Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19: Transmission, prevention, and potential therapeutic opportunities

Melika Lotfi\textsuperscript{a,b}, Michael R. Hamblin\textsuperscript{c,d,e}, Nima Rezaei\textsuperscript{f,g,h,\ast}

\textsuperscript{a} School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
\textsuperscript{b} Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Zanjan, Iran
\textsuperscript{c} Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
\textsuperscript{d} Laser Research Centre, Faculty of Health Science, University of Johannesburg, Doornfontein 2028, South Africa
\textsuperscript{e} Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Boston, MA, USA
\textsuperscript{f} Research Center for Immunodeficiencies, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
\textsuperscript{g} Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
\textsuperscript{h} Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Stockholm, Sweden

\textbf{A R T I C L E I N F O}

\textbf{Keywords:}
COVID-19  
SARS-CoV-2  
Treatment  
Transmission  
Prevention

\textbf{A B S T R A C T}

The novel coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global challenge. Despite intense research efforts worldwide, an effective vaccine and viable treatment options have eluded investigators. Therefore, infection prevention, early viral detection and identification of successful treatment protocols provide the best approach in controlling disease spread. In this review, current therapeutic options, preventive methods and transmission routes of COVID-19 are discussed.

\section{1. Introduction}

Although the emergence of new coronavirus diseases, probably originating from bats in China, had been predicted by early March 2019 [1], no international preventive action was taken. Finally, after several cases of pneumonia with an unfamiliar etiology were observed at the end of 2019, the National Health Commission of China released more details about the epidemic in early 2020 [2]. The causative virus was initially called “novel coronavirus 2019” (2019-nCoV) by the World Health Organization (WHO), but it was then renamed as “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) by the international committee of the Coronavirus Study Group (CSG), and the disease called “coronavirus disease 2019” (COVID-19) by WHO [3]. It is thought that the Hunan seafood market in Wuhan city in China was the origin of the outbreak. Although it had been proposed that the COVID-19 patients in China might have utilized infected animals as a foodstuff, or might have visited the seafood market, further investigation revealed that some patients had not visited the seafood market. Therefore, the human-to-human transmission of this virus through coughing, sneezing, and the spread of respiratory droplets or aerosols was accepted. In addition, almost all countries in continents throughout the world reported disease spread caused by aerosol penetration into the upper respiratory tract and lungs via inhalation [4,5]. There followed a rapid growth in the number of cases all around the world. A mathematical model examined whether the control of SARS-CoV-2 infection could be achieved by isolating affected patients, and tracking their contacts with other individuals. This model concluded that isolating people and reviewing their contacts would be insufficient to control the COVID-19 pandemic within three months, because there would be too much delay between the onset of symptoms and isolation [6]. Thus, observing preventive measures, especially isolation and lockdown, would be essential.

SARS-CoV-2 is highly contagious, and there has not yet been any vaccine or effective treatment that has received approval. So, the best solution for controlling the pandemic will be the simultaneous application of preventive methods, sensitive diagnostic approaches, and using current available drugs, while still developing novel treatments [7–9]. This study presents the latest information about COVID-19 transmission, prevention, and potential therapeutic options.

\section{2. SARS-CoV-2 characteristics}

SARS-CoV-2 is an enveloped, positive-sense, and single-stranded 29.9 kb RNA beta-coronavirus [10,11]. Investigation of the SARS-CoV-2 genome proved that it has 88% similarity with the bat-SL-CoVZC45 and bat-SL-CoVZXC21 sequences, and was 96.2% identical to another bat
CoV RaTG13 [12]. However, some recent investigations have suggested that pangolins that were smuggled from Malaysia to China, along with other possible intermediate hosts like turtles or snakes could be the direct origin of the virus instead of a bat [13].

Moreover, the protein-coding genes of SARS-CoV-2 have 79.5% and 51% sequence similarity to SARS-CoV and MERS-CoV, respectively. The SARS-CoV-2 virus employs the Angiotensin-Converting Enzyme 2 (ACE2) receptor for cellular entry, similar to SARS-CoV [3,14]. Therefore, previous treatments that were used to control the SARS-CoV and MERS-CoV epidemics, might also be effective in SARS-CoV-2.

3. Clinical consequences

The first symptoms are commonly recognized as fever, dry cough, tachypnea, and shortness of breath [15]. Although diarrhea was present in about 20–25% of patients with MERS-CoV or SARS-CoV infection, intestinal symptoms are rarely seen in patients with COVID-19. In another study, confusion, chest pain, vomiting, and nausea were also reported as COVID-19 symptoms [16]. Other symptoms include, sore throat, sneezing, nasal congestion, sputum production, anosmia and dysgeusia, rash on the skin, or discoloration of fingers or toes, and viral conjunctivitis. Some laboratory studies have shown the occurrence of cytokine storm, sepsis, and RNAemia in COVID-19 [17,18].

Clinical chemistry studies have shown increases in lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT), C-reactive protein (CRP), creatinine kinase (CK), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, D-dimer level, procalcitonin, urea, and creatinine. Decreases in hemoglobin, lymphocyte count, eosinophil count, and serum albumin have been detected in COVID-19 patients [17].

The most common radiological findings in patients with COVID-19 were a ground-glass opacity in the lungs [19]. Moreover, SARS-CoV-2 can affect the cardiovascular system [16], gastrointestinal tract [20], and can cause acute kidney failure [2,19]. Moreover, evaluation of liver manifestations in 148 patients with COVID-19 indicated that more than one-third of the COVID-19 patients admitted to the hospital had abnormal liver function, and these patients were hospitalized for a more extended period [21]. It must be mentioned that it is likely that a substantial number of asymptomatic patients can be carriers of the virus. The variable clinical manifestations and outcomes underline the importance of adhering to hygienic and preventive principles, in addition to finding and developing new sensitive diagnostic approaches and therapeutic options.

4. Infection in children

Unlike adults, children with COVID-19 have milder symptoms and better clinical outcomes [22]; among the COVID-19 patients under 18 years of age, children under one year old seem to be at the highest risk of the severe form of the disease [23]. Although early studies showed that children with COVID-19 were less likely to develop severe symptoms than other age groups, one new study has shown that children are as likely to develop COVID-19 as adults [24]. So, prevention and finding appropriate treatment for children is as important as for adults.

In one study, 1391 children with a median age of 6.7 years were surveyed, and 171 were diagnosed with COVID-19. Intensive Care Unit (ICU) and mechanical ventilation were needed for only three children, who had underlying conditions. By March 8th, 2020, one child with intussusception had died, 21 children remained in a stable condition in the ward, and 149 cases were discharged [25].

It should be mentioned that recently scientists and clinicians have reported that young infants who were diagnosed with COVID-19, also had classic Kawasaki disease (KD) or a KD-like disease, which indicates that more investigation into the clinical manifestations of pediatric COVID-19 and its potential association with KD is needed [26].

5. Transmission of COVID-19

SARS-CoV-2 can spread through both direct means (droplet and human-to-human transmission) and by indirect contact (contaminated objects and airborne contagion). Meanwhile personal protective equipment (PPE) could also be the source of airborne infections [27]. As mentioned before, person-to-person spread of SARS-CoV-2 is supposed to occur mainly via respiratory droplets, when a patient coughs, sneezes, or even talks or sings. Droplets typically cannot traverse more than six feet (almost two meters) and remain in the air for a limited time. However, SARS-CoV-2 remains intact and contagious in droplets (less than five microns in diameter) and can be suspended in the air for up to three hours [28]. Therefore, airborne isolation, room ventilation, and appropriate application of disinfectant (especially in toilets) might restrict aerosol spread of the virus [29].

COVID-19 can occur if a person touches a surface contaminated with SARS-CoV-2, and then the hands come into direct contact with mucous membranes such as the eyes, nose, or mouth [30]. Thus, sufficient washing of hands with soap and water or hand sanitizers is recommended.

The reported contagion rates from a patient with symptomatic infection vary by location and efficiency of infection control measures. Based on a joint WHO-China report, the rate of secondary COVID-19 infection ranged from one to five percent among tens of thousands of confirmed patients in China [30].

The spread of SARS-CoV-2 from asymptomatic individuals (or individuals within the incubation period), without any radiological findings, has also been reported [31–33]. Therefore, there is a need for improvements in rapid and sensitive diagnostic methods for detecting infected individuals.

In a study on four hospital staff who became infected, although each patient had at least two negative tests, the RT-PCR was still positive from 5 to 13 days after being discharged [34]. Also, viral shedding in the stool likely occurs up to five weeks (the longest time of shedding was 37 days [35] and in deceased patients until the moment of death) with a mean of 11.2 days after the respiratory tract test was negative [36]. So, because SARS-CoV-2 can be transmitted from recovered patients, it is wise to change the current discharge criteria. The current discharge criteria are as follows:

- (1) Two consecutive RT-PCR negative results in at least a 24 h interval; (2) Complete resolution of the patient’s acute exudative pulmonary lesions on chest Computed Tomography (CT) examination; (3) Normalization of temperature for over 72 h; and (4) Resolution of the patient’s respiratory symptoms [34,37].

Although SARS-CoV-2 RNA has been discovered in blood and stool samples [38] and living SARS-CoV-2 has been cultured from stool in some COVID-19 patients [39], a joint WHO-China report indicated that fecal-oral transmission route did not appear to be an important factor in the spread of infection [30].

It should be mentioned that a study of semen and testicular specimens of COVID-19 patients suggested that SARS-CoV-2 could not be transmitted through sexual contact [40].

As pregnant women are at a high risk of contracting COVID-19, investigating the possible vertical transmission of COVID-19 is important. An infant delivered from an affected mother was reported to test negative for seven duplicate samples of neonatal blood, stool, and oropharynx [41]; however, recent studies showed immunoglobulin M (IgM) antibodies to SARS-CoV-2 were present in newborn infant blood; so, possible transmission of SARS-CoV-2 from mother to fetus could not be ruled out [42,43].

Although it is unknown whether the SARS-CoV-2 was transmitted from infected animals (civet cat, snake, or other species) to humans at the Huanan seafood market or not, there is a clear possibility for animal-to-human transmission [44]. Ferrets, cats, dogs, and other domesticated animals are susceptible to SARS-CoV-2 [45]. It has been demonstrated that cats can be infected with SARS-CoV-2 and transmit it...
to other cats. Nevertheless, it is not yet clear if cats can transmit the virus to their owners; so at present this not a problem for cat owners. Moreover, ducks, pigs, chickens, and dogs are not likely to be infected. However, it should be mentioned that a German shepherd pet dog died (the cause of death could not be determined as the owner declined to conduct an autopsy) two days after the owner was in COVID-19 quarantine [46]. So, possible animal-to-human transmission of the virus must be taken into account.

