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Review

An update of coronavirus disease 2019 (COVID-19): an essential brief for clinicians

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Abstract: During 2019, the number of patients suffering from cough, fever and reduction of WBC's count increased. At the beginning, this mysterious illness was called "fever with unknown origin". At the present time, the cause of this pneumonia is known as the 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The SARS-CoV-2 is one member of great family of coronaviruses. Coronaviruses can cause different kind of illnesses including respiratory, enteric, hepatic, and neurological diseases in animals like cat and bat. Coronaviruses are enveloped positive-stranded RNA viruses. The SARS-CoV-2 has some particular structures for binding to host cells, reproducing itself in cells and damaging human cells. The SARS-CoV-2 can bind angiotensin-converting enzyme 2 (ACE-2) receptors and cause various difficulties for human. The SARS-CoV-2 can cause either not-serious issues like fever and cough or serious concerns such as multi-organ failure. Source(s) of SARS-CoV-2 is under debate. Malayan pangolin and bat are the most suspicious candidate for being sources of the SARS-CoV-2. The SARS-CoV-2 can be transmitted by various ways such as transmitting from infected human to healthy human and can make severe pneumonia, which can lead to death. The SARS-CoV-2 can infect different kind of people with different ages, races, and social and economic levels. The SARS-CoV-2 infection can cause various sorts of clinical manifestations like cough and fever and intensity of signs and symptoms depends on sufferer conditions. Clinicians use all of available documents and tests like laboratory, histopathological and radiological findings for diagnosing new cases and curing patients with high accuracy. At the present time, there is no particular way for treating SARS-CoV-2 infection; neither antiviral drugs nor palliative agents. It seems that the best way for standing against the SARS-CoV-2 infection is preventing from it by social distancing and vaccination. This review tries to prepare an essential brief update about SARS-CoV-2 infection for clinicians.

Keywords: keyword 1; keyword 2; keyword 3 (List three to ten pertinent keywords specific to the article yet reasonably common within the subject discipline.)

1. Introduction

Reports demonstrate an increasing trend in number of sufferers with fever, cough and deduction in white blood cell count at the end of 2019. "Fever with unknown origin" was chosen for the name of this mysterious illness (1). Based on different documents including clinical characteristics, various analysis of body fluid samplings and radiological

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examinations, this illness was known as viral pneumonia by clinicians (2). Nowadays, "the 2019 novel coronavirus (2019-nCoV), coronavirus disease 2019 (COVID-19), or the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2)" has been chosen for this infection (3).

The SARS-CoV-2 is a member of the vast family of coronaviruses (2). The SARS-CoV-2 can bind angiotensin-converting enzyme-2 (ACE-2) receptors and cause various difficulties for human including either not-serious issues like fever and cough or serious concerns such as multi-organ failure (2, 4). The SARS-CoV-2 has high potential to transmit between human to human and it has the ability to make severe pneumonia, which can eventually kill humans (3, 5). The SARS-CoV-2 has high potential to infect human and after a short time it revealed in Wuhan, China, it has spread all over the world. Therefore, in January 30, 2020, WHO announced that the SARS-CoV-2 infection is a worldwide issue and a global emergency situation because this infection threats human life (3, 6, 7).

At the present time, health care providers don't have any particular curative method for treatment of the SARS-CoV-2 infection; neither antiviral drugs nor palliative agents (8, 9). Symptomatic treatment strategies are recommended for clinical practice (10). In addition, several drugs with potential therapeutic ability such as dexamethasone and remdesivir have been evaluated for the treatment of the SARS-CoV-2 (9, 11, 12). However, as we mentioned before, no antiviral agents have yet been proved to be beneficial for the SARS-CoV-2 infection (11, 13). The aim of the present review was to give a general overview about this new virus considering essential brief for clinicians.

2. Virology of SARS-CoV-2

Coronaviruses are enveloped positive-stranded RNA viruses (14). Coronaviridae family (order Nidovirales) has a subfamily called Orthocoronavirinae (15). Orthocoronavirinae include four type of CoVs: Alphacoronavirus (alpha-CoV), Betacoronavirus (beta-CoV), Deltacoronavirus (delta-CoV), and Gammacoronavirus (gamma-CoV) (15). The SARS-CoV-2 belongs to of Betacoronaviruses (16, 17). These viruses are spherical, oval, or pleomorphic with a diameter of about 60-140 nm (18). SARS-CoV-2's structure consists of genome (RNA), nucleocapsid, membrane protein (M) and the envelope (E) protein (2) (Figure 1).

Two-third of viral RNA is finally translated into two polyproteins, pp1a and pp1ab, and 16 non-structural proteins (nsp), while other parts of the genome encoding subsidiary and structural proteins (19) (Figure 2). In the other words, the remainder of the virus genome encodes four basic structural proteins, including the spear-like proteins (S protein), membrane proteins (M proteins), envelope proteins (E proteins), and nucleocapsid proteins (N proteins) (19, 20). The SARS-CoV-2 major particles contain genome, spear-like appendages (S protein), non-structural proteins (nsp), and envelope (18) (Table 1).

The nucleocapsid is located deeply inside phospholipid bilayers and coated by two diverse sorts of spear-like proteins: the spear-like glycoprotein trimmer (S) and the hemagglutinin-esterase (HE) and the sites between the S proteins are filled by the membrane protein (M) and the envelope (E) protein in the viral envelope (2, 21). The SARS-CoV-2 has spear-like structure made from glycoprotein (Glycoprotein S) and this spear-like structure causes binding SARS-CoV-2 to the ACE-2 receptor on the surface of human cells (22). The glycoprotein S contains of two portions, S1 and S2 (23). The S1 divided into three domains, A, B and C (24). The domain A of the S1 for plays role in binding to the host receptors and the domain B has duty to facilitate the entry of SARS-CoV-2 into target cells (19, 24). The S2 causes modulating of fusion between the virus and the host cell (25, 26).

After membrane fusion, viral genome (RNA) releases into the cytoplasm of the host cell and this uncovered RNA starts to translate two polyproteins: pp1a and pp1ab (27). These two polyproteins, pp1a and pp1ab, encode non-structured proteins (NSP) and form the transcription-replication complex (RTC) within a dual-membrane vesicle (28). The

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RTC then replicates and transcribes a set of nested RNAs that encode accessory and structural proteins (29). By means of endoplasmic reticulum and Golgi's body, recently formed RNAs, nucleocapsid proteins and glycoproteins of the viral coat are collected and form the particles of the virus. Finally, the vesicles comprising the virus combine with the plasma membrane for releasing the virus (30).

3. Origin of SARS-CoV-2

The primitive surveys demonstrated that the first cases who suffer from the SARS-CoV-2 infection had been reported from local Huanan seafood market (2). Although SARS-CoV-2 was extracted from Huanan seafood market, the origin of the SARS-CoV-2 is under debate because the first SARS-CoV-2 case reported had no connection to the mentioned market (2, 7). Moreover, it was discovered that at least two diverse types of the SARS-CoV-2 had been officially reported before COVID-19 and recent surveys presented that the SARS-CoV-2 may imported from other sites to Huanan seafood market (31, 32).

Coronaviruses, first found in the 1960s, have been found in birds and mammals, including in camels, bats and rats (33). SARS-CoV-2 has a single-stranded positive-sense RNA genome, which has 74% and 99% similarity with coronavirus from the pangolin (Manis javanica) and (1, 34-37) the Malayan pangolin (38), respectively. One portion of spear-like protein (S protein) called receptor-binding domain (RBD) in pangolin-CoV has only one different amino acid compared with that of SARS-CoV-2. In addition, the infected pangolins show pathological symptoms as same as humans infected with COVID-19 and the antibodies in their blood are able to react with the spike protein of SARS-CoV-2 (39, 40). Accordingly, the pangolin is considered as one of the probable intermediate hosts between bat and human (38) (Figure 3).

On the other hand, bats have been introduced as the remarkable origin of coronaviruses (41, 42). SARS-CoV-2's genome has 99% similarity with that of horseshoe bat (Rhinolophus sinicus) (Bat-CoVRaTG13) (1, 34-37). Although, the genome of coronavirus separated from bat has approximately 96% identity with SARS-CoV-2, its receptor-binding domain (RBD) is different compared to that of the later, showing a low potential to bind to the human ACE-2 (43). Recently, SARS-CoV-2 has been suggested as a modified coronavirus originated from bat transmitting to humans through zoonotic transmission (36, 44-46). Other animals were under investigation as the possible intermediate hosts of SARS-CoV-2 like snakes, minks and turtles (47, 48).

Five out of the six major amino acids in the structure of the RBD of the S-protein from SARS-CoV and SARS-CoV-2 are different, unlike the theories on the laboratory origin of SARS-CoV-2 by manipulating other coronaviruses (48). Different surveys demonstrated that SARS-CoV-2 is an animal virus transmitted to humans through undergoing evolutionary adaptations (36, 49). Analysis of different studies has suggested that SARS-CoV-2 formed by recombining the pangolin-CoV and the bat-CoV-RaTG13-like virus (19, 39, 50, 51). However, more studies are needed for confirming the intermediate hosts of coronaviruses for stopping zoonotic transmission and avoiding the outbreak of such viral infections in feature (52).

3.1. Mutant type(s) of SARS-CoV-2

Mutation rate in RNA viruses is extensively high and this rate is associated with virulence modulation and evolvability, behaviors considered to be useful for viral adaptation (53). Early reported studies demonstrated that fast spread of SARS-CoV-2 across world and emergence of the genomes containing new mutation hotspots. Mutation rate of RNA virus plays role in viral adaptation making equilibrium between the integrity of various genetic data and genome variability (54-56).

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Biological characterization of viral mutations can supply valuable intuitions for evaluating immune escape, viral drug resistance, immune escape and pathogenesis dependent mechanisms. In addition, it can be vital for drafting new vaccines, antiviral medications and diagnostic tests (57). Therefore, it seems to be necessary to know about mutant types of SARS-CoV-2.

In late January or early February 2020, a mutant type of SARS-CoV-2 was appeared that has D614G replacement in the gene encoding the spike protein. This new strain became dominant type of SARS-CoV-2 in china and spread globally after a short period of time (58). Researches revealed that compared to the initial virus strain, this new class of SARS-CoV-2 has enhanced transmission and infectivity (59, 60). The SARS-CoV-2 virus with the D614G replacement does not make more intense illness or change the efficacy of current laboratory diagnostics, medications, vaccines, or public health preventative criteria (58).

First mutant strain of SARS-CoV-2 United Kingdom was observed in Wales on September and mid-November that was called 501Y lineage (501Y Variant 1). After that, on 14 December 2020, second mutant strain was reported in United Kingdom and named SARS-CoV-2 VOC 202012/01 (Variant of Concern, year 2020, month 12, variant 01or 501Y Variant 2, also named as B.1.1.7). In November/December 2020, this new strain has also become the predominant strain in England (61). This mutant strain includes 23 nucleotide replacements and is not phylogenetically linked to the SARS-CoV-2 virus circulating in the United Kingdom at the time the mutant type was identified. According to surveys, SARS-CoV-2 VOC 202012/01 is more transmittable than early virus strain and it has the capability of reinfection. Although infectivity of this new strain is not obvious (62). Moreover, origination of SARS-CoV-2 VOC 202012/01 is unclear (61).

On 18 December 2020, South African government declared the discovery of a new mutant type of SARS-CoV-2, which quickly spread in three provinces of South Africa. Because of a N501Y mutation, South Africa named this variant 501Y.V2, on the other hand, SARS-CoV-2 VOC 202012/01, which was detected in UK, also has the N501Y mutation, but phylogenetic analysis has demonstrated that 501Y.V2 originating from South Africa is different from mentioned strain in UK (58). Recent surveys revealed that 501Y.V2 is more transmittable in comparison to early strain. In addition, studies showed that this new strain has high affinity to human ACE-2 receptor (63). Furthermore, mutation in this new strain gives ability to stabilize viral bindings with ACE-2 receptor (64-66) as well as ability to escape from human immune system (67). The severity of infection caused by this new viruses is under investigation (67).

4. Transmission of SARS-CoV-2

Symptomatic patients with coronavirus are the most important distributors; but asymptomatic patients can be one of the important source of viral transmission (68). Transmission through close person-to-person contact, hand shaking, touching contaminated surfaces, contaminated hand contact with eyes, mouth and ears, respiratory droplets and wound, and oral-fecal transmission are known as viral transmission routes (5, 68).

Vertical transmission from mother to infant has been reported (69), but, no intrauterine vertical transmission has been reported for any infant with SARS and MERS in the past (70, 71). In addition, based on all available data, amniotic fluid, umbilical cord blood, neonatal pharyngeal swab and breast milk samples from six newborns born by infected mothers were examined for SARS-CoV-2 and all cases were negative for the virus (71, 72).

5. Epidemiology of SARS-CoV-2

In a study conducted in China in 2020 on 44,672 patients, it was obtained that the highest number of patients ranged between 50 to 59 years. The lowest number of patients

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was in the age range of 0 to 9 years. In addition, mentioned survey revealed that occupationally, patients who were retired, workers, and farmers, had the highest incidence of the disease. Additionally, most patients had a mild form of the illness. In addition, the mortality rate was higher in men than women, retirees had the highest mortality rate, age group ≥80 showed the highest mortality rate among all age groups, the mortality rate in patients who had other underlying disease in addition to SARS-CoV2 infection was much higher than in patients without underlying disease. Among patients with underlying problems (cardiovascular disorder, diabetes, chronic respiratory disorder, hypertension and cancer) and patients with cardiovascular problems have the highest mortality rate because of SARS-CoV-2 infection (73).

Data obtained from various studies to date show that in general, different age groups are susceptible to SARS-CoV-2. However, ACE-2 is significantly expressed more in Asian populations than European and American populations, and ACE-2 in male cells is higher compared to the female cells that may partly justify the fact that the incidence of coronavirus pneumonia is higher in men and in Asia. The elderly and people with the disease are more probable to progress a severe and fatal form of the illness. The most common underlying problems that predispose a person to SARS-CoV-2 infection are cardiovascular disorder, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD) (5). Severe complications that this disease can cause in individuals include respiratory distress syndrome (RDS), septic shock and metabolic acidosis that respond poorly to treatment and cause multiple organ failure and coagulation problems (5, 6, 74, 75).

6. Pathophysiology of SARS-CoV-2

SARS-CoV-2 uses ACE-2 receptors to transport itself to human cells (76, 77). The fluid obtained from bronchoalveolar lavage of a SARS-COV-2 patient demonstrated that SARS-CoV-2 enters in human cells by using the ACE-2 receptors (36). ACE-2 is a surface molecule that is extensively expressed in different regions of human body include lung AT2 cells, upper esophageal epithelial cells, and enterocytes in the ileum and colon so this fact demonstrates a high potent passage in the gastrointestinal and respiratory tract for SARS-CoV-2 virus (76, 77). Different organs of human body can be affected by SARS-CoV-2 infection (15). ACE-2, found in the lower portion of human respiratory tract, is known as a receptor for SARS-CoV-2 and regularizes human-to-human and cross-species viral transmission (43, 78).

7. Diagnosis of SARS-CoV-2

SARS-COV-2 is diagnosed based on history taking, radiographic images, and detailed laboratory tests (6, 79). Current diagnostic tools include nucleic acid testing or virus genome detection (6, 79). Samples included nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, and feces (6, 79). The nasopharyngeal swab is the most common example; however, the number of positive cases is less than 50% (6, 79). Repeated diagnostic testing is necessary to increase diagnostic accuracy (6, 79). The number of positive cases in bronchoalveolar lavage fluid was high; however, this method is not suitable for most patients due to the increased risk of cross-infection (6, 79).

7.1. Clinical manifestations

1 to 14 days and the average of 8 days have been estimated as the incubation period of COVID-19 (80). Fever and cough has been reported as the most common symptoms, while upper respiratory symptoms and gastrointestinal have been rarely reported as the symptoms of this disease (2, 4). SARS-CoV-2 infection can cause various sorts of clinical manifestations depends on patient situation (Table 2 and Figure 4). SARS-CoV-2 clinical

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manifestations related to pregnant women, neonates and children are summarized in Table 3.

7.2. Laboratory examinations

Laboratory examinations along with taking history and radiographic analysis are three bases for finding and curing COVID-19 sufferers (125). Studies show different laboratory finding and we gathered different laboratory findings in Table 4.

7.3. Histopathological findings

Autopsy of different cases infected by SARS-CoV-2, revealed that this virus can damage various organs; based on this fact, SARS-CoV-2 can cause diverse histopathological views in body organs (126, 127). Although, histopathological findings are not certain documents for clinicians to make decision for patients suffering from COVID-19, but they give us remarkable information about pathological changes, pathogenesis of the disease, and the cause of death in COVID-19 cases (125). In Table 5, we discussed histopathologic changes in lung tissues after being infected by SARS-CoV-2.

7.4. Radiological findings

Radiological findings in this disease are varied. These findings have been presented in Table 6. It is important to note that radiological diagnostic sensitivity is limited. Therefore, it is necessary to check with clinical signs and diagnosis of RNA virus (5).

8. Prevention of SARS-CoV-2

The best prevention for the general population at this period of time is to avoid being exposed to the virus (128). Some actions that may deduct amount of exposure of SARS-COV-2 infection include using face masks, utilizing tissue or flexed arm when person coughs or sneezes, washing hands regularly with soap or disinfect hands with sanitizer consists of 60% alcohol at minimum, refusing close contact with suspicious or infected people and keeping a proper distance as much as possible to other people and refraining from touching eyes, nose, and mouth with unwashed hands (129).

9. Vaccines of SARS-CoV-2

Vaccines are biological drugs that are highly monitored and controlled. Unlike other drugs, which are administered on sick people, vaccines are administered on a huge number of healthy people, so the process of developing them takes a long time and should be strictly observed (130). There are several studies on developing vaccines for COVID-19 and each of them is at different stages. Some of them use messenger RNA methods and some of them use DNA, which is then translated and produces specific immunogenic proteins. Each of them uses different generic platforms, such as inactivated virus, purified recombinant viral proteins with or without adjuvant, replicating and non-replicating viral vectored antigens, antigen-encoding DNA or mRNA (131). Some of the vaccine designs are based on old methods and technologies that have been approved for other vaccines and some of them are built on completely new and novel technologies and have not been tested on large scales vaccinations (131).

Developing vaccines using the traditional ways takes a very long time almost 15 years. The vaccine developing process begins with designing and evaluating vaccine in animal models. Next, several years can take by other steps which are preclinical experiments for designing vaccine production and performing toxicology studies. Then, phase I clinical trials are the new drug on less than 100 people and this phase takes almost 2

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years to see if the vaccine candidate is safe enough and has gained preliminary immunogenicity data. If the results are good, the vaccine candidate can move to phase II of clinical trials to test on a few hundred people and it takes another two years. In this phase appropriate dose and optimal vaccine regimen is determined. After this step, if the results are promising, the vaccine development process can move forward to phase III clinical trials in which the vaccine is tested on thousands of individuals to evaluate the effectiveness and safety of vaccine. This phase, which is a very costly process, takes another two years. If the outcome is encouraging and meets the defined end points, an agency like United States Food and Drug Administration (FDA) or the European Medicine Agency approves the biological license application. This licensing process can take approximately two years.

Since the pandemic of SARS-COV-2 has started in December 2019, rapid action and development of vaccine is required. A considerable amount of time is saved by omitting some of the initial steps of exploratory vaccine design due to data from the preclinical development of vaccine candidates for SARS-COV and MERS-COV. In March 2020, the first clinical trial of a vaccine candidate for SARS-COV-2 was started. In this condition, trials are designed such that clinical phases are parallel and have overlaps. Phase I and II are started at the same time and are followed by rapid progression to phase III. Vaccine approval can be expedited through an emergency use authorization. In order to develop SARS-COV-2 vaccine, at least 50% efficacy is required according to FDA guidance (132). In this pandemic, the COVID-19 vaccines should reach at least three goals of reducing severe infection, clinically symptomatic patients and the requirement of their hospitalization, being able to prevent the transmission of the disease between individuals and being capable of generate a strong neutralization response, which prevent the viral protein S from attaching to human cells by binding to it (130).

Currently, there are four main types of COVID-19 vaccines that are going to large scale clinical trials. In Table 7 clinically approