macrophages) occurs within 1-3 days after infection, and then the activated immune cells will release many cytokines (e.g., interleukins, interferon) within 4-7 days, which can activate more immune cells through cascade amplification, even include T cells and B cells. In the final stage (Days 7-9), B cells may become mature and will produce some specific antibodies, or neutralizing antibodies, which can control the virus as soon as possible. In addition, the immune response of specific T cells can also control the virus (Openshaw & Tregoning, 2005). Antibodies and cytokines produced through immune activation can attack viruses. At the same time, these cytokines and activated immune cells will reach various organs with blood circulation. Once this attack is too aggressive, it is easy to attack its own substances as foreign substances, which then cause damage to organs. Therefore, when dealing with viruses, we should also pay attention to the treatment of excessive immune response. Otherwise the damage to the body still exists. Currently, new methods for treating cytokine storms can be achieved through the following main inhibitors: IL-1 inhibitors, IL-6 inhibitors (mentioned above), GM-CSF inhibitors, and JAK inhibitors.

A retrospective study on IL-1 antagonists (Anakinra) indicated that among moderate-to-severe ARDS, and hyperinflammation patients (aged [?]18 years) with COVID-19, 29 of them used high doses of IL-1 antagonists. 16 people were enrolled in the reference group. It can be seen that after 21 days of treatment, the group using the IL-1 receptor antagonist had a 10% mortality rate, and the reference group was 44%, indicating that IL-1 antagonist can reduce the mortality rate (Cavalli et al., 2020). In addition to anakinra, other anti-IL-1 antibodies, such as canakinumab, are also undergoing clinical trials.

The study found that there were two cytokines increased in novel coronavirus patients, one is IL-6, and the other is GM-CSF. An open-label clinical trial on the anti-GM-CSF receptor antibody, Mavrilimumab, revealed that among the severe patients without invasive ventilator, the experimental group was 13 people, and the control group was 26 people, then after 14 days treatment, 85% of the treatment group had improved clinical symptoms, and the control group was lower, only 42% improved. The key data was that there was zero death in the treatment group and 27% in the control group. In addition, the mortality rate of patients using mechanical ventilation is 8% in the treatment group and 35% in the control group, so the treatment also reduces this rate(Y. Zhou et al., 2020).

4.3 Convalescent Plasma

Convalescent plasma refers to the plasma collected from patients recovered from an infection and the development of the corresponding antibodies. The plasma is infused into patients with the disease. This passive antibody administration may provide immediate immunity to susceptible individuals (Bloch et al., 2020). The unique characteristic of convalescent plasma is that it does not only contain antibodies but instead has all the "molecular tools" extracted from the COVID-19 healer. The repertoire of plasma-based factors that are infused with neutralizing antibodies include anti-inflammatory cytokines, anti-clotting factors, natural antibodies, specialized pro-resolving mediators (e.g., resolvins, protectins, maresins), defensins, pentaxins, collectins, plus an undefined number of unknown mediators (Rojas et al., 2020). This molecular arsenal can play a role in improving virus clearance, participating in B and T lymphocytes, limiting the cascade of inflammation, preventing microembolism and promoting tissue repair (Rojas et al., 2020). Anti-SARS-CoV-2 non-neutralizing antibodies that bind to the virus without hindering virus replication can still promote recovery by recruiting innate immune cells (Rojas et al., 2020). Convalescent plasma has aroused great interest for prophylaxis in health care workers and other caregivers while no other treatment for virus infections is available or in an emergency (Jahrling, Frame, Rhoderick, & Monson, 1985; Jahrling & Peters, 1984). Historical data have reported the safety and effectiveness of convalescent plasma in other infectious diseases. Spanish flu was the first viral infection that is effectively responded to convalescent plasma in clinical studies. A meta-analysis of 8 studies on Spanish influenza (1703 patients) showed that treatment with convalescent plasma can reduce mortality (Luke, Kilbane, Jackson, & Hoffman, 2006). There are studies on the treatment of SARS-CoV (Cheng et al., 2005), MERS-CoV (Ko et al., 2018), and H1N1 (Hung et al., 2011) with convalescent plasma. Prior studies reveal that three infected healthcare workers recovered from SARS-CoV infection after administration of convalescent plasma from three recovered SARS-CoV patients, and there

was no residual virus from the convalescent plasma as determined using RT-PCR. The ultimate results of no viral load and increased anti-SARS-CoV IgM and IgG indicated that efficacy of convalescent plasma and it can be a potential treatment for virus infections. One of the healthcare workers got pregnant later and positive anti-SARS-CoV IgG was detected in the newborn, which indicated a possibility that anti-SARS-CoV antibody can transfer from mother to newborn passively (Yeh et al., 2005).

There is new data on convalescent plasma used to treat COVID-19 in the current pandemic. Mechanical ventilation was given to five crucially ill COVID-19 patients (age range, 36-65 years; 2 women); all had received antiviral agents and methylprednisolone concurrently. The patients recovered from SARS-CoV-2 infection after plasma transfusion from donors (age range, 18-60 years) and continuously improved as follows; 4 of 5 patients got their body temperatures normalized within 3 days. The viral loads declined and became negative within 12 days after the transfusion, while SARS-CoV-2–specific ELISA and neutralizing antibody titers increased after the transfusion. 3 patients was released from the hospital (hospitalization time : 53, 51, and 55 days), and 2 were in stable condition 37 days after transfusion (Shen et al., 2020). The administration of convalescent plasma was monitored in this preliminary uncontrolled case series, and improved the patient's clinical status. However, the limited sample size cannot effectively demonstrate the efficacy and safety of convalescent plasma. Therefore, clinical trials of COVID-19 patients treated with convalescent plasma are needed. A pilot study on 10 patients with severe COVID-19 showed that the tolerance is good and clinical symptoms improved with the increase of oxyhemoglobin saturation after a single dose of 200 mL convalescent plasma transfusion (K. Duan et al., 2020). The advantages of convalescent plasma include potencial clinical efficacy, easier accessibility from a large donor pool, prophylactic benefits for healthcare workers, short-time (Casadevall & Pirofski, 2020), and low-cost over some experimental antivirals (Leider, Brunker, & Ness, 2010). However, there are risks of passive administration of convalescent plasma, including identification of ideal donors due to the lack of widely available and validated SARS-CoV-2 antibody assays, finding donors with a robust humoral response, consenting, collecting, and testing donors (Arabi et al., 2016; Park et al., 2015; Sullivan & Roback, 2020). There are known risks concerning blood substances transferation. One among the risks is that convalescent sera administration could imbue individuals with pulmonary disease, which would cause plasma infusion and pose certain risks for transfusion-related acute lung injury (TRALI) (Gajic et al., 2007). The phenomenon of antibody-dependent enhancement of infection (ADE) is another theoretical risk. Evidence from 245 COVID-19 patients who take the treatment of convalescent plasma suggests that it is safe (Viswanathan et al., 2020). Therefore, the advantages and disadvantages of convalescent plasma therapy must be weighed through the data in the literature review and specific patient situation.

4.4 Neutralizing antibody

The neutralizing antibody-mediated humoral response is a decisive role in prevention of viral infections. The neutralizing antibodies (NAbs) induced by vaccines or infected virus will bind to the surface epitopes of viral particles, and thus can reduce viral infectivity. In this way, they block entry of the virus into an infected cell (Klasse, 2014). Given the high affinity of the S protein for human ACE2 which explains the high rate of human-to-human transmission, the S protein is a potential target for antibody-mediated neutralization. It was reported that RBD within S1 unit is the most critical target for SARS-CoV Nabs (Wong, Li, Moore, Choe, & Farzan, 2004). There is evidence that RBD region can be recognized by most of Nabs (Coughlin et al., 2007; Duan et al., 2005; Greenough et al., 2005; Sui et al., 2004; ter Meulen et al., 2006; van den Brink et al., 2005; Z. Zhu et al., 2007). In a previous study, specific antibodies against SARS-CoV, such as, 80R (Sui et al., 2004), CR3014 (van den Brink et al., 2005), CR3022 (ter Meulen et al., 2006), and m396 (Z. Zhu et al., 2007), were identified by phage from both naive and immune antibody libraries, which led to the blockage of the binding of S1 domain and ACE2. In addition, 80R, CR3013, and m396 showed virus neutralization and prophylaxis capability *in vitro*or animal models (ter Meulen et al., 2006). Two NAbs, 201 and 68 which are effective for virus prophylaxis in animal models, were identified in transgenic mice transgenic mice carrying human immunoglobulin genes. The mice have been used for producing NAbs against SARS-CoV via antigen immunization (Coughlin et al., 2007; Greenough et al., 2005).

The fasted and simple method of combating SARS-CoV-2 is the use of convalescent plasma mentioned above, which can induce polyclonal Nabs (Cheng et al., 2005), but SARS-CoV-2-specific neutralizing monoclonal antibodies have also been reported. These neutralizing antibodies can effectively treat COVID-19 (P. Zhou et al., 2020). However, it been observed that SARS-CoV NAbs do not effectively bind to SARS-CoV-2 S protein (X. Tian et al., 2020; Wrapp et al., 2020). As showed in a study, a SARS-CoV antibody, CR3022, bound to SARS-CoV-2 RBD with high affinity, but its neutralization capability is unkown (X. Tian et al., 2020). There is another study recording that SARS-CoV RBD-specific polyclonal antibodies and SARS-CoV-2 infection in HEK293T cells neutralized each other, stably expressing the human ACE2 receptor, hence it can be used to develop SARS-CoV RBD-based vaccines that might eventually prevent SARS-CoV-2 and SARS-CoV infection (Tai et al., 2020). In the treatment of Ebola and SARS viruses, a mix of NAbs showed stronger neutralization capability than onefold NAbs (Davey et al., 2016; ter Meulen et al., 2006). Therefore, by using the mixture of several potent Nabs, escape virus is less likely to be isolated with decreased sensitivity to neutralization. Since there are no SARS-CoV-2-specific vaccines and antibodies, it is also possible that a single use or combination of SARS-CoV RBD-targeting NAbs might provide prophylaxis and treatment benefits against SARS-CoV-2 infection.

4.5 Ιντερφερον-α ανδ -β

Human immune system fight against viral infections by release interferon (Alpha, Beta), which inhibits the proliferation of viruses by inducing the synthesis of antiviral proteins. Interferon drugs are used as a broad-spectrum antiviral drug in clinical practice. Previous study has demonstrated that interferon-α and -β showed antiviral activity against MERS (Morra et al., 2018; Stockman, Bellamy, & Garner, 2006). A study demonstrated the antiviral effects of interferon-α2β and ribavirin on the replication of nCoV isolates hCoV-EMC / 2012 in Vero and LLC-MK2 cells (Falzarano et al., 2013). National Health Commission issued the "Diagnosis and treatment protocol for novel coronavirus pneumonia (version 7)", which recommend that interferon alpha is taken by atomization inhalation. Adults should take 50μg in 2ml of sterile water via injection each time twice a day. Interferon alpha can be used as a novel drug to improve virus clearance effect of the respiratory mucosa of patients (Commission, 2020). Currently, a multi-center, blank-controlled, randomized, open, multi-stage clinical study is ongoing aimed at evaluating the efficacy and safety of recombinant human interferon α1β in treating patients with COVID-19 in Wuhan (NCT04293887) (ClinicalTrails.gov, 2020). However, there is no data on animal or human studies to recommend their clinincal use to combat COVID-19. Further verification of its safety and efficacy is required.

4.6 Corticosteroids

Acute lung injury (ALI) or ARDS was seen in cases of late phase severe SARS. Corticosteroids were adopted to suppress lung inflammation in MERS and SARS due to their immunomodulatory properties. Some clinical trials suggested that high-dose of corticosteroids reduced mortality of SARS without increasing the risk of life-threatening complications (Ho et al., 2003; Sung et al., 2004; Zhong, 2004). A retrospective study on adverse outcomes of SARS patients with hormone therapy showed that patients developed adverse reactions, and hormone therapy increased the risk of admission to the intensive care unit or death by 20.7 times (Auyeung et al., 2005). Elsewhere, a retrospective study showed that appropriate use of hormones in patients with severe SARS can reduce mortality and shorten hospital stay. Moreover, they found that hormones did not cause serious secondary lower respiratory tract infections and other complications (R. C. Chen et al., 2006). In February, 7, 2020, an article published on *the Lancet* suggested that it is insufficient for current clinical evidence to support the hormone therapy in treating ALI resulting from SARS-CoV-2 (Russell, Millar, & Baillie, 2020). Following the epidemic of SARS, the efficacy and safety of glucocorticoids is considerably understood. Corticosteroids should be used with caution for patients with COVID-19. Furthermore, physicians should strictly follow the indications, drug dosage and course of treatment. However, for critically ill patients with rapid progression, appropriate use of corticosteroids in addition to a ventilator support should be measured to prevent the progression of acute respiratory distress syndrome.

5 Traditional Chinese medicine

In the latest treatment guidelines, Chinese doctors included traditional Chinese medicine as one of the drugs for COVID-19 (Guan, Ni, Hu, Liang, Ou, He, Liu, Shan, Lei, Hui, Du, Li, Zeng, Yuen, Chen, Tang, Wang, Chen, Xiang, Li, Wang, Liang, Peng, Wei, Liu, Hu, Peng, Wang, Liu, Chen, Li, Zheng, Qiu, Luo, Ye, Zhu, Zhong, et al., 2020). Earlier studies showed that traditional Chinese medicine products used for the treatment of respiratory infectious diseases may provide treatment benefits to COVID-19. For instance, Lianhuaqingwen capsule and Shufengjiedu capsule have independent antiviral effect and synergistic antiviral effect on influenza virus, respectively (Ding et al., 2017).

In addition, Qingfei Paidu decoction and Glycyrrhiza Ganjiang decoction, two general medicines, have been proposed as treatments for COVID-19 in China (Ren, Zhang, & Wang, 2020) A research showed that 4 cases of COVID-19 showed improvement after treatment with Lopinavir / Ritonavir, Abido, and Shufeng jiedu capsule. However, the efficacy, safety and mechanisms of these drugs against COVID-19 should be further confirmed in clinical experiments (Guan, Ni, Hu, Liang, Ou, He, Liu, Shan, Lei, Hui, Du, Li, Zeng, Yuen, Chen, Tang, Wang, Chen, Xiang, Li, Wang, Liang, Peng, Wei, Liu, Hu, Peng, Wang, Liu, Chen, Li, Zheng, Qiu, Luo, Ye, Zhu, Zhong, et al., 2020). Currently, there are no specific antiviral drugs or vaccines for COVID-19. The drugs used to treat patients are selected in accordance with experience from previous treatments of SARS, MERS, or other new influenza viruses (Lu, 2020). Moreover, traditional Chinese medicines not only weaken the virus, but also prevent infection, regulate immune response, block inflammation, and help the patients recover. Furthermore, the prevention and treatment measures of COVID-19 fully reflect the idea of "prevention and treatment of diseases" (Ren et al., 2020).

Vaccines of SARS-CoV-2

As of April 8, 2020, 115 candidate vaccines for COVID-19 were being tested globally, of which 78 vaccines have been confirmed to be effective. Among them, 73 vaccines are in the exploratory or preclinical stage. The most advanced candidates, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio), have recently entered the clinical development stage. These advanced vaccines can be used in conjunction with newly developed COVID-19 vaccines (Thanh Le et al., 2020).

Vaccines work by exposing the body to antigens that do not cause disease, but trigger an immune response that can block or kill the virus if a person is infected. At least four types of vaccines are used against coronaviruses including, virus vaccines, nucleic-acid vaccines,viral vector vaccines, and protein-based vaccines(Callaway, 2020). To data, many vaccines are in different stages of clinical trials to evaluate their effectiveness and safety (Figure 2, table 2).

Multiple strategies are applied to produce vaccines against COVID-19. The commonest is exposed spike (S) glycoprotein or S protein which serves as the main trigger of neutralizing antibody, such as full-length S protein or S1 receptor binding domain (RBD) and expressing in virus-like particles (VLP), DNA or viral vector (Graham, Donaldson, & Baric, 2013). Our team uncovered a role of a recombinant vaccine for COVID-19 (A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity) last month (J. Yang et al., 2020).

In fact, effective vaccines and treatments against this new virus will be facilitated by the achievements in developing SARS-CoV vaccines, MERS-CoV vaccines/therapies, and recent advances in COVID-19 (Dhama et al., 2020).

Conclusion

The global pandemic of novel coronavirus has attracted much research attention into the pathogenesis mechanism, immune mechanism, and treatment strategies. Currently, there is current no definite and specific drug for prevention or treatment of COVID-19. Patients are often treated with the reported medicines showing efficacy against SARS-CoV from historical experience. Such drugs include, CQ, HCQ, ribavirin, remdesivir and Lopinavir/ritonavir. In 17, June, the latest reports indicate that the branch clinical trials on HCQ have been discontinued due to lack of efficacy in reducing fatality rate of patients with COVID-19. In addition to drug therapy, immunotherapy has also been developed. For instance, interferon therapy,

neutralizing antibody therapy and convalescent plasma therapy have been studied, but their efficacy and safety should be investigated in detail. In addition, severe patients with COVID-19 show elevated secretion of cytokines caused by excessive immune response. In cases where immune overexpression causes death of novel coronavirus, effective control of cytokine may decrease the mortality rate of COVID-19. The production of cytokine can be achieved using the following main inhibitors: IL-6 inhibitors, IL-1 inhibitors, GM-CSF inhibitors and JAK inhibitors. For the suppression of excessive immune response, there may not be a single specific medicine, while combination therapy of inhibitors can lower the cytokine storm curve. In conclusion, COVID-19 can be controlled by reducing the spread range of novel coronavirus by isolating. Furthermore, specific medicine, immunotherapy and preventive or therapeutic vaccines can be developed via further studies of pathogenesis and immune mechanism.

Last, we would like to thank all the medical staff who fought against the SARS-CoV-2, and thank all research teams working on SARS-CoV-2 for their outstanding contribution. The world will eventually defeat the virus.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgements

All authors read and approved the final manuscript. Furong Qin wrote the initial manuscript. Weiqi Hong contributed writing material and new ideas, and created the figures, and Xiawei Wei revised the manuscript and approved the final version.

Funding

This work is supported by the National Natural Science Foundation of China (No. 81602492), the National Key Research and Development Program of China (No. 2016YFA0201402), the National Major Scientific and Technological Special Project for "Significant New Drugs Development" (No. 2018ZX09733001) and by the Excellent Youth Foundation of Sichuan Scientific Committee Grant in China (No. 2019JDJQ0008).

Reference

Altınbas, S., Holmes, J. A., & Altınbas, A. (2020). Hepatitis C Virus Infection in Pregnancy: An Update. *Gastroenterol Nurs, 43* (1), 12-21. doi:10.1097/sga.0000000000000404

Anand, K., Ziebuhr, J., Wadhwani, P., Mesters, J. R., & Hilgenfeld, R. (2003). Coronavirus main proteinase (3CLpro) Structure: Basis for design of anti-SARS drugs. *Science, 300* (5626), 1763-1767. doi:10.1126/science.1085658

Arabi, Y. M., Hajeer, A. H., Luke, T., Raviprakash, K., Balkhy, H., Johani, S., . . . Alahmadi, M. (2016). Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. *Emerg Infect Dis, 22* (9), 1554-1561. doi:10.3201/eid2209.151164

Arentz, M., Yim, E., Klaff, L., Lokhandwala, S., Riedo, F. X., Chong, M., & Lee, M. (2020). Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *Jama, 323* (16), 1612-1614. doi:10.1001/jama.2020.4326

Auyeung, T. W., Lee, J. S., Lai, W. K., Choi, C. H., Lee, H. K., Lee, J. S., . . . Yeung, Y. M. (2005). The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study.*J Infect, 51* (2), 98-102. doi:10.1016/j.jinf.2004.09.008

Bao, L., Deng, W., Gao, H., Xiao, C., Liu, J., Xue, J., . . . Qin, C. (2020). Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. *bioRxiv* , 2020.2003.2013.990226. doi:10.1101/2020.03.13.990226

Bloch, E. M., Shoham, S., Casadevall, A., Sachais, B. S., Shaz, B., Winters, J. L., . . . Tobian, A. A. (2020). Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest, 130* (6), 2757-2765. doi:10.1172/jci138745

Booth, C. M., Matukas, L. M., Tomlinson, G. A., Rachlis, A. R., Rose, D. B., Dwosh, H. A., . . . Detsky, A. S. (2003). Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *Jama, 289* (21), 2801-2809. doi:10.1001/jama.289.21.JOC30885

Callaway, E. (2020). The race for coronavirus vaccines: a graphical guide. *Nature, 580* (7805), 576-577. doi:10.1038/d41586-020-01221-y

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., . . . Wang, C. (2020). A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med, 382* (19), 1787-1799. doi:10.1056/NEJMoa2001282

Casadevall, A., & Pirofski, L. A. (2020). The convalescent sera option for containing COVID-19. *J Clin Invest, 130* (4), 1545-1548. doi:10.1172/jci138003

Cavalli, G., De Luca, G., Campochiaro, C., Della-Torre, E., Ripa, M., Canetti, D., . . . Dagna, L. (2020). Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study.*Lancet Rheumatol, 2* (6), e325-e331. doi:10.1016/s2665-9913(20)30127-2

Chan, J. F., Kok, K. H., Zhu, Z., Chu, H., To, K. K., Yuan, S., & Yuen, K. Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect, 9* (1), 221-236. doi:10.1080/22221751.2020.1719902

Chan, J. F., Yao, Y., Yeung, M. L., Deng, W., Bao, L., Jia, L., . . . Yuen, K. Y. (2015). Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. *J Infect Dis, 212* (12), 1904-1913. doi:10.1093/infdis/jiv392

Chang, C. H., Chen, K. Y., Lai, M. Y., & Chan, K. A. (2002). Meta-analysis: ribavirin-induced haemolytic anaemia in patients with chronic hepatitis C. *Aliment Pharmacol Ther, 16* (9), 1623-1632. doi:10.1046/j.1365-2036.2002.01326.x

Chang, D., Lin, M., Wei, L., Xie, L., Zhu, G., Dela Cruz, C. S., & Sharma, L. (2020). Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China.*Jama, 323* (11), 1092-1093. doi:10.1001/jama.2020.1623

Channappanavar, R., & Perlman, S. (2017). Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol, 39* (5), 529-539. doi:10.1007/s00281-017-0629-x

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., . . . Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.*Lancet, 395* (10223), 507-513. doi:10.1016/s0140-6736(20)30211-7

Chen, R. C., Tang, X. P., Tan, S. Y., Liang, B. L., Wan, Z. Y., Fang, J. Q., & Zhong, N. (2006). Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. *Chest, 129* (6), 1441-1452. doi:10.1378/chest.129.6.1441

Cheng, Y., Wong, R., Soo, Y. O. Y., Wong, W. S., Lee, C. K., Ng, M. H. L., . . . Cheng, G. (2005). Use of convalescent plasma therapy in SARS patients in Hong Kong. *European Journal of Clinical Microbiology and Infectious Diseases, 24* (1), 44-46. doi:10.1007/s10096-004-1271-9

Chu, C. M., Cheng, V. C., Hung, I. F., Wong, M. M., Chan, K. H., Chan, K. S., . . . Yuen, K. Y. (2004). Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax, 59* (3), 252-256. doi:10.1136/thorax.2003.012658

Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. (2020).*Nat Med* . doi:10.1038/s41591-020-0877-5

ClinicalTrails.gov. (2020). Efficacy and Safety of IFN-α2β in the Treatment of Novel Coronavirus Patients.

Colson, P., Rolain, J.-M., Lagier, J.-C., Brouqui, P., & Raoult, D. (2020). Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *International Journal of Antimicrobial Agents, 55* (4), 105932. doi:*https://doi.org/10.1016/j.ijantimicag.2020.105932*

Commission, N. H. (2020). Diagnosis and treatment protocol for novel

coronavirus pneumonia.

Coughlin, M., Lou, G., Martinez, O., Masterman, S. K., Olsen, O. A., Moksa, A. A., . . . Prabhakar, B. S. (2007). Generation and characterization of human monoclonal neutralizing antibodies with distinct binding and sequence features against SARS coronavirus using XenoMouse. *Virology, 361* (1), 93-102. doi:10.1016/j.virol.2006.09.029

Coutard, B., Valle, C., de Lamballerie, X., Canard, B., Seidah, N. G., & Decroly, E. (2020). The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res, 176* , 104742. doi:10.1016/j.antiviral.2020.104742

Cristiani, L., Mancino, E., Matera, L., Nenna, R., Pierangeli, A., Scagnolari, C., & Midulla, F. (2020). Will children reveal their secret? The coronavirus dilemma. *Eur Respir J, 55* (4). doi:10.1183/13993003.00749-2020

Croxtall, J. D., & Perry, C. M. (2010). Lopinavir/Ritonavir. *Drugs, 70* (14), 1885-1915. doi:10.2165/11204950-000000000-00000

D'Alessandro, S., Scaccabarozzi, D., Signorini, L., Perego, F., Ilboudo, D. P., Ferrante, P., & Delbue, S. (2020). The Use of Antimalarial Drugs against Viral Infection. *Microorganisms, 8* (1). doi:10.3390/microorganisms8010085

Davey, R. T., Jr., Dodd, L., Proschan, M. A., Neaton, J., Neuhaus Nordwall, J., Koopmeiners, J. S., . . . Malvy, D. (2016). A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. *N Engl J Med, 375* (15), 1448-1456. doi:10.1056/NEJMoa1604330

de Olano, J., Howland, M. A., Su, M. K., Hoffman, R. S., & Biary, R. (2019). Toxicokinetics of hydroxychloroquine following a massive overdose. *Am J Emerg Med, 37* (12), 2264.e2265-2264.e2268. doi:10.1016/j.ajem.2019.158387

Deng, L., Li, C., Zeng, Q., Liu, X., Li, X., Zhang, H., . . . Xia, J. (2020). Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. *J Infect, 81* (1), e1-e5. doi:10.1016/j.jinf.2020.03.002

Dhama, K., Sharun, K., Tiwari, R., Dadar, M., Malik, Y. S., Singh, K. P., & Chaicumpa, W. (2020). COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. *Hum Vaccin Immunother* , 1-7. doi:10.1080/21645515.2020.1735227

Ding, Y., Zeng, L., Li, R., Chen, Q., Zhou, B., Chen, Q., . . . Zhang, F. (2017). The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. *BMC Complement Altern Med, 17* (1), 130. doi:10.1186/s12906-017-1585-7

Duan, J., Yan, X., Guo, X., Cao, W., Han, W., Qi, C., . . . Jin, G. (2005). A human SARS-CoV neutralizing antibody against epitope on S2 protein. *Biochem Biophys Res Commun, 333* (1), 186-193. doi:10.1016/j.bbrc.2005.05.089

Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., . . . Yang, X. (2020). Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A, 117* (17), 9490-9496. doi:10.1073/pnas.2004168117

Duan, Y. J., Liu, Q., Zhao, S. Q., Huang, F., Ren, L., Liu, L., & Zhou, Y. W. (2020). Trial of Chloroquines in the Treatment of COVID-19 and Its Research Progress in Forensic Toxicology. *Fa Yi Xue Za Zhi, 36* (2), 157-163. doi:10.12116/j.issn.1004-5619.2020.02.002

[Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]. (2020). *Zhonghua Jie He He Hu Xi Za Zhi, 43* (3), 185-188. doi:10.3760/cma.j.issn.1001-0939.2020.03.009

Falzarano, D., de Wit, E., Martellaro, C., Callison, J., Munster, V. J., & Feldmann, H. (2013). Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. *Sci Rep, 3* , 1686. doi:10.1038/srep01686

Gajic, O., Rana, R., Winters, J. L., Yilmaz, M., Mendez, J. L., Rickman, O. B., . . . Moore, S. B. (2007). Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. *Am J Respir Crit Care Med, 176* (9), 886-891. doi:10.1164/rccm.200702-271OC

Gao, J., Tian, Z., & Yang, X. (2020). Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends, 14* (1), 72-73. doi:10.5582/bst.2020.01047

Gao, Q. (2020). [Pharmacological characteristics of chloroquine and suggestions for its use in treatment of coronavirus disease 2019 (COVID-19)]. *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi, 32* (2), 119-122. doi:10.16250/j.32.1374.2020092

Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., . . . Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* , 105949. doi:10.1016/j.ijantimicag.2020.105949

Ge, X.-Y., Li, J.-L., Yang, X.-L., Chmura, A. A., Zhu, G., Epstein, J. H., . . . Shi, Z.-L. (2013). Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature, 503* (7477), 535-538. doi:10.1038/nature12711

Götz, V., Magar, L., Dornfeld, D., Giese, S., Pohlmann, A., Höper, D., . . . Schwemmle, M. (2016). Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import.*Scientific Reports, 6* (1), 23138. doi:10.1038/srep23138

Graham, R. L., Donaldson, E. F., & Baric, R. S. (2013). A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol, 11* (12), 836-848. doi:10.1038/nrmicro3143

Greenough, T. C., Babcock, G. J., Roberts, A., Hernandez, H. J., Thomas, W. D., Jr., Coccia, J. A., . . . Ambrosino, D. M. (2005). Development and characterization of a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody that provides effective immunoprophylaxis in mice. *J Infect Dis, 191* (4), 507-514. doi:10.1086/427242

Guan, W.-j., Ni, Z.-y., Hu, Y., Liang, W.-h., Ou, C.-q., He, J.-x., . . . Zhong, N.-s. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine, 382* (18), 1708-1720. doi:10.1056/NEJMoa2002032

Guan, W.-J., Ni, Z.-Y., Hu, Y., Liang, W.-H., Ou, C.-Q., He, J.-X., . . . China Medical Treatment Expert Group for, C. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine* . doi:10.1056/NEJMoa2002032

Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., . . . Lu, Z. (2020). Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* . doi:10.1001/jamacardio.2020.1017

Ho, J. C., Ooi, G. C., Mok, T. Y., Chan, J. W., Hung, I., Lam, B., . . . Tsang, K. W. (2003). High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Respir Crit Care Med, 168* (12), 1449-1456. doi:10.1164/rccm.200306-766OC

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., . . . Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell, 181* (2), 271-280.e278. doi:10.1016/j.cell.2020.02.052

Holshue, M. L., DeBolt, C., Lindquist, S., Lofy, K. H., Wiesman, J., Bruce, H., . . . Pillai, S. K. (2020). First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med, 382* (10), 929-936. doi:10.1056/NEJMoa2001191

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., . . . Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet, 395* (10223), 497-506. doi:10.1016/s0140-6736(20)30183-5

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., . . . Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet, 395* (10223), 497-506. doi:*https://doi.org/10.1016/S0140-6736(20)30183-5*

Hung, I. F., To, K. K., Lee, C. K., Lee, K. L., Chan, K., Yan, W. W., . . . Yuen, K. Y. (2011). Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis, 52* (4), 447-456. doi:10.1093/cid/ciq106

Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., . . . Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature, 436* (7047), 112-116. doi:10.1038/nature03712

Jahrling, P. B., Frame, J. D., Rhoderick, J. B., & Monson, M. H. (1985). Endemic Lassa fever in Liberia. IV. Selection of optimally effective plasma for treatment by passive immunization. *Trans R Soc Trop Med Hyg, 79* (3), 380-384. doi:10.1016/0035-9203(85)90388-8

Jahrling, P. B., & Peters, C. J. (1984). Passive antibody therapy of Lassa fever in cynomolgus monkeys: importance of neutralizing antibody and Lassa virus strain. *Infect Immun, 44* (2), 528-533.

Jaillon, S., Berthenet, K., & Garlanda, C. (2019). Sexual Dimorphism in Innate Immunity. *Clinical Reviews in Allergy & Immunology, 56* (3), 308-321. doi:10.1007/s12016-017-8648-x

Jordan, P., Brookes, J. G., Nikolic, G., & Le Couteur, D. G. (1999). Hydroxychloroquine overdose: toxicokinetics and management. *J Toxicol Clin Toxicol, 37* (7), 861-864. doi:10.1081/clt-100102466

Jordan, P. C., Stevens, S. K., & Deval, J. (2018). Nucleosides for the treatment of respiratory RNA virus infections. *Antivir Chem Chemother, 26* , 2040206618764483. doi:10.1177/2040206618764483

Kadam, R. U., & Wilson, I. A. (2017). Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proc Natl Acad Sci U S A, 114* (2), 206-214. doi:10.1073/pnas.1617020114

Kalil, A. C. (2020). Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. *Jama* . doi:10.1001/jama.2020.4742

Keyaerts, E., Li, S., Vijgen, L., Rysman, E., Verbeeck, J., Van Ranst, M., & Maes, P. (2009). Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. *Antimicrob Agents Chemother, 53* (8), 3416-3421. doi:10.1128/aac.01509-08

Khamitov, R. A., Loginova, S., Shchukina, V. N., Borisevich, S. V., Maksimov, V. A., & Shuster, A. M. (2008). [Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures]. *Vopr Virusol, 53* (4), 9-13.

Kim, J. Y., Choe, P. G., Oh, Y., Oh, K. J., Kim, J., Park, S. J., . . . Oh, M. D. (2020). The First Case of 2019 Novel Coronavirus Pneumonia Imported into Korea from Wuhan, China: Implication for Infection Prevention and Control Measures. *J Korean Med Sci, 35* (5), e61. doi:10.3346/jkms.2020.35.e61

Klasse, P. J. (2014). Neutralization of Virus Infectivity by Antibodies: Old Problems in New Perspectives. *Adv Biol, 2014* . doi:10.1155/2014/157895

Knowles, S. R., Phillips, E. J., Dresser, L., & Matukas, L. (2003). Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin Infect Dis, 37* (8), 1139-1142. doi:10.1086/378304

Ko, J. H., Seok, H., Cho, S. Y., Ha, Y. E., Baek, J. Y., Kim, S. H., . . . Peck, K. R. (2018). Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antivir Ther, 23* (7), 617-622. doi:10.3851/imp3243

Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., . . . Penninger, J. M. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med, 11* (8), 875-879. doi:10.1038/nm1267

Kwiek, J. J., Haystead, T. A., & Rudolph, J. (2004). Kinetic mechanism of quinone oxidoreductase 2 and its inhibition by the antimalarial quinolines. *Biochemistry, 43* (15), 4538-4547. doi:10.1021/bi035923w

Lam, T. T., Jia, N., Zhang, Y. W., Shum, M. H., Jiang, J. F., Zhu, H. C., . . . Cao, W. C. (2020). Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* . doi:10.1038/s41586-020-2169-0

Le, R. Q., Li, L., Yuan, W., Shord, S. S., Nie, L., Habtemariam, B. A., . . . Pazdur, R. (2018). FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *Oncologist, 23* (8), 943-947. doi:10.1634/theoncologist.2018-0028

Leider, J. P., Brunker, P. A., & Ness, P. M. (2010). Convalescent transfusion for pandemic influenza: preparing blood banks for a new plasma product? *Transfusion, 50* (6), 1384-1398. doi:10.1111/j.1537-2995.2010.02590.x

Li, G., & De Clercq, E. (2020). Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov, 19* (3), 149-150. doi:10.1038/d41573-020-00016-0

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., . . . Feng, Z. (2020). Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *The New England journal of medicine* , 10.1056/NEJMoa2001316. doi:10.1056/NEJMoa2001316

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., . . . Feng, Z. (2020). Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med, 382* (13), 1199-1207. doi:10.1056/NEJMoa2001316

Lim, J., Jeon, S., Shin, H. Y., Kim, M. J., Seong, Y. M., Lee, W. J., . . . Park, S. J. (2020). Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *J Korean Med Sci, 35* (6), e79. doi:10.3346/jkms.2020.35.e79

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., . . . Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov, 6* , 16. doi:10.1038/s41421-020-0156-0

Lu, H. (2020). Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends, 14* (1), 69-71. doi:10.5582/bst.2020.01020

Lukassen, S., Chua, R. L., Trefzer, T., Kahn, N. C., Schneider, M. A., Muley, T., . . . Eils, R. (2020). SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells.*Embo j, 39* (10), e105114. doi:10.15252/embj.20105114

Luke, T. C., Kilbane, E. M., Jackson, J. L., & Hoffman, S. L. (2006). Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med, 145* (8), 599-609. doi:10.7326/0003-4819-145-8-200610170-00139

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., . . . Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol, 77* (6), 1-9. doi:10.1001/jamaneurol.2020.1127

Michele, C., Maria Anna Rachele De, G., & Giovanni Nicola, R. (2020). SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopi- navir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remde-

sivir, Favipiravir and Other Drugs for the Treatment of the New Coronavirus.*Current Medicinal Chemistry, 27* , 1-6. doi:*http://dx.doi.org/10.2174/0929867327666200416131117*

Morra, M. E., Van Thanh, L., Kamel, M. G., Ghazy, A. A., Altibi, A. M. A., Dat, L. M., . . . Huy, N. T. (2018). Clinical outcomes of current medical approaches for Middle East respiratory syndrome: A systematic review and meta-analysis. *Rev Med Virol, 28* (3), e1977. doi:10.1002/rmv.1977

Mulangu, S., Dodd, L. E., Davey, R. T., Jr., Tshiani Mbaya, O., Proschan, M., Mukadi, D., . . . Nordwall, J. (2019). A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med, 381* (24), 2293-2303. doi:10.1056/NEJMoa1910993

Nicol, M. R., Joshi, A., Rizk, M. L., Sabato, P. E., Savic, R. M., Wesche, D., . . . Cook, J. (2020). Pharmacokinetics and Pharmacological Properties of Chloroquine and Hydroxychloroquine in the Context of COVID-19 Infection. *Clin Pharmacol Ther* . doi:10.1002/cpt.1993

Nutho, B., Mahalapbutr, P., Hengphasatporn, K., Pattaranggoon, N. C., Simanon, N., Shigeta, Y., . . . Rungrotmongkol, T. (2020). Why Are Lopinavir and Ritonavir Effective against the Newly Emerged Coronavirus 2019? Atomistic Insights into the Inhibitory Mechanisms.*Biochemistry, 59* (18), 1769-1779. doi:10.1021/acs.biochem.0c00160

Openshaw, P. J., & Tregoning, J. S. (2005). Immune responses and disease enhancement during respiratory syncytial virus infection.*Clin Microbiol Rev, 18* (3), 541-555. doi:10.1128/cmr.18.3.541-555.2005

Park, W. B., Perera, R. A., Choe, P. G., Lau, E. H., Choi, S. J., Chun, J. Y., . . . Oh, M. D. (2015). Kinetics of Serologic Responses to MERS Coronavirus Infection in Humans, South Korea. *Emerg Infect Dis, 21* (12), 2186-2189. doi:10.3201/eid2112.151421

Phan, L. T., Nguyen, T. V., Luong, Q. C., Nguyen, T. V., Nguyen, H. T., Le, H. Q., . . . Pham, Q. D. (2020). Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. *New England Journal of Medicine, 382* (9), 872-874. doi:10.1056/NEJMc2001272

Porche, D. J. (2001). Lopinavir/ritonavir. *J Assoc Nurses AIDS Care, 12* (2), 101-104. doi:10.1016/s1055-3290(06)60137-4

Ren, J. L., Zhang, A. H., & Wang, X. J. (2020). Traditional Chinese medicine for COVID-19 treatment. *Pharmacol Res, 155* , 104743. doi:10.1016/j.phrs.2020.104743

Rojas, M., Rodríguez, Y., Monsalve, D. M., Acosta-Ampudia, Y., Camacho, B., Gallo, J. E., . . . Anaya, J. M. (2020). Convalescent plasma in Covid-19: Possible mechanisms of action. *Autoimmun Rev, 19* (7), 102554. doi:10.1016/j.autrev.2020.102554

Rothe, C., Schunk, M., Sothmann, P., Bretzel, G., Froeschl, G., Wallrauch, C., . . . Hoelscher, M. (2020). Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *New England Journal of Medicine, 382* (10), 970-971. doi:10.1056/NEJMc2001468

Russell, C. D., Millar, J. E., & Baillie, J. K. (2020). Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet, 395* (10223), 473-475. doi:10.1016/s0140-6736(20)30317-2

Salata, C., Calistri, A., Parolin, C., Baritussio, A., & Palù, G. (2017). Antiviral activity of cationic amphiphilic drugs. *Expert Rev Anti Infect Ther, 15* (5), 483-492. doi:10.1080/14787210.2017.1305888

Sanders, J. M., Monogue, M. L., Jodlowski, T. Z., & Cutrell, J. B. (2020). Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *Jama* . doi:10.1001/jama.2020.6019

Savarino, A., Boelaert, J. R., Cassone, A., Majori, G., & Cauda, R. (2003). Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis, 3* (11), 722-727. doi:10.1016/s1473-3099(03)00806-5

Savarino, A., Di Trani, L., Donatelli, I., Cauda, R., & Cassone, A. (2006). New insights into the antiviral effects of chloroquine.*Lancet Infect Dis, 6* (2), 67-69. doi:10.1016/s1473-3099(06)70361-9

Scott, J. D. (2005). Simplifying the treatment of HIV infection with ritonavir-boosted protease inhibitors in antiretroviral-experienced patients. *Am J Health Syst Pharm, 62* (8), 809-815. doi:10.1093/ajhp/62.8.809

Sheahan, T. P., Sims, A. C., Leist, S. R., Schäfer, A., Won, J., Brown, A. J., . . . Baric, R. S. (2020). Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun, 11* (1), 222. doi:10.1038/s41467-019-13940-6

Shen, C., Wang, Z., Zhao, F., Yang, Y., Li, J., Yuan, J., . . . Liu, L. (2020). Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *Jama, 323* (16), 1582-1589. doi:10.1001/jama.2020.4783

Sheppard, M., Laskou, F., Stapleton, P. P., Hadavi, S., & Dasgupta, B. (2017). Tocilizumab (Actemra). *Hum Vaccin Immunother, 13* (9), 1972-1988. doi:10.1080/21645515.2017.1316909

Siegel, D., Hui, H. C., Doerffler, E., Clarke, M. O., Chun, K., Zhang, L., . . . Mackman, R. L. (2017). Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. *J Med Chem, 60* (5), 1648-1661. doi:10.1021/acs.jmedchem.6b01594

Smith, A. I., & Turner, A. J. (2004). What's new in the renin-angiotensin system? *Cell Mol Life Sci, 61* (21), 2675-2676. doi:10.1007/s00018-004-4319-1

Stockman, L. J., Bellamy, R., & Garner, P. (2006). SARS: Systematic Review of Treatment Effects. *PLOS Medicine, 3* (9), e343. doi:10.1371/journal.pmed.0030343

Sui, J., Li, W., Murakami, A., Tamin, A., Matthews, L. J., Wong, S. K., . . . Marasco, W. A. (2004). Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. *Proc Natl Acad Sci U S A, 101* (8), 2536-2541. doi:10.1073/pnas.0307140101

Sullivan, H. C., & Roback, J. D. (2020). Convalescent Plasma: Therapeutic Hope or Hopeless Strategy in the SARS-CoV-2 Pandemic.*Transfus Med Rev* . doi:10.1016/j.tmrv.2020.04.001

Sung, J. J., Wu, A., Joynt, G. M., Yuen, K. Y., Lee, N., Chan, P. K., . . . Hui, D. S. (2004). Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax, 59* (5), 414-420. doi:10.1136/thx.2003.014076

Tai, W., He, L., Zhang, X., Pu, J., Voronin, D., Jiang, S., . . . Du, L. (2020). Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. *Cell Mol Immunol, 17* (6), 613-620. doi:10.1038/s41423-020-0400-4

Tan, E. L., Ooi, E. E., Lin, C. Y., Tan, H. C., Ling, A. E., Lim, B., & Stanton, L. W. (2004). Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. *Emerg Infect Dis, 10* (4), 581-586. doi:10.3201/eid1004.030458

ter Meulen, J., van den Brink, E. N., Poon, L. L., Marissen, W. E., Leung, C. S., Cox, F., . . . Goudsmit, J. (2006). Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants. *PLoS Med, 3* (7), e237. doi:10.1371/journal.pmed.0030237

Thanh Le, T., Andreadakis, Z., Kumar, A., Gómez Román, R., Tollefsen, S., Saville, M., & Mayhew, S. (2020). The COVID-19 vaccine development landscape. *Nat Rev Drug Discov, 19* (5), 305-306. doi:10.1038/d41573-020-00073-5

Tian, X., Li, C., Huang, A., Xia, S., Lu, S., Shi, Z., . . . Ying, T. (2020). Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerging Microbes & Infections, 9* (1), 382-385. doi:10.1080/22221751.2020.1729069

Tian, X., Li, C., Huang, A., Xia, S., Lu, S., Shi, Z., . . . Ying, T. (2020). Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect, 9* (1), 382-385. doi:10.1080/22221751.2020.1729069

Treatment Plan Edition 5 revision edition. (2020).

van den Brink, E. N., Ter Meulen, J., Cox, F., Jongeneelen, M. A., Thijsse, A., Throsby, M., . . . Goudsmit, J. (2005). Molecular and biological characterization of human monoclonal antibodies binding to the spike and nucleocapsid proteins of severe acute respiratory syndrome coronavirus. *J Virol, 79* (3), 1635-1644. doi:10.1128/jvi.79.3.1635-1644.2005

Vincent, M. J., Bergeron, E., Benjannet, S., Erickson, B. R., Rollin, P. E., Ksiazek, T. G., . . . Nichol, S. T. (2005). Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J, 2* , 69. doi:10.1186/1743-422x-2-69

Viswanathan, T., Arya, S., Chan, S. H., Qi, S., Dai, N., Misra, A., . . . Gupta, Y. K. (2020). Structural basis of RNA cap modification by SARS-CoV-2. *Nature Communications, 11* (1), 3718. doi:10.1038/s41467-020-17496-8

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., . . . Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama, 323* (11), 1061-1069. doi:10.1001/jama.2020.1585

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., . . . Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res, 30* (3), 269-271. doi:10.1038/s41422-020-0282-0

Wang, Z., Chen, X., Lu, Y., Chen, F., & Zhang, W. (2020). Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends, 14* (1), 64-68. doi:10.5582/bst.2020.01030

Wong, S. K., Li, W., Moore, M. J., Choe, H., & Farzan, M. (2004). A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. *J Biol Chem, 279* (5), 3197-3201. doi:10.1074/jbc.C300520200

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., . . . McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science, 367* (6483), 1260-1263. doi:10.1126/science.abb2507

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., . . . Song, Y. (2020). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* . doi:10.1001/jamainternmed.2020.0994

Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., . . . Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature, 579* (7798), 265-269. doi:10.1038/s41586-020-2008-3

Wu, Z., & McGoogan, J. M. (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *Jama* . doi:10.1001/jama.2020.2648

Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., . . . Wei, H. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A, 117* (20), 10970-10975. doi:10.1073/pnas.2005615117

Xu, X. W., Wu, X. X., Jiang, X. G., Xu, K. J., Ying, L. J., Ma, C. L., . . . Li, L. J. (2020). Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *Bmj, 368* , m606. doi:10.1136/bmj.m606

Yang, J., Wang, W., Chen, Z., Lu, S., Yang, F., Bi, Z., . . . Wei, X. (2020). A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. *Nature* . doi:10.1038/s41586-020-2599-8

Yang, X. H., Deng, W., Tong, Z., Liu, Y. X., Zhang, L. F., Zhu, H., . . . Qin, C. (2007). Mice transgenic for human angiotensin-converting enzyme 2 provide a model for SARS coronavirus infection. *Comp Med, 57* (5), 450-459.

Yanturali, S., Aksay, E., Demir, O. F., & Atilla, R. (2004). Massive hydroxychloroquine overdose. *Acta Anaesthesiol Scand, 48* (3), 379-381. doi:10.1111/j.0001-5172.2004.0302.x

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., . . . Liu, D. (2020). In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* . doi:10.1093/cid/ciaa237

Yeh, K. M., Chiueh, T. S., Siu, L. K., Lin, J. C., Chan, P. K., Peng, M. Y., . . . Chang, F. Y. (2005). Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. *J Antimicrob Chemother, 56* (5), 919-922. doi:10.1093/jac/dki346

Young, B. E., Ong, S. W. X., Kalimuddin, S., Low, J. G., Tan, S. Y., Loh, J., . . . Lye, D. C. (2020). Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *Jama, 323* (15), 1488-1494. doi:10.1001/jama.2020.3204

Yusuf, I. H., Sharma, S., Luqmani, R., & Downes, S. M. (2017). Hydroxychloroquine retinopathy. *Eye (Lond), 31* (6), 828-845. doi:10.1038/eye.2016.298

Zhang, C., Wu, Z., Li, J. W., Zhao, H., & Wang, G. Q. (2020). Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents, 55* (5), 105954. doi:10.1016/j.ijantimicag.2020.105954

Zhang, J., Zhou, L., Yang, Y., Peng, W., Wang, W., & Chen, X. (2020). Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *Lancet Respir Med, 8* (3), e11-e12. doi:10.1016/s2213-2600(20)30071-0

Zhong, N. (2004). Management and prevention of SARS in China.*Philos Trans R Soc Lond B Biol Sci, 359* (1447), 1115-1116. doi:10.1098/rstb.2004.1491

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., . . . Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.*Lancet, 395* (10229), 1054-1062. doi:10.1016/s0140-6736(20)30566-3

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., . . . Shi, Z.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* , 10.1038/s41586-41020-42012-41587. doi:10.1038/s41586-020-2012-7

Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., . . . Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579* (7798), 270-273. doi:10.1038/s41586-020-2012-7

Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., . . . Wei, H. (2020). *Aberrant pathogenic GM-CSF + T cells and inflammatory CD14 + CD16 + monocytes in severe pulmonary syndrome patients of a new coronavirus* .

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., . . . Tan, W. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019.*N Engl J Med, 382* (8), 727-733. doi:10.1056/NEJMoa2001017

Zhu, Z., Chakraborti, S., He, Y., Roberts, A., Sheahan, T., Xiao, X., . . . Dimitrov, D. S. (2007). Potent cross-reactive neutralization of SARS coronavirus isolates by human monoclonal antibodies. *Proc Natl Acad Sci U S A, 104* (29), 12123-12128. doi:10.1073/pnas.0701000104

Figure legends:

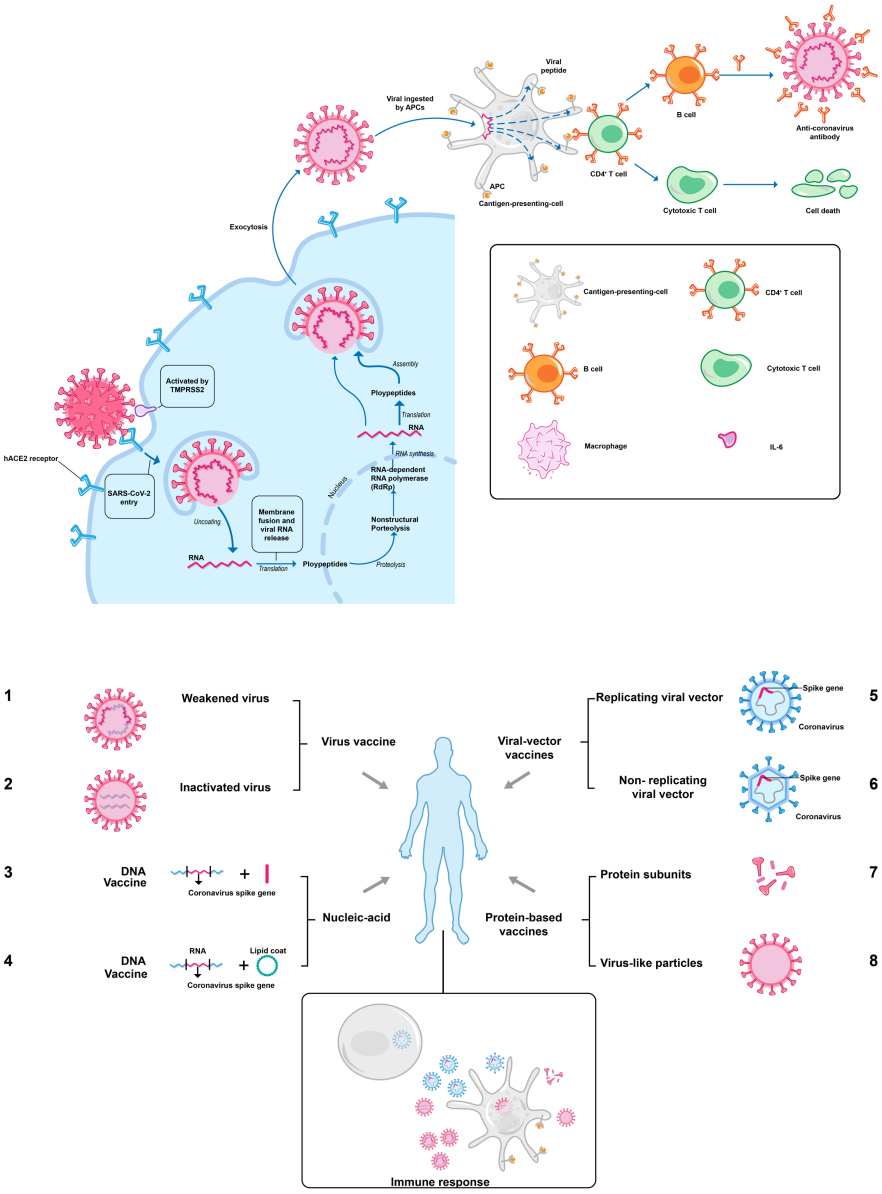
Figure 1. Infection Mechanism of SARS-CoV-2. The infection mechanism of coronaviruses starts from attachment and entry. Binding and viral entry via membrane infusion rely on interactions between the Spike protein and its ACE2 receptor. Then, cleavage of S protein by a protease enzyme (TMPRSS-2) facilitates the entry. Once enter the cell successfully, the RNA from virus begins its translation and proteolysis. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Following replication and RNA synthesis, Structural proteins are synthesized leading to completion of assembly and release of viral particles. Following release, virus is ingested by antigen-presenting-cell (APCs), which can activate T-helper cells via viral peptide. And T-helper cells enable other immune response. B cells produce antibodies that can block the virus from infecting cells. In addition to this cellular immune response, cytotoxic T cells identify and destroy virus-infected cells.

Figure 2. Four types of vaccines are used against coronaviruses via immune response. Vaccines can be prophylactic or therapeutic in clinical practice and are able to be broadly divided into virus vaccines (weakened virus and inactivated virus), viral-vector vaccines (replicating viral vector and non-replicating viral vector), nucleic acid vaccines (DNA vaccines and RNA vaccines), and protein-based vaccines (protein subunits and virus like particles), which rely on different viruses or viral parts. 1. A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. However, only under the precisely controlled and characterized conditions can live attenuated (weakened virus) vaccines provide the required protective immunity to avoid obvious disease symptoms in the host animal. 2. In inactivated vaccines, the virus is rendered uninfectious using chemicals, such as formaldehyde, or heat. Making them, however, requires starting with large quantities of infectious virus. And inactivated vaccines must be totally innocuous and non-infective. Inactivated vaccines have certain restrictions on the way of presentation, resulting in a limited immune response, which requires adjuvants or immunostimulants to enhance the response. 3. DNA vaccines are generated by inserting a gene encoding for the antigens into a bacteria-derived plasmid, which needs to be controlled by a powerful promoter (in most cases a CMV-promoter). DNA vaccines can affect not only humoral immunity but also cellular immunity. The limitation of DNA vaccines is lower immunogenicity profiles, which impede the desired clinical application. 4. RNA vaccine is often encased in a lipid coat so it can enter cells. The three major challenges in the delivery of RNA vaccines is instability due to RNase-mediated degradation and high molecular weight. 5. Replicating vaccines tend to be safe and provoke a strong immune response. Ebola vaccine is an example of a viral-vector vaccine that replicates within cells. 6. For non-replicating vaccines, booster shots can be needed to induce long-lasting immunity. 7. Protein subunit-based vaccines are typically used via combined adjuvants or delivery systems to elicit a protective effect, and most of them are focusing on the virus's spike protein or a key part of it called the receptor binding domain. 8. Virus like particle (VLP) vaccines utilize empty virus shells for mimicking the coronavirus structure, but they show non-infectious ability because they lack genetic material. VLP vaccines can trigger a strong immune response while can be difficult to manufacture.

Table

Table 1 Clinical trials of drugs for the treatment of SARS-CoV-2

Table 2 Clinical trials of vaccines for the treatment of COVID-19



Hosted file

Tables.docx available at https://authorea.com/users/355166/articles/478514-summary-of-the-clinical-manifestations-infection-mechanisms-and-current-drug-treatment-of-sars-cov-2-infection