Based on the above-mentioned evidence, transmission of the virus could be more complicated than that seen in previous pandemics. The virus is highly contagious, and there is no successful treatment or a vaccine. Also, a relatively long incubation period, presence of asymptomatic patients, and continued viral shedding after recovery all underline the importance of home quarantine through lockdown of the entire society like the Chinese government carried out [47].

6. Temperature and humidity and SARS-CoV-2 infection

One study investigated the relationship between the mean daily average temperature and the average rate of increase of new patients with COVID-19. Five countries (Iran, Italy, Germany, Spain, and United States) were studied. To minimize the impact of confounding factors like the imposition of government measures or cultural differences between these countries, different areas in each country were compared separately. The results of this study found that in all studied areas, a significant difference in the average daily air temperature between the two regions was associated with a substantial difference in the daily average cumulative rate of new patients in those two regions [48].

In addition, the average temperature and humidity of infected cities were found to be 5 °C to 11 °C and 47 to 79%, respectively, and the optimum temperature and humidity for the survival of SARS-CoV-2 in vitro were 4 °C and 20 to 80%, respectively. Also, the average temperature in the contaminated cities was never below zero degrees Celsius. Additionally, the virus spread in the latitude corridor was 30 to 50° north (South Korea, Japan, Iran, and North Italy). Furthermore, at this time, the SARS-CoV-2 had not been able to spread quickly in southern China [49].

Although the above-mentioned reports suggest a relationship between temperature and the distribution of the virus, comparing the global climate and COVID-19 distribution maps [50,51], it could be concluded that there was no significant relationship between temperature, humidity, and the virus distribution.

7. Preventive approaches

The WHO has stated that education, isolation, prevention, controlling the transmission, and treatment of infected persons are the critical steps in controlling contagious diseases like COVID-19 [52]. It is possible to minimize the spread of infection by making the following recommendations.

Staying at home (home quarantine) and avoiding any direct contact with any healthy (possible asymptomatic patients) or infected person, which has been called shielding; avoiding nonessential travel; observing social distancing rules like avoiding crowded public places and maintaining at least two meters of distance between each person, especially if they are coughing or sneezing; avoiding shaking hands when greeting others; frequently washing hands for at least 20 s with soap and water or hand sanitizer with at least 60% alcohol, especially after touching common surface areas, using the bathroom, or shaking hands, avoiding touching eyes, nose, and mouth with unwashed hands; and disinfecting surfaces using household sprays or wipes.

It should be mentioned that due to the long incubation period and presence of asymptomatic patients, using a medical mask (especially N95) or a respirator (especially FFP3) could be recommended. Also, sterilizing the used respirator, only reusing it for a limited time, and proper disposal of the used masks, have been recommended. Although respirators (the protective classes, including FFP1, FFP2, and FFP3 [53]) are produced as single-use items, they could be used again for a limited time unless there is a risk for contamination through the deposition of infectious particles on the surface [54]. When the respirator becomes soiled or wet with bodily fluids or it can no longer be appropriately fitted, or if breathing via the respirator becomes difficult, it should be discarded. Also, masks should be discarded after being used during an aerosol-generating procedure (AGP). Until now, manufacturers have had no reason to disinfect masks or to produce masks for repeated use. However, there is a vital need to be able to disinfect masks and reuse them. SARS-CoV-2 remains viable in the environment, including on the surface of different materials like cardboard, iron, or tissue for some time. This suggests that there is a risk for rapid contamination of the outer surface of respirators and surgical masks. Contamination of the respiratory surface could be prevented through placing a medical mask over it, or wearing a face shield that can be cleaned. Because of the severe contamination of respirators and surgical masks in the COVID-19 pandemic, several methods could be considered for the sterilization of used masks, including steam, hydrogen peroxide, or radiation.

Besides, the use of medical shields or wearing protective suits is recommended, especially for health care workers. It should be mentioned that wearing gloves in public is not an adequate protection against COVID-19, because gloves can easily be contaminated. So, frequent washing of hands is the best way to protect against SARS-CoV-2 infection [55].

A study in six departments of a hospital in Wuhan, China demonstrated that the use of N95 masks, disinfectants, and handwashing by doctors and nurses were effective in preventing against COVID-19 infection [56].

In terms of vaccines, there are a large number of vaccination strategies against SARS-CoV, MERS-CoV being tested in animals, including a live-attenuated virus, viral vectors, inactivated virus, subunit vaccines, recombinant DNA, and proteins vaccines (1 1 6). Although, until now, there has not been any approved vaccine against SARS-CoV-2, several clinical trials have been launched for testing the effects of various vaccines against SARS-CoV-2.

8. COVID-19 therapeutic options

Huang et al. [57] reported that acute respiratory distress syndrome (ARDS) was the most common complication in COVID-19 patients [58], followed by anemia, acute cardiac injury, and secondary infections. Hence, empirical antibiotics, antiviral drugs, and systemic corticosteroids are used as treatments [59]. Moreover, Holshue et al. [60] suggested the use of invasive mechanical ventilation for patients with intractable hypoxemia. So, the treatments of patients with COVID-19 infection are mainly symptomatic in nature.

It should be mentioned that the panel of National Institutes of Health (NIH) does not recommend the application of any agent for pre- or post-exposure prophylaxis against SARS-CoV-2 outside the setting of a clinical trial [61]. Except for the clinical trials, some medications are not recommended for use in the clinic, like the combination of Hydroxychloroquine and Azithromycin because of the potential for toxicity. Other conceivable treatments are not recommended such as Lopinavir/Ritonavir or other protease inhibitors (used for human immunodeficiency virus (HIV)) because of unfavorable pharmacodynamics and negative clinical trial data, Interferons because of lack of efficacy in the treatment of SARS and MERS, Janus kinase inhibitors (e.g., Baricitinib [62]) because of their broad immunosuppressive effects, and systemic corticosteroids during the treatment of mechanically ventilated patients with COVID-19 without ARDS.

Scientists are trying hard to develop new potential therapeutic strategies, consisting of monoclonal antibodies, vaccines, peptides, Interferon-based therapies, protease inhibitors, and small-molecule drugs to defeat the COVID-19 pandemic. However, it might take several
| Clinical trials                                                                 | Identifier       | Status                     | country   |
|-------------------------------------------------------------------------------|------------------|----------------------------|-----------|
| Tocilizumab in COVID-19 Pneumonia                                            | NCT04317092      | Recruiting                 | Italy     |
| Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 | NCT04315298      | Recruiting                 | United States |
| A Pilot Study of Sildenafil in COVID-19                                       | NCT04304313      | Recruiting                 | China     |
| ACE Inhibitors, Angiotensin II Type-1 Receptor Blockers, and Severity of COVID-19 (CODIV-ACE) | NCT04318418      | Not yet recruiting         | Italy     |
| Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention (JCO4COV19) | NCT04304053      | Recruiting                 | Spain     |
| The Use PUL-042 Inhalation Solution to Prevent COVID-19 in Adults Exposed to SARS-CoV-2 | NCT04313023      | Not yet recruiting         |          |
| The Use of Angiotensin-Converting Enzyme Inhibitors and Incident Respiratory Infections, Are They Harmful or Protective? | NCT04322786      | Not yet recruiting         |          |
| Nitric Oxide Gas Inhalation for Severe Acute Respiratory Syndrome in COVID-19 | NCT04290871      | Withdrawn                  |          |
| Prophylaxis With Azithromycin and Chloroquine in Hospitalized Patients With COVID-19 | NCT04322396      | Not yet recruiting         |          |
| Identifying Critically Ill Patients With COVID-19 Who Will Benefit Most From Nutrition Support Therapy; Validation of the NUTRIC Nutritional Risk Assessment Tool | NCT04274322      | Not yet recruiting         |          |
| Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - SARIMUNO-19 - SARIMUNO-19 - SARIMUNO-19 | NCT04324073      | Not yet recruiting         | France    |
| Hydroxychloroquine Versus Placebo in Patients Presenting COVID-19 Infection and at Risk of Secondary Complication: a Prospective, Multicentre, Randomised, Double-blind Study | NCT04325893      | Not yet recruiting         | China     |
| Efficacy and Safety of IFN-α2b in the Treatment of Novel Coronavirus Patients | NCT04293887      | Not yet recruiting         |          |
| Xiyanpi Injection for the Treatment of New Coronavirus Infected Pneumonia     | NCT04275388      | Not yet recruiting         |          |
| Chloroquine Diphosphate for the Treatment of Severe Acute Respiratory Syndrome Secondary to SARS-CoV2 | NCT04323527      | Recruiting                 | Brazil    |
| Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Propyllosis SARS-CoV-2 Infection | NCT04283461      | Recruiting                 | United States |
| Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA)                            | NCT04322682      | Recruiting                 | Canada    |
| Tocilizumab for SARS-CoV2 Severe Pneumonitis                                 | NCT04315480      | Not yet recruiting         | Italy     |
| Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV | NCT04252274      | Recruiting                 | China     |
| Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection | NCT04251871      | Recruiting                 | China     |
| COVID19: A Study to Investigate the Efficacy of Tadipatin in Treating Severe or Critical COVID-19 Infection | NCT04326426      | Not yet recruiting         |          |
| Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19 | NCT04306393      | Recruiting                 | United States |
| Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections | NCT043331445     | Active, not recruiting     | Canada    |
| NK Cells Treatment for Novel Coronavirus Pneumonia                           | NCT04280224      | Recruiting                 | China     |
| Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection | NCT04261907      | Not yet recruiting         |          |
| A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia | NCT04276987      | Not yet recruiting         |          |
| Post-exposure Prophylaxis / Preemptive Therapy for SARS-CoV2-2               | NCT04308668      | Recruiting                 | United States |
| STOP-PIV - Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects | NCT04308092      | Recruiting                 | United States |
| Norwegian Coronavirus Disease 2019 Study                                     | NCT04316377      | Recruiting                 | United States |
| Lessening Organ Dysfunction With VITamin C                                    | NCT04368027      | Recruiting                 | Canada    |
| Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure | NCT04244591      | Recruiting                 | China     |
| Convalescent Plasma to Limit Coronavirus Associated Complications           | NCT04325672      | Not yet recruiting         | United States |
| Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia  | NCT04265433      | Recruiting                 | China     |
| Anti-IFNβ Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure Drug; Ruxetemra iv, Ruxetemra sc, Ketoza sc | NCT04322773      | Not yet recruiting         | Denmark   |
| Safety and Efficacy of Hydroxychloroquine Associated With Azythromycin in SARS-CoV-2 Virus | NCT04322123      | Not yet recruiting         | Brazil    |
| Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19) | NCT04307693      | Recruiting                 | Korea     |
| Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19) | NCT04292899      | Recruiting                 | United States |
| NestCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE) | NCT04315987      | Not yet recruiting         |          |
| Bevacizumab in Severe or Critically Severe Patients With COVID-19 Pneumonia-RCT (BEST-RCT) | NCT04305106      | Recruiting                 | China     |
| The Efficacy and Safety of Thalidomide in the Adjuvant Treatment of Moderate New Coronavirus (COVID-19) Pneumonia | NCT04273529      | Not yet recruiting         |          |
| The Efficacy and Safety of Thalidomide Combined With Low-dose Hormones in the Treatment of Severe COVID-19 Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells | NCT04313322      | Recruiting                 | Jordan    |
| Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection (HYDRA Trial) (HYDRA) | NCT04315896      | Not yet recruiting         |          |
| Tetraneurin Tablets Used in the Treatment of COVID-19 (TT-NPC)               | NCT04308317      | Enrolling by invitation    | China     |
| Fingolimid in COVID-19                                                      | NCT04280588      | Recruiting                 | China     |
| GCD424 as a Non-antiviral Immunomodulator in COVID-19 Treatment (SAC-COVIDtv) | NCT04317040      | Not yet recruiting         | United States |
| Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019(COVID-19) | NCT04288102      | Recruiting                 | China     |
| The Clinical Study of Carrimycin on Treatment Patients With COVID-19         | NCT04286503      | Not yet recruiting         | United States |
| Efficacy and Safety of Corticosteroids in COVID-19 Methylprednisolone         | NCT04273321      | Recruiting                 | China     |
| Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19) | NCT04318444      | Not yet recruiting         | China     |
| Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial) | NCT04318015      | Not yet recruiting         |          |
| Safety and Immunity of Covid-19 aAPC Vaccine                                | NCT04299724      | Recruiting                 | China     |
| Immunity and Safety of Covid-19 Synthetic Mitigene Vaccine                  | NCT04276896      | Recruiting                 | China     |
| A Phase I Clinical Trial in 18-60 Adults (APICHT/vaccine)                    | NCT04313127      | Recruiting                 | China     |
| Faviapiravim Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019 | NCT04310228      | Recruiting                 | China     |
| Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells | NCT04302519      | Not yet recruiting         |          |
| Multicenter Clinical Study on the Efficacy and Safety of Xiyanpiing Injection in the Treatment of New Coronavirus Infection Pneumonia (General and Severe) | NCT04295551      | Not yet recruiting         |          |
| Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV) | NCT04303507      | Not yet recruiting         | China     |
| Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19) | NCT04273763      | Enrolling by invitation    | China     |
| Yinhu Qiongwen Decoction for the Treatment of Mild / Common CoVid-19       | NCT04279863      | Active, not recruiting     | China     |

(continued on next page)
| Clinical trials                                                                 | Identifier  | Status          | country         |
|--------------------------------------------------------------------------------|-------------|-----------------|-----------------|
| Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COV19: A Randomized Control Trial (THDMS-COVID19) | NCT04303299 | Not yet recruiting | Thailand        |
| The Effect of T89 on Improving Oxygen Saturation and Clinical Symptoms in Patients With COVID-19 | NCT04285190 | Not yet recruiting | China           |
| Immunoregulatory Therapy for 2019-nCoV: PD1-blocking antibody + standard treatment, Thymosin + standard treatment, standard treatment | NCT04268537 | Not yet recruiting | China           |
| Tocilizumab vs. CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS) | NCT04306705 | Recruiting      | China           |
| Mild/Moderate 2019-nCoV Remdesivir RCT | NCT04252664 | Recruiting      | United States   |
| Losartan for Patients With COVID-19 Requiring Hospitalization | NCT04312009 | Not yet recruiting | United States   |
| Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVery) | NCT04315948 | Not yet recruiting | China           |
| Drug: Remdesivir, Lopinavir/ritonavir, Interferon Beta-1A, Standard of care | NCT04311177 | Not yet recruiting | United States   |
| Losartan for Patients With COVID-19 Not Requiring Hospitalization | NCT04279197 | Recruiting      | China           |
| Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia | NCT04273766 | Not yet recruiting | China           |
| Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus | NCT04252118 | Recruiting      | China           |
| The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia | NCT04264126 | Not yet recruiting | China           |
| A Prospective/Retropective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia | NCT04255017 | Recruiting      | China           |
| Drug: Abdol hydrochloride, Oseltamivir, Lopinavir/ritonavir | NCT04254874 | recruiting      | China           |
| Treatment of Pulmonary Fibrosis Due to 2019-nCoV Pneumonia With Fuzheng Huayu | NCT04279197 | Recruiting      | China           |
| Drug: N-acetylcysteine + Fuzheng Huayu Tablet, N-acetylcysteine + Placebo | NCT04312243 | Not yet recruiting | China           |
| NO Prevention of COVID-19 for Healthcare Providers | NCT04288713 | Available        | China           |
| Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured Patients | NCT04264858 | Not yet recruiting | China           |
| Drug: Immunoglobulin of cured patients, γ-Globulin | NCT04293887 | Not yet recruiting | China           |
| Drug: Recombinant human interferon α1β | NCT04320238 | Recruiting      | China           |
| Experimental Trial of rhFhNas Nasal Drops to Prevent 2019-nCoV in Medical Staff | NCT04292340 | Recruiting      | China           |
| Drug: recombinant human Interferon Alpha-1b, thymosin alpha 1 | NCT04291279 | Recruiting      | China           |
| Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19 | NCT04292340 | Recruiting      | China           |
| Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus | NCT04260594 | Not yet recruiting | China           |
| Evaluation of Ganovo (Danoprevir) Combined with Ritonavir in the Treatment of Novel Coronavirus Infection | NCT04291729 | Completed        | China           |
| Drug: Ganovo + ritonavir + /-Interferon nebulization | NCT04288713 | Available        | China           |
| Eculizumab (Soliris) in Covid-19 Infected Patients | NCT04265925 | Recruiting      | China           |
| Severe 2019-nCoV Remdesivir RCT | NCT04257666 | Recruiting      | United States   |
| Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19 | NCT04305457 | Recruiting      | China           |
| Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019 novel Coronavirus(CoV) Pneumonia | NCT04266952 | Recruiting      | China           |
| Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection | NCT04261907 | Not yet recruiting | China           |
| Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia | NCT04264533 | Recruiting      | China           |
| Expanded Access Remdesivir (RDV, GS-5734™) | NCT04302766 | Recruiting      | China           |
| Xinyanping Injection for the Treatment of New Coronavirus Infected Pneumonia NCT04279197 | Recruiting | China           |
| Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) to Prevent SARS-CoV-2 Infection | NCT04283461 | Not yet recruiting | United States   |
| Tocilizumab for SARS-CoV-2 Severe Pneumonitis | NCT04315840 | Recruiting      | Italy           |
| Efficacy and Safety of Darunavir and Cobicitabat for Treatment of Pneumonia Caused by 2019-nCoV | NCT04255274 | Recruiting      | United States   |
| Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV) | NCT04261517 | Complete        | China           |
| Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection | NCT04251871 | Recruiting      | China           |
| Drug: Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and lopinavir/ritonavir) and Traditional Chinese Medicines (TCMs) granules, Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and lopinavir/ritonavir) | NCT04275245 | Recruiting      | China           |
| Clinical Study of Anti-CIDE147 Humanized Mepolizumab for Injection to Treat With 2019-nCoV Pneumonia | NCT04299152 | Not yet recruiting | China           |
| Stem Cell Educator Therapy Treat the Viral Inflammation Caused by Severe Acute Respiratory Syndrome Coronavirus 2 | NCT04280224 | Recruiting      | China           |
| NK Cells Treatment for Novel Coronavirus Pneumonia | NCT04244591 | Recruiting      | China           |
| Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure | NCT04290871 | Withdrawn        | United States   |
| Drug: methylprednisolone therapy | NCT04290871 | Withdrawn        | United States   |
| Norwegian Coronavirus Disease 2019 Study | NCT04316377 | Not yet recruiting | China           |
| Drug: Hydroxychloroquine Sulfate | NCT04276688 | Recruiting      | China           |
| Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment | NCT04308668 | Recruiting      | United States   |
| A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia | NCT04276987 | Not yet recruiting | United States   |
| Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID19 Infection | NCT04290871 | Withdrawn        | United States   |
| Nitric Oxide Gas Inhalation for Severe Acute Respiratory Syndrome in COVID-19. | NCT04290871 | Withdrawn        | United States   |
months to test their efficacy in vitro and in vivo, and the results of clinical trials may take even longer. In order to shorten this time, WHO is organizing a large clinical trial (Solidarity clinical trial), encompassing over 100 countries from all around the world.

8.1. Virally targeted agents

Antiviral drugs and systemic corticosteroids, including neuraminidase inhibitors (Oseltamivir, Peramivir, and Zanamivir), Ganciclovir, Acyclovir, and Ribavirin, as well as Methylprednisolone which reduced the risk of death in ARDS patients [63–65], are used in the clinic for viral infections. However, they have not been shown to have any effect on COVID-19, thus they are not recommended [66].

8.1.1. Nucleoside analogs

Nucleoside analogs are derivatives of adenine or guanine that block the RNA-dependent RNA polymerase enzyme and affect the structure of viral RNA in a large spectrum of RNA viruses, including human coronaviruses [67].

8.1.1.1. Favipiravir (T-705). Favipiravir is a guanine analog that is approved for influenza treatment. It can inhibit the RNA-dependent RNA polymerase of RNA viruses such as Influenza, Yellow fever, Chikungunya, Ebola, Norovirus, and Enterovirus [67]. Besides, in one recent study, scientists have reported its effectiveness against 2019-nCoV [69]. Patients with COVID-19 are being enrolled in randomized clinical trials to test the efficacy of Favipiravir plus Interferon-α (ChiCTR2000029600), and Favipiravir plus Baloxavir marboxil (an approved Influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544).

8.1.1.2. Faviilavir. Faviilavir is an approved treatment for Influenza, which inhibits the RNA-dependent RNA polymerase. It has been approved as an experimental coronavirus drug against SARS-CoV-2 [70].

8.1.1.3. Ribavirin. Ribavirin is a guanine derivative approved for treating respiratory syncytial virus (RSV) and hepatitis C virus (HCV) infections, which also showed positive results in patients with SARS and MERS, but its side effects such as anemia may be severe at high doses [71]. Besides, its potency against SARS-CoV-2 is unknown [72,73]. One in-silico study revealed the potential ability of Sofosbuvir, Ribavirin, and Remdesivir to inhibit SARS-CoV-2 polymerase [74]. However, another study, mentioned above, ruled it out as an effective therapy for COVID-19. So, it is not yet clear whether it is effective against COVID-19 or not, and more investigation is needed.

8.1.1.4. Remdesivir (GS-5734). Remdesivir is a phosphoramidite prodrug of an adenine derivative with a chemical structure similar to Tenofovir alafenamide, an approved inhibitor of HIV reverse transcriptase. Remdesivir had broad-spectrum activity against a diverse range of coronaviruses, including human CoVs, zoonotic bat CoVs, and pre-pandemic zoonotic CoVs, in addition to Ebola in cell culture and animal models [75]. The results of the latest studies suggested that Remdesivir can inhibit 2019-nCoV [69,76]. Moreover, a phase III clinical trial of Remdesivir against COVID-19 was launched in Wuhan on February 4th, 2020. Remdesivir is not expected to be widely available as an experimental drug for treating a vast number of patients [77]. However, the Food and Drug Administration (FDA) has approved Remdesivir as an effective COVID-19 treatment [78].

8.1.1.5. Galidesivir (BCX4430). Galidesivir is an adenine analog that was initially developed to treat HCV, and its efficacy against Yellow fever revealed its antiviral activity in preclinical studies against many RNA viruses, including SARS-CoV and MERS-CoV [71]. At present, it is in primary clinical trials to assess its safety in healthy individuals. So, it might be useful against SARS-CoV-2.

8.1.1.6. Protease inhibitors

8.1.1.6.1. Chymotrypsin-like (3C-like protease, 3CLpro) and papain-like protease (PLP) inhibitors. 3C-like protease or 3CLpro and PLP are non-structural proteins, which play a critical role in the replication of coronaviruses, and can also inhibit the host innate immune responses [79]. So, 3CLpro inhibitors and PLP inhibitors might be effective against SARS-CoV-2.

8.1.1.6.2. Lopinavir. Lopinavir was primarily supposed to inhibit the 3-chymotrypsin-like protease of SARS and MERS. Although it improved the clinical outcomes in SARS patients in a non-randomized open-label trial [71], it is questionable whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of SARS-CoV-2 or not. This is because the molecular design of HIV protease inhibitors was explicitly optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer, however, this C2-symmetric pocket is absent in coronavirus proteases [80]. In contrast to previous studies that showed after administration of Lopinavir/Ritonavir, β-coronavirus the viral loads were significantly reduced, and coronavirus titers were low or absent [81], it has been shown that the combination of Lopinavir and Ritonavir is not effective in treating patients with severe COVID-19 [82].

8.1.1.6.3. Disulfiram. Disulfiram is a drug used for treating chronic alcoholism by inducing an acute intolerance to ethanol (drinking alcohol). Disulfiram was reported to inhibit the papain-like protease of MERS and SARS in cell culture, but clinical evidence is lacking [83]. It could be effective against SARS-CoV-2, but further investigations are needed.

8.1.1.6.4. Other 3CLpro inhibitors and PLP inhibitors. Other 3CLpro inhibitors, such as Cinanserin [84], Flavonoids [85], Cobicitast [86], Atazanavir, Elavirenz, Ritonavir, Dolutegravir [87], Thymopentin, Carfilzomib, Saquinavir [88], Ledipasvir, and Velpatasvir [89] and PLP inhibitors, like Diarylethanoids [90], Grazoprevir, Telaprevir, Boceprevir [91], Darunavir [92], and Formoterol chloroquine [93] are other potential approaches to combat SARS-CoV-2, but their efficacy remains to be tested.

8.1.1.6.5. Danoprevir. Danoprevir is an NS3/4A protease inhibitor that is used as an anti-HCV drug. It interferes with virus replication and suppresses the effects of the virus on the host response to viral infection. In a small clinical trial of 11 COVID-19 patients, after 4 to 12 days of use of Danoprevir, all the patients recovered [94]. So, it might be suggested that Danoprevir could be effective against SARS-CoV-2.

8.1.1.6.6. Camostat mesylate. Scientists reported in one study how the spike-like glycoprotein of the SARS-CoV-2 virus binds to the ACE2 receptor. Accordingly, the presence of transmembrane protease serine2 (TMPRSS 2) is required for spike protein priming. The researchers found that Camostat mesylate, a serine protease inhibitor, could block the entry of SARS-CoV-2 into lung cells. So, it might be effective against COVID-19. However the application of this drug as a treatment for COVID-19 requires clinical trials [95].

8.1.1.6.7. Griffithsin. Griffithsin has antiviral effects against HCV and HIV in vitro [96,97]. It is a red-alga-derived lectin, which binds to oligosaccharides on the surface of various viral glycoproteins, including HIV glycoprotein 120 and SARS-CoV spike glycoprotein [71]. Besides, it can inhibit virus entry, reverse transcriptase activity, integrase activity, and protease activity [98]. So, it might be effective against SARS-CoV-2, but further investigation is needed.

8.1.1.7. Arbidol. Arbidol is a non-nucleoside antiviral and immunomodulatory drug for treatment and prevention of influenza, which could be effective against COVID-19 [99]. Several clinical trials for investigating its effectiveness against COVID-19 are in progress.
8.2. Chloroquine (CQ) and Hydroxychloroquine (HCQ)

CQ is an anti-malarial drug [100] with practical activity against SARS-CoV-2 infection [101], which could help in the treatment of COVID-19. It has immunomodulatory effects, such as suppression of the production and release of tumor necrosis factor-α (TNF-α), and Interleukin (IL-6). It also works as a novel type of autophagy inhibitor [102], which probably interferes with viral infection and replication. Moreover, scientists have reported in a number of studies that CQ interferes with the glycosylation of the cellular ACE2 receptor, the spike protein of SARS-CoV, and the entry of the virus [101,103]. Besides, CQ increases the pH of acidic intracellular organelles such as endosomes and lysosomes, which are essential for membrane fusion [104]. So, this drug can reduce fever and improve the radiological characteristics of the lungs in COVID-19. Also, it reduced the time to recovery. Besides, CQ is one of three drugs that could be promising for the treatment of new coronavirus disease; the other two drugs, described above, are Favipiravir and Remdesivir [105], where the percentage of patients with a negative viral nucleic acid test was higher with anti-malarial drugs. Until now, no severe side effects have been reported in more than 100 participants treated with CQ in trials. It has been shown that oral absorption of CQ and HCQ in humans is useful in SARS-CoV-2 treatment. Considering that HCQ was less toxic than CQ in animal models [106], and because that an overdose of CQ could result in acute poisoning and death [107]; the safe dosage (6–6.5 mg/kg per day) [108] of HCQ sulfate could effectively treat SARS-CoV-2 infections. It must be mentioned that although the combination of HCQ plus Azithromycin was an effective treatment of COVID-19 [109], the NIH has not recommended it as a routine treatment for clinical use due to the potential for toxicity.

8.3. Cytokine-based therapy

The cytokine storm or cytokine release syndrome (CRS) results from the widespread release of pro-inflammatory cytokines following the activation of the immune system by microorganisms or even by therapeutic interventions [110]. In SARS-CoV and MERS-CoV infections, overproduction of pro-inflammatory cytokines, such as IL-6, IL-1β, IL-12, IL-18, IL-33, Interferon-α (IFN-α), IFN-γ, and TNF-α, or chemokines such as chemokine C-C motif ligand 2 (CCL-2), CCL-3, CCL-5, C-X-C motif chemokine ligand 8 (CXCL-8), CXCL-9, and CXCL-10 were included in the cytokine storm [111–113]. It has been shown that by activating type 1 macrophages (M1) and T helper 1 (Th1) cells, COVID-19 increases the production of inflammatory cytokines like IL-6, IFN-γ, and granulocyte monocyte-colony stimulating factor (GM-CSF) [114]. It must be mentioned that IL-6 and GM-CSF (can significantly enhance the production of IL-6 by stimulating monocytes [115,116]) which are secreted by monocytes and T cells, are more important in inducing the cytokine storm than other pro-inflammatory cytokines.

The cytokine storm is one of the fundamental causes of COVID-19 pathogenesis, resulting in excessive inflammation, lung damage, ARDS, and other organ failure. Also, the presence of high levels of TNF-α, granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein 1A (MIP-1A), monocyte chemoattractant protein-1 (MCP-1), CXCL-10, IL-10, and IL-7 in severe COVID-19 patients indicates the importance of CRS in the disease progression [16]. So, CRS is considered to be a principal cause of death in COVID-19 patients [117,118].

Therefore, it is important to investigate the control of CRS through various methods like immunomodulation approaches, mesenchymal stem cells (MSCs), or Interferon-based therapy [119].

8.3.1. Immunomodulation approaches

8.3.1.1. Monoclonal antibodies (mAb). As mentioned before, IL-6 is an important component of the cytokine storm. So, the use of anti-IL-6 inhibitory agents, like Tocilizumab, Sarilumab, Siltuximab, which are all humanized mAbs, might reduce the adverse effects of CRS [17]. It must be noted that anti-GM-CSF mAbs like TJO03234, Gimsilumab, and Lenzilumab are also being evaluated against COVID-19. Moreover, inhibitors of the IL-1 family, IFN-γ cytokines, and the Janus kinase signal transducer and activator of transcription proteins (JAK-STAT) signaling pathway might also be useful for controlling the cytokine storm [120].

8.3.1.2. Hyaluronidase and 4-Methylumbelliferone (4-MU). It has been demonstrated that the increased levels of pro-inflammatory cytokines, including IL-6, IL-1, and TNF-α in the lungs of COVID-19 patients, can result in the production of hyaluronic or hyaluronic acid (HA) by inducing the expression of HA-synthase-2 (HAS2) this may contribute to ARDS and death [117,121]. So, lowering HA levels through administration of hyaluronidase, or 4-methylumbelliferone (4-MU), and blocking the inflammatory cytokines could be effective for treating dyspnea and reducing the mortality rate of COVID-19 patients [122].

8.3.1.3. Corticosteroids. Corticosteroids can be useful in controlling CRS, for instance in cancer immunotherapy. Initially, dexamethasone was proposed as an effective agent for managing CRS. However, due to the enhanced risk of vascular necrosis and diabetes (which are mortality risk factors for COVID-19), corticosteroid administration for COVID-19 patients is not recommended [123].

8.3.1.4. Immune cell depletion. Immune cells are responsible for the secretion of inflammatory factors. So, decreasing the lymphocyte count might result in CRS suppression. Rituximab, Etoposide, and Lenunam are Mabs used to reduce CD8⁺ T cells, decrease the release of interferon-gamma, and to treat CRS and hemophagocytic lymphohistiocytosis (FHLH) [124,125].

8.3.1.5. Interferon-based therapy. Interferons regulate the innate immune system, which is vital for killing viruses by regulating gene transcription [126]. IFNs regulate the transcription of genes through activating the JAK-STAT signaling pathway after binding to their receptors on the cell surface. IFN type1 is composed of IFN-β and IFN-α, and IFN-α2b has been shown to rapidly suppress the replication of animal and human coronaviruses [127]. SARS-CoV-2 can inhibit the activity of IFN type1 through the suppression of the STAT-1 intracellular signaling pathway [128]. So, IFN-based therapies could be useful for treating COVID-19.

Interestingly, the low morbidity and mortality rates of COVID-19 in children might be due to the low secretion threshold of IFNs in children, and the rapid production of IFNs after infection. Thus, the high secretion threshold of IFNs in adults could be responsible for the higher mortality rate in these patients. So, IFN-based therapies might be effective against COVID-19, especially in the early phase of the disease [128].

In addition to the direct suppression of the SARS-CoV-2, which could contribute to the therapeutic response, IFN-based therapy can stimulate the innate immune. So, pegylated IFNα-2a and IFNα-2b could be tested in patients with COVID-19, as they stimulate innate antiviral responses.

Nevertheless, clinicians must be wary of administering IFNs alone, due to the possibility of increasing the cytokine storm with high doses of IFNs.

8.3.1.6. Stem cell therapy. Stem-cell therapy has demonstrated a possible therapeutic benefit in almost all incurable diseases [128]. Among stem cells, MSCs have received most attention because of their many advantages. These include, a high proliferation rate, self-renewal ability, reparative properties, availability from different tissues, multidirectional differentiation, lack of adverse reactions, and long-term storage ability. In addition to tissue regeneration, they are used for...
their anti-inflammatory and immunoregulatory activity [129]. Chinese scientists have reported the use of MSCs as an anti-inflammatory approach to cytokine storm-like disorders. So, they could be effective in controlling CRS.

MSCs based immunomodulatory activities include suppressing the over-activation of T cells and macrophages stimulating the anti-inflammatory macrophage 2 phenotype (M2) stimulating T-reggs and suppressing pro-inflammatory cytokines. MSC-based therapy might decrease the risk of CRS in COVID-19 patients by reducing the production of TNF-α, IFN-α, IL-1, IL-6, and IL-12 [130].

Moreover, MSCs might improve ARDS, regenerate lung tissue, and lessen lung fibrosis through secreting IL-10, vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) in SARS-CoV-2 patients [130]. It is possible that MSC-based therapy could remove the need for ventilation in COVID-19 patients, return the T-cell counts to a normal range, restore pulmonary function, decrease the level of inflammatory cytokines, and increase the level of anti-inflammatory cytokines [131,132].

In order to improve the effectiveness of MSC-induced anti-inflammatory response, they could be pretreated with IFN-γ, which is low or absent in severe COVID-19 [133].

These cytokine-licensed MSCs could be more effective in the suppression of hyperactive immune response and promotion of tissue repair, because it is known that cytokine-licensed MSCs were effective in preventing lipopolysaccharide (LPS)-induced acute lung damage [134]. So, several clinical trials are being carried out for evaluating the effectiveness of MSCs against COVID-19.

### 8.4. Passive antibody therapy and convalescent plasma therapy

Plasma antibodies contribute to the elimination of infection via directly binding to pathogens and neutralizing them, or by activating indirect immune responses, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, or phagocytosis [135,136]. In COVID-19 patients, their plasma contains active specific neutralizing antibodies (which mediate the anti-infective function of plasma therapy) and non-neutralizing antibodies (which might boost prophylaxis and improvement of patients).

Hyper-immune immunoglobulin therapy or convalescent plasma (CP) is a passive-adaptive-immunotherapy applied to protect individuals from clinical infection or prevent disease development. The early administration of CP or hyper-immune immunoglobulin that contains high antibody titers could decrease the viral load, reduce disease mortality, and shorten hospital stays [137,138].

While passive antibody therapy involves the pooling of immunoglobulin preparations with high antibody titers, plasma therapy is applied as an emergency treatment, especially in epidemics and pandemics, when there is limited time or resources for pooled immunoglobulin preparation. Compared to passive antibody therapy which generates short-term rapid immunity, persistent immunity is produced by monoclonal antibodies or hyper-immune globulin (fractionated plasma products) [139]. Therefore, convalescent plasma is employed as a rapid immune-based therapy in the early stages of the disease [140], to increase infected patients immunity against the virus, stop COVID-19 progression, and enhance the therapeutic success rate [141]. Moreover, plasma therapy can decrease viremia and reduce new infections (through neutralizing antibodies), clear free virus and infected cells, and alleviate the symptoms (like dry cough, fever, sputum, muscle pain) and pulmonary damage. Moreover, it can increase the lymphocyte ratio and blood oxygen saturation without any adverse effects [141–144].

The FDA has approved the administration of convalescent plasma containing specific antibodies against SARS-CoV-2 [145]. Besides, the FDA has recommended that people who have recovered from COVID-19 (for at least two weeks) should donate their plasma to help other patients. It is estimated that each donation can provide sufficient plasma for four patients [146].

However, there are some challenges in the collection of plasma from donor serum during the recovery period or after recovery, and confirming the proper level of neutralizing antibody titer. Some of these challenges are the availability of willing qualified donors, clinical conditions, eliminating host interactions, and the viral kinetics of SARS-CoV-2, that will need to be solved before convalescent plasma can become a generalized therapeutic option.

A qualified donor must be selected based on a confirmed history of COVID-19 infection, including a negative follow-up molecular test, the absence of symptoms, normal physical examination, and pre-donation screening assays. It should be mentioned that since plasma with a high neutralizing antibody titer is only obtained at 14 days after the resolution of symptoms, this is the best time to harvest the plasma [143]. Besides, it has been suggested that apheresis might be better for optimizing the convalescent plasma product, rather than whole blood donation. The appropriate dose convalescent plasma therapy in COVID-19 was determined based on past experience of applying plasma therapy in SARS-CoV, which was 5 mL/kg of plasma with ≥ 1:160 titer [140]. It must be taken into account that transfusion-transmitted SARS-CoV-2, acute transfusion-related injuries, other transfusion-transmissible infections, transfusion-associated circulatory overload, and allergic transfusion reactions could be risks of plasma therapy in the treatment of COVID-19 [147,148].

It must be mentioned that in some patients, COVID-19 antibodies are not always found after recovery, which suggests that some patients recover without antibodies [149] or else the antibodies vanish after recovery. Although one study evaluated the effectiveness of plasma therapy in five patients (who were mechanically ventilated and received methylprednisolone) all of them showed a reduction in COVID-19 symptoms and viral load, it is not yet clear that the antibodies from donors are active and effective or not [150].

Even considering the risks of plasma therapy, it could still be effective as an emergency COVID-19 treatment.

### 8.5. Monoclonal antibodies (mAbs)

Monoclonal antibodies (mAbs) can be obtained from COVID-19 patients or by laboratory preparation. They are characterized by high specificity and purity, high safety, and a low rate of blood-borne infections that can overcome the limitations of intravenous immunoglobulins and convalescent plasma therapy. mAbs can be chosen to target the specific epitopes of surface SARS-CoV-2 proteins and could inhibit the virus entry into host cells (including receptor binding, membrane fusion, and sialic acid-binding sites), and reduce replication and infection progression.

Some mAbs that target the spike protein in SARS-CoV and MERS-CoV have shown promising results in vitro and in vivo, that could be potentially useful against SARS-CoV-2 [151]. For example, specific neutralizing mAbs against the receptor-binding domain (RBD) in spike protein (CR3014 [152], CR3022 [153], 311mab–31B5, 311mab-32D4, and 311mab–31B9), or specific mAbs that bind to ACE2 could all effectively block virus entry [139]. It must be mentioned that contrary to 311mab–31B9 (without any neutralization capability) [154], 311mab-31B5 and 311mab-32D4 can both potently suppress the SARS-CoV-2 RBD protein and interaction with the human ACE2 (hACE2) protein, leading to virus neutralization. Moreover, using CR3022 as a monoclonal therapy, or else in combination with other drugs might result in COVID-19 patient improvement. Besides, 47D11 could powerfully suppress the infection of SARS-CoV and SARS-CoV-2 through an unknown mechanism [155].

Furthermore, m396, CR3014 [156], and Meplazumab (which is an anti-CD147 mAb [157], could be alternative monoclonal antibodies to be used against SARS-CoV-2 [153]. So, mAbs can be considered as potential therapeutic options against COVID-19.
8.6. Polyclonal antibodies

Polyclonal antibodies can be used as prophylactic or therapeutic agents against viral infections [75]. For example, SAB-301 is a well-tolerated antiviral treatment for MERS-CoV [158]. So, polyclonal antibodies might also be effective against COVID-19.

8.7. Intravenous immunoglobulin (IVIg)

IVIg is an effective immunomodulatory agent, which has been applied in autoimmune and inflammatory diseases, bacterial infections, severe viral infections, fungal infections, and also in graft versus host disease (GVHD). It is composed of polyclonal immunoglobulin G or IgG. IVIg can modulate the immune system through various mechanisms, like reducing and preventing the production of cytokines, enhancing anti-inflammatory cytokines, and inducing immune system responses against the virus [159]. IVIg has been used to treat infections of the upper and lower respiratory tracts [160,161]. Besides, IVIg therapy showed a clinical benefit and good tolerability in SARS and MERS cases [162,163]. So, IVIg therapy could be a potential therapeutic option against COVID-19 [59]. High-dose IVIg therapy, 0.3–0.5 g per kg body weight over five days, has been proposed for COVID-19 patients. Scientists have shown that the application of high-dose IVIg at the appropriate time point could prevent disease progression to a severe state and enhance the patient recovery rate in early phases of the disease. Moreover, after administration of IVIg no adverse effects were reported [164]. So, immunotherapy with IVIg either alone or in combination with other anti-SARS-CoV-2 therapies could be an alternative option for COVID-19 patients.

8.8. Anakinra

In one small retrospective cohort study in Italy, the effect of Anakinra, a recombinant Interleukin-1 receptor antagonist, was studied in the treatment of COVID-19. In this study, 29 patients received the drug, while 16 patients received only standard treatment for COVID-19. Twenty-one patients (72%) of the intervention group had a CRP level below the standard after 21 days, and most of them recovered; while five patients were mechanically ventilated, and three died. Only eight (50%) of the 16 control patients had improved respiratory status after 21 days, of which one person was mechanically ventilated, and seven died. Survival rates at 21 days in the intervention and control groups were 90% and 56%, respectively with a significant difference. Anakinra could increase the survival of patients with COVID-19 and improve respiratory status, and may be an effective treatment [165].

8.9. Ibuprofen

Ibuprofen has shown problems with safety [166]. Discussions over the safety of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of COVID-19 has involved the European Medicines Agency. It had been proposed that NSAIDs could be considered for treating the emerging viral illness in some cases, but most patients with COVID-19 symptoms should use Paracetamol rather than Ibuprofen, because the latter could worsen the condition. Reports in French media showed a deterioration in the condition of four young people with COVID-19 after taking Ibuprofen [167]. So, it is wise to use Paracetamol instead of Ibuprofen for COVID-19 patients.

8.10. Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blocker (ARB)

It had been suggested that the use of ACE-I and ARB drugs for cardiovascular indications could lead to an up-regulation of ACE2 receptors, and hence the development of more severe COVID-19 [168]. However, the European Heart Association as well as three major American cardiology bodies, including the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America, have all emphasized that patients who have been taking ACE-I or ARB drugs should continue their treatment.

8.11. Human recombinant solution ACE2 (hrsACE2)

The hrsACE2 solution, previously clinically tested in phase one and two clinical trials (2017), could significantly inhibit COVID-19 infection in the early stage and prevent the virus from attaching to the cell. It reduced SARS-CoV-2 levels in Vero-E6 cells (cells used for virus isolation) up to 1000–5000 times (in terms of viral load) in laboratory studies [169]. It must be mentioned that this study had some limitations, for example, lung organoids were not tested, and the experiment only simulated the early stages of COVID-19. So, because SARS-CoV-2 can directly infect human blood vessels and enter the kidneys, hrsACE2 could prevent this occurrence, it might be used in the clinic. However, further investigations are needed.

8.12. CRISPR Cas13

Clustered regularly interspaced short palindromic repeats (CRISPR) is a novel genome engineering tool, which is composed of two components, including a guide RNA (gRNA), which is specific to the target DNA or RNA sequence, and a non-specific CRISPR associated endonuclease protein or Cas protein.

CRISPR Cas13 is a type VI CRISPR-associated RNA-guided ribonuclease, which targets a specific sequence of RNA. Three protein families have been recognized, including Cas13a (formerly known as C2c2), Cas13b, and Cas13c [170,171]. Cas13a enzymes can also be a suitable tool for nucleic acid sequence detection [172]. In addition, since Cas13 and inactive Cas13 target specific RNA sites for cleavage and inhibition, respectively, they could be used as an effective COVID-19 therapy. However, further investigations are essential.

8.13. Nitric oxide

Newborns with severe ARDS, are treated with high-dose pulmonary surfactant, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation. This approach might be effective for patients of COVID-19 with ARDS [173,174] as well.

8.14. Oxygen therapy

Almost all patients are administered oxygen therapy, and WHO has recommended extracorporeal membrane oxygenation (ECMO) for patients with refractory hypoxemia [175].

8.15. Lithium

Because lithium reduces apoptosis and inhibits glycogen synthase kinase3 beta (GSK-3β), which interacts with receptors and triggers signal transduction events, it might be effective against COVID-19 [176].

8.16. Antibiotics

Antibiotics have been suggested for alleviating the pneumonitis symptoms, and it was shown in an in vitro study that Telicoplanin could prevent the entry of SARS-CoV-2 into the cytoplasm [177]. Moreover, Azithromycin has shown some success against COVID-19.

8.17. Ivermectin

Ivermectin is an FDA-approved drug for the treatment of parasitic amnesia, which is widely available. It was shown in one study that...
adding five μM of Ivemectin to virus-infected Vero/hSLAM cells reduced the levels of viral RNA by 5,000 times after 48-hour culture [178]. So, it could be effective against COVID-19.

8.18. Nitazoxanide

Nitazoxanide is an antidiarrheal drug that has been proposed to inhibit 2019-nCoV [69], but more investigation is needed. Besides, the combination of Nitazoxanide and Azithromycin could be more effective than using them as single agents against COVID-19 [179]. Nevertheless, combining several therapies may increase the side effects and lead to drug-drug interactions, which must be taken into account when proposing new treatments for COVID-19.

8.19. Bacillus Calmette–Guérin (BCG)

Bacillus Calmette–Guérin (BCG) vaccination is being considered in clinical trials to test its efficacy to decrease COVID-19 morbidity and mortality rates [179].

8.20. Colchicine

Colchicine has an immunomodulatory effect, and is commonly used in the treatment of gout. Due to its immunomodulatory effects, it could be useful for ameliorating the clinical manifestations of COVID-19 [180].

Because of the wide variety of therapeutic options either as a single drug or in combination with other drugs, it is difficult for clinical trials to be conclusive. This is why WHO is conducting the Solidarity clinical trial; up to April 21st, 2020, over 100 countries have joined this clinical trial to defeat SARS-CoV-2. [181].

8.21. Vitamin C

It has been demonstrated in several studies that vitamin B3 (niacin or nicotinamide) was effective in reducing injury in animal models with bleomycin-induced lung damage [182]. Vitamin C could also be effective in preventing COVID-19 as it can reduce the severity of lower respiratory tract infections [183]. Moreover, it was suggested that the supplementation with vitamin D and vitamin E might increase the efficacy of clinical trials to test its efficacy against COVID-19.

Moreover, it was suggested that the supplementation with vitamin D and vitamin E might increase the efficacy of clinical trials to test its efficacy against COVID-19.

9. Clinical trials

At the time of the preparation of this study (March 29th, 2020), more than 200 clinical trials of COVID-19 had been listed in https://clinicaltrials.gov/. Trials involving vaccines, antiviral drugs, immunotherapies, monoclonal antibodies, stem cells, and nitric oxide are summarized in Table 1.

10. Conclusion

In conclusion, SARS-CoV-2 is a novel and highly contagious virus, and there is no specific treatment for COVID-19 disease up to now. It must be taken into account that if no effective action is taken and if drugs, vaccines, and patient tracking measures are not widely implemented or effective, intermittent social distancing is likely to continue until 2022. By that time COVID-19 might have affected 90% of the world population and kill over 40 million people [185,186]. Therefore, it is wise to continue preventive methods and public health measures until an appropriate vaccine and effective drugs are discovered. Combinational therapies with some of the above-mentioned drugs or supplements, plus an appropriate immunomodulatory diet, proper mental support and adherence to standards, will eventually be effective against COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Fan Y, Zhao K, Shi Z-L, Zhou P. Bat Coronaviruses in China. Viruses. 2019;11(3):210.
[2] C. Wang, P.W. Horby, F.G. Hayden, G.F. Gao, A novel coronavirus outbreak of global health concern, The Lancet. 395 (10223) (2020) 470–473.
[3] Y. R. Guo, Q. D. Cao, Z. S. Hong, Y. Y. Tan, S. D. Chen, H.-J. Jin, et al., The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status, Mil. Med. Res. 7 (1) (2020) 1–10.
[4] Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan novel coronavirus (2019-nCoV), December 19 to January 2020. Eurosurveillance. 2020;25(4).
[5] Parry J. China coronavirus: cases surge as official admits human to transmission. British Medical Journal Publishing Group; 2020.
[6] J. Hellewell, S. Abbott, A. Gimma, N.I. Bosse, C.J. Jarvis, T.W. Russell, et al., Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. The Lancet Global Health. (2020).
[7] K. Mohamed, E. Rodríguez-Román, F. Rahmani, H. Zhang, M. Ivanovska, S.A. Makhda, et al., Borderless collaboration is needed for COVID-19: a disease that knows no borders, Infect Control Hosp Epidemiol (2020).
[8] S. Montanari, N.D. Ols, L.Q. Uddin, M. Perc, J.M. Routes, D. Nuno Vieira, et al., All together to Fight Novel Coronavirus Disease (COVID-19), The American Journal of Tropical Medicine and Hygiene. (2020).
[9] S. Hanafi, N. Rezaei, COVID-19: Developing from an outbreak to a pandemic, Arch Med Res (2020).
[10] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, et al., Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin, BioRxiv (2020).
[11] F. Wu, S. Zhao, B. Yu, Y.-M. Chen, W. Wang, Z.-G. Song, et al., A new coronavirus associated with human respiratory disease in China, Nature 579 (7798) (2020) 265–269.
[12] Zhou P, Yang X, Wang X, Hu B, Zhang L, Wang Z, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. Published online February 3, 2020. 2020.
[13] T.T.-Y. Lam, M.-H.H. Shum, H.-C. Zhu, Y.-G. Tong, X.-B. Ni, Y.-S. Liao, et al., Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China, BioRxiv (2020).
[14] D. Paraskevis, E.G. Kostaki, G. Magiorkinis, G. Panayiotakopoulos, G. Sourvinos, S. Tsioudis, Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event, Infection, Genetics and Evolution. 79 (2020).
[15] Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing evolution and RNA concentration of SARS-CoV-2. [internet]. Nature. Published online February 3, 2020. 2020.
[16] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, The Lancet. 395 (10223) (2020) 507–513.
[17] M. Cascella, M. Rajnik, A. Cuomo, S.C. Dulebohn, R. Di Napoli, Features, evaluation, and RNA concentration of SARS-CoV-2. [internet]. StatPearls [internet], StatPearls Publishing (2020).
[18] (WHO) WHO. Q&A on coronaviruses (COVID-19) 2020 17 April [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses#:~:text=symptoms.]
[19] A.R. Sahin, A. Erdogan, P.M. Agaoglu, Y. Dineri, A.Y. Cakirci, M.E. Senel, et al., 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature, EJMO. 4 (1) (2020) 1–7.
[20] W.K. Leung, K.-f To, P.K. Chan, H.L. Chan, A.K. Wu, N. Lee, et al., Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection, Gastroenterology 125 (4) (2003) 1011–1017.
[21] Z. Fan, L. Chen, J. Li, X. Cheng, L. Yang, C. Tian, et al., Clinical Features of COVID-19-Related Liver Damage, Clinical Gastroenterology and Hepatology (2020).
[22] N. Rezaei, COVID-19 affects healthy pediatrics more than pediatric patients, Infection Control & Hospital Epidemiology (2020).
[23] Y. Dong, X. Mo, Y. Hu, X. Qi, F. Jiang, Z. Jiang, et al., Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in Pediatrics, (2020).
[24] Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and Transmission of COVID-19 in Shenzhen, China: Analysis of 391 cases and 1,286 of their close contacts. medRxiv. 2020.
[25] X. Lu, L. Zhang, H. Du, J. Zhang, Y.Y. Li, J. Qu, et al., SARS-CoV-2 infection in Children, N. Engl. J. Med. (2020).
[26] Y.G. Jones, M. Mills, D. Suarez, C.A. Hogan, D. Hogen, D. Yeh, J.B. Segal, et al., COVID-19 and Kawasaki disease: novel virus and novel case. Hospital Pediatrics (2020) 2020–10123.
[27] Liu Y, Ning Z, Chen Y, Guo M, Liu Y, Gall NK, et al. Aerodynamic characteristics and RNA concentration of SARS-CoV-2 aerosol in Wuhan hospitals during COVID-
19 outbreak. bioRxiv, 2020.

[28] N. van Doremalen, T. Bushmaker, D.H. Morris, M.G. Holbrook, A. Gamble, B.N. Williamson, et al., Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV.1, N. Engl. J. Med. (2020).

[29] Santarpia JL, Rivera G, Crocco V, Moronitzer MJ, Creager H, Santarpia GW, et al., Transmission Potential of SARS-CoV-2 in Viral Shedding Observed at the University of Nebraska Medical Center. medRxiv. 2020.

[30] McIntosh K, Hirsch MS, Bloom A, E.S. Morrow, A. Roseweir, J. Edwards, The role of gamma delta T lymphocytes in transmission of 2019-nCoV. InfectDis. 2020.

[31] Wang X, Pan Z, Cheng Z, Wu Q, Du Y, and C. Wang, Association between 2019-nCoV transmission and N95 masks and respirators 2020 March 26 [Available from: https://www.ecdc.europa.eu/en/publications-data/facemask-gui-dance-guidance].

[32] P. Richardson, I. Givens, C. Tucker, D. Smith, O. Oechel, A. Phelan, et al., Baricitinib as potential treatment for 2019-nCoV acute respiratory disease, The Lancet. 2020:2020.03.31.20042333.

[33] D. Wang, B. Hu, C. Hu, Y. Zhu, X. Liu, J. Zhang, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infectured pneumonia in Wuhan, China. JAMA. 2020:200370.

[34] Li H, Wang Y, Xu J, Cao B, Potential antiviral therapies for 2019 novel Coronavirus. Zhonghua jiehe he huxi zazhi = Zhonghualiejiehehuxizhii = Chinese journal of tuberculosis and respiratory diseases. 2020;43:E002.

[35] Wu, X. Chen, Y. Cai, X. Zhou, S. Xu, H. Huang, et al., Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA. 2020.

[36] Li H, Wang Y, J. Xu, Cao B, Potential antiviral therapies for 2019 novel Coronavirus. Zhonghua jiehe he huxi zazhi = Zhonghualiejiehehuxizhii = Chinese journal of tuberculosis and respiratory diseases. 2020;43:E002.

[37] De Clercq E. New Nucleoside Analogues for the Treatment of Hemorrhagic Fever Virus Infections. Chemistry—An Asian Journal. 2019;14(22):3962-8.

[38] L. Ostermann, A. Li, M. Frey, T. Rieger, C. Mutenzi-Fotela, S. Günther, Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model, Antiviral Res. 105 (2014) 17–21.

[39] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, et al., Remdesivir and chloroquine effectively inhibit the severe acute respiratory syndrome coronavirus 2 in vitro, Cell Res. 30 (3) (2020) 269–271.

[40] Arena CT. Favipiravir approved as experimental coronavirus drug. 2020 FEBRUARY 21..

[41] A. Zumla, J.F. Chan, E.L. Azhar, K.-Y. Yuen, Coronaviruses—drug discovery and therapeutic options, Nat. Rev. Drug Discovery 15 (5) (2016) 327.

[42] D. Falzarano, E. De Wit, A.L. Rasmussen, F. Feldmann, A. Okumura, D.P. Scott, et al., Treatment with interferon-a2b and ribavirin improves outcome in MERS-CoV infected rhesus macaques, Nat. Microbiol. 4 (2019) 1313-1317.

[43] Y.M. Arabi, S. Shalhoub, Y. Mandourah, A. Al-Omari, E. Al Qasim, et al., Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study, Clin. Infect. Dis. 2020:200370.

[44] A.A. Elketty, Anti-HCV, nucleotide inhibitors, repurposing against COVID-19, Life Sci. 117477 (2020).

[45] Sheikhani TP, Sims AC, Graham RL, Menachedy VA, Gralinski LE, Case JB, et al., Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Science translational medicine. 2017;9(396).

[46] M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, et al., N. Engl. J. Med. (2020).

[47] L. Lan, D. Xu, G. Ye, C. Xie, S. Wang, Y. Li, et al., Positive RT-PCR test results in asymptomatic contacts in Germany, N. Engl. J. Med. (2020).

[48] P. Yu, J. Zhu, Z. Zhang, Y. Han, L. Huang, A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period, J Infect Dis. (2020).

[49] Y. Bao, J. Tuo, W. D. Yin, J. Chen, et al., Presumed asymptomatic carrier transmission of COVID-19, JAMA. (2020).

[50] Pan F, Ye T, Sun P, Gui S, Li B, Li et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020.

[51] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, The Lancet. (2020).

[52] L. Lan, D. Xu, Z. Song, C. Xia, Y. Dong, L. Zhou, et al., Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. The Lancet, Gastroenterology & Hepatology. (2020).

[53] J. Lan, D. Xu, G. Ye, C. Xie, S. Wang, Y. Li, et al., Positive RT-PCR test results in patients recovered from COVID-19, JAMA. (2020).

[54] Tang A, Tong Z, Wang H, Dai Y, Li K, Liu J, et al. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. Emerging infectious diseases. 2020;26(6).

[55] W. Wang, Y. Xie, R. Gao, B. Cao, et al., Detection of SARS-CoV-2 in Different Types of, Clinical Specimens. Jama. (2020).

[56] Song C, Wang Y, L. Wu, X. Li, H. Pan, Q. Wu, et al. Detection of 2019 novel coronavirus in semen and testicular biopsy specimen of COVID-19 patients. medRxiv. 2020:2020.03.03.20033423.

[57] Li Y, Zhao R, Zeng J, Shen X, Wang J, Sheng X, et al. Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. Emerging infectious diseases. 2020;26(6).

[58] International Committee on Taxonomy of Viruses. Novel Coronavirus (nCoV) Virus and Codon Usage. March 2020. (2020) 1

[59] N. Engl. J. Med. (2020).
drug repurposing candidates, ChemRxiv (2020).

[90] J.Y. Park, H.H. Jeong, J.H. Kim, Y.M. Kim, S.-J. Park, D. Kim, et al., Diurethiazainoids from Alnus japonica inhibit papain-like protease of severe acute respiratory syndrome coronavirus, Biopharm. Bull. (2012) b12-0084.

[91] Elbky AA, Ibrahim KM, Antiviral and Antibacterial Drug Repurposing Against the Papain-like Protease of the Newly Emerged Coronavirus (2019-nCoV). 2020.

[92] L. Dong, S. Hu, J. Gao, Discovering drugs to treat coronavirus disease 2019 (COVID-19), Drug Discoveries & Therapeutics, 14 (1) (2020) 58–60.

[93] R. Aya, A. Dav, E. Pypaert, M. Kuma, Potential inhibitors against papain-like protease of novel coronavirus (SARS-CoV-2) from FDA approved drugs. 2020.

[94] Chen H, Zhang Z, Wang L, Huang Z, Gong F, Li X, et al. First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naive and Experienced COVID-19 Patients. 2020.

[95] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell (2020). 2020.

[96] P. Meulman, A. Albecka, S. Belouard, K. Vercauteren, L. Verhoey, C. Wychowski, et al., Griffithsin has antiviral activity against hepatitis C virus, Antimicrob. Agents Chemother. 55 (11) (2011) 5159–5167.

[97] T. Mori, B.R. O’Keefe, R.C. Sower, S. Brings, R. Gardella, S. Berg, et al., Isolation and characterization of griffithsin, a novel HIV-inactivating protein, from the red alga Griffithsia sp, J. Biol. Chem. 280 (10) (2005) 9345–9353.

[98] C. Lee, Griffithsin, A Highly Potent Broad-Spectrum Antiviral Lectin from Red Algae: From Discovery to Clinical Application, Mar. Drugs 17 (10) (2019) 567.

[99] L. Huang, Y. Liu, R. Luo, L. Zeng, I. Telegina, V.V. Vlassov, et al., Arbidos for preventing and treating influenza in adults and children. The Cochrane database of systematic reviews, (2017;2017(2)). 2017.

[100] A.C. Aguir, E.M. Tardieux, A.S. Cortepass, M.M. Almeida, D.G. Barros, et al., Chloroquine analogs as antimarial candidates with potent in vitro and in vivo activity, International Journal for Parasitology: Drugs and Drug Resistance. 8 (3) (2018) 459–464.

[101] M.J. Vincent, J. Behron, S. Benjannet, B.R. Erickson, P.E. Rollin, T.G. Ksiazek, et al., The clinical trial of remdesivir for SARS-CoV-2 novel coronavirus, Antivir. Chem. Chemother. 30 (1) (2020) E154.

[102] A. Savarino, L. Di Trani, I. Donatelli, R. Cauda, A. Cassone, New insights into the mechanisms of ivermectin action, Autophagy. 14 (8) (2018) 1455–1464.

[103] G. Wang, K. Cao, K. Liu, Y. Xue, A.I. Roberts, F. Li, et al., Kynurenic acid, an IDO metabolite, controls TSG-6-mediated immunosuppression of human mesenchymal stem cells, Autophagy. 14 (8) (2018) 1435–1455.

[104] ARENA CT. Coronavirus: Chloroquine yields positive data in Covid-19 trial 2020 FEBRUARY 18 [Available from: https://www.clinicaltrialsharena.com/news/corona-virus-ch-19-chloroquine-data/].

[105] E.W. McChesney, Animal toxicity and pharmacokinetics of hydroxychloroquine sulphate, The American journal of medicine. 75 (1983) (11)–18.

[106] H. Weniger, W.H. Organization, Review of side effects and toxicity of chloroquine. World Health Organization, Geneva, 1979.

[107] A.-L. Laaksonen, V. Koskiahde, K. Juva, Dosage of antimalarial drugs for children with febrile illness in a rural area of Western Kenya, Br. J. Clin. Pharmacol. 54 (5) (2002) 499–504.

[108] M.J. Cameron, J.F. Bermejo-Martin, A. Danesh, M.P. Muller, D.J. Kelvin, Human cytomegalovirus is a selective activator of autophagy, Autophagy. 11 (11) (2014) 1009.

[109] B. Liang, J. Chen, T. Li, H. Wu, W. Yang, Y. Li, et al., Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells, ChinaXiv (2020).

[110] Z. Leng, R. Zhu, W. Hou, Y. Peng, Y. Yang, Q. Han, et al., Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia, Neurol. Neurosurger. Focus 38 (3) (2020) 216–226.

[111] Y. Xiong, W. Chen, C. Wai, Y. Shi, Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications, Nat. Immunol. 15 (11) (2014) 1095–1099.

[112] G. Wang, K. Cao, K. Liu, Y. Xue, A.I. Roberts, F. Li, et al., Kynurenic acid, an IDO metabolite, controls TSG-6-mediated immunosuppression of human mesenchymal stem cells, Dev. Cell 25 (7) (2015) 1209–1223.

[113] Van Esp EA, Luytjes W, Ferwerda G, Vun Kasteren PB. FeMediated Antibody Efferor Functions During Respiratory Viral Infection and Disease Frontiers in immunology. 2019;10.

[114] Gunn BM, Yu W-H, Karim MM, Branman JM, Herbert AS, Wee AC, et al. A role for Fe function in therapeutic monoclonal antibody-mediated protection against Ebola virus. Cell host & microbe. 2018;24(2):221-33. e5.

[115] Z. Leng, R. Zhu, W. Hou, Y. Peng, Y. Yang, Q. Han, et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia, Neurol. Neurosurg. Focus 38 (3) (2020) 216–226.

[116] K.-M. Yeh, T.-S. Chiueh, L. Jou, J.-C. Lin, P.K. Chan, M.-Y. Peng, et al., Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwanese hospital, J. Antimicrob. Chemother. 56 (5) (2005) 919–922.

[117] J. Mair-Jenkins, M. Saavedra-Campos, J.K. Baillie, P. Cleary, M.-F. Khaw, W.S. Lim, et al., The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis, J. Infect. Dis. 211 (1) (2020) 81–90.

[118] B. Shanmugaraj, K. Siriwattananon, K. Wangkanont, Phoolcharoen W., Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19), Asian Pac. J. Allergy Immunol. (2020).

[119] Cheng Y, Wong R, Soo Y, Wong W, Lee C, Ng M, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. European Journal of Clinical Microbiology and Infectious Diseases. 2005;24(1):44-6.

[120] Law PK. Emergent Serum Therapy and Antibody Medicine to Counteract Sudden Attacks of COVID-19 and Other Pathogenic Epidemics. Scientific Research Publishing; 2020.

[121] C. Shen, Z. Wang, F. Zhao, Y. Yang, J. Li, J. Yuan, et al., Treatment of 5 critically ill patients with COVID-19 with convalescent plasma, JAMA (2020).

[122] Duan K, Liu B, Zhang H, Yu T, Qu J, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv. 2020.

[123] L. Chen, J. Xiong, B. Lao, Y. Shi, Convalescent plasma as a potential therapy for COVID-19, Lancet. Infect. Dis. 20 (4) (2020) 396–400.

[124] (FDA) FaDA. Recommendations for Investigation of COVID-19 Convalescent Plasma 2020 APRIL 13 [Available from: https://www.fda.gov/vaccines-blood-biotherapy-guidance/advisory-committees/recommendations-investigation-covid-19-convalescent-plasma].

[125] (FDA) FaDA. Coronavirus (COVID-19) Update for Patients to Donate Plasma 2020 April 16 [Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-encourages-recovered-patients-donate-plasma].

[126] M.P. Busch, E.M. Bloch, S. Kleinman, Prevention of transmission-transmitted infections, Blood 133 (17) (2019) 1854–1864.

[127] J.E. Hendrickson, C.D. Hilfer, Noninfectious serious hazards of transfusion, Anesth. Analg. 108 (3) (2009) 759–769.
[149] Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. 2020.

[150] C. Shen, Z. Wang, F. Zhao, Y. Yang, J. Li, J. Yuan, et al., Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma, JAMA (2020).

[151] V.S. Raj, H. Mou, S.L. Smiths, D.H. Dekkers, M.A. Müller, R. Dijkman, et al., Dipetidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC, Nature 495 (7440) (2013) 251–254.

[152] 360dx. Coronavirus Test Tracker: Commercially Available COVID-19 Diagnostic Tests 2020 April 15 [Available from: https://www.360dx.com/coronavirus-test-tracker-launched-covid-19-tests.]

[153] X. Tian, C. Li, A. Huang, S. Xia, S. Lu, Z. Shi, et al., Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody, Emerging Microbes Infect. 9 (1) (2020) 382–385.

[154] X. Chen, R. Li, Z. Pan, C. Qian, Y. Yang, R. You, et al., Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor, Cell. Mol. Immunol. 1–3 (2020).

[155] C. Wang, W. Li, D. Drabek, N.M. Okba, R. van Haperen, A.D. Osterhaus, et al., A human monoclonal 1 antibody blocking SARS-CoV-2 infection, Biorxiv. (2020).

[156] L. Zhang, Y. Liu, Potential interventions for novel coronavirus in China: A systematic review, J. Med. Virol. (2020).

[157] Bian H, Zheng Z-H, Wei D, Zhang Z, Kang W-Z, Hao C-Q, et al. Meplazumab treats syndrome coronavirus infection, Ann. Intern. Med. 160 (6) (2014) 389–397.

[158] H. Momattin, A.Y. Al-Ali, J.A. Al-Tawaﬁq, A Systematic Review of therapeutic agents for the treatment of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Travel Med. Infect. Dis. 30 (2019) 9–18.

[159] S. Jawhara, Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients? Int. J. Mol. Sci. 21 (7) (2020) 2272.

[160] D. De Ranieri, N.S. Fenny, Intravenous immunoglobulin in the treatment of primary immunodeficiency diseases, Pediatr. Ann. 46 (1) (2017) e8–e12.

[161] C. Galeotti, S.V. Kaveri, J. Bayry, IVIG-mediated e inflammatory diseases, Int. Immunol. 29 (11) (2017) 491–498.

[162] J.-T. Wang, W.-H. Sheng, C.-T. Fang, Y.-C. Chen, J.-L. Wang, C.-J. Yu, et al., Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients, Emerg. Infect. Dis. 10 (5) (2004) 818.

[163] Y.M. Arabi, A.A. Arif, H.H. Balkhy, H. Najm, A.S. Aldawood, A. Ghabashi, et al., Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection, Ann. Intern. Med. 160 (6) (2014) 389–397.

[164] W. Cao, X. Liu, T. Bai, H. Fan, K. Hong, H. Song, et al., editors. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open forum infectious diseases, Oxford University Press UK, 2020.

[165] G. Cavalli, G. De Luca, C. Campochiaro, E. Della-Torre, M. Ripa, D. Canetti, et al., Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. The Lancet, Rheumatology (2020).

[166] Hub AE. Coronavirus (COVID-19) Update: Early Safety Signals Around Ibufrofen and Renin-Angiotensin Inhibitors 2020 March 23 [Available from: https://edhub. ama-assn.org/jn-learning/audio-player/b18329925.]

[167] Day M. Covid-19: Ibufrofen should not be used for managing symptoms, say doctors and scientists. British Medical Journal Publishing Group; 2020.

[168] L. Fang, G. Karakulis, M. Roth, Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? The Lancet, Respir. Med. (2020).

[169] V. Monteil, H. Kwon, P. Prado, A. Hagelkruys, R.A. Wimmer, M. Stahl, et al., Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2, Cell (2020).

[170] S. Shmakov, A. Smargon, D. Scott, D. Cox, N. Pyzocha, W. Yan, et al., Diversity and evolution of class 2 CRISPR-Cas systems, Nat. Rev. Microbiol. 15 (3) (2017) 169.

[171] Smargon AA, Cox DB, Pyzocha NK, Zheng K, Shlakman EM, Gootenbreg JS, et al. Cas13b is a type VI-B CRISPR-associated RNA-guided RNAse differentially regulated by accessory proteins Csx27 and Csx28. Molecular cell. 2017;65(4):618–30. e7.

[172] J.S. Gootenbreg, O.O. Abudayeh, J.W. Lee, P. Eseltschibjer, A.J. Dy, J. Joung, et al., Nucleic acid detection with CRISPR-Cas13a/C2c2, Science 356 (6366) (2017) 438–442.

[173] Q. Lu, Y. Shi, Coronavirus disease (COVID-19) and neonate: What neonatologist need to know, J. Med. Virol. (2020).

[174] Berra L, Lei C, Su B, Dong H, Fahkr BS, Grassi LG, et al. Protocol for a randomized controlled trial testing inhaled nitric oxide therapy in spontaneously breathing patients with COVID-19. medRxiv. 2020.

[175] W.H. Organization, Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020, World Health Organization, 2020.

[176] Nowak JK, Walkowick J. Is lithium a potential treatment for the novel Wuhan (2019-nCoV) an infection? A Scoping review. F1000Research. 2020;9(93):93.

[177] Zhang J, Ma X, Yu F, Liu J, Zou F, Pan T, et al. Teicoplanin potently blocks the cell entry of 2019-nCoV. bioRxiv. 2020.

[178] L. Cały, J.D. Druce, M.G. Catton, D.A. Jans, K.M. Wagstaff, The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antiviral Res. 104787 (2020).

[179] M. Kelleni, Nitazoxanide/Azithromycin Combination for COVID-19: A Suggested New Protocol for COVID-19 Early, Management. (2020).

[180] Kaplan MM, editor The use of methotrexate, colchicine, and other immunomodulatory drugs in the treatment of primary biliary cirrhosis. Seminars in liver disease; 1997: 1997 by Thieme Medical Publishers, Inc.

[181] (WHO) WHO. “Solidarity” clinical trial for COVID-19 treatments 2020 April 21 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.]

[182] A. Nagai, H. Matsumiya, M. Hayashi, S. Yasui, H. Okamoto, K. Konno, Effects of nicotinamide and niacin on bleomycin-induced acute injury and subsequent fibrosis in hamster lungs, Exp. Lung Res. 20 (4) (1994) 263–281.

[183] H. Hemilä, Vitamin C intake and susceptibility to the common cold, Br. J. Nutr. 77 (1) (1997) 59–72.

[184] Wang L-s, Wang Y-r, Ye D-w, Liu Q-q. A review of the 2019 Novel Coronavirus (SARS-CoV-2) infection. Clinica Chimica Acta 508 (2020) 254–266.

[185] London IC. Report 12: Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries 2020 March 30 [Available from: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/.

[186] S.M. Kissler, C. Tedijanto, E. Goldstein, Y.H. Grad, M. Lipsitch, Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period, Science (2020:) eabb5793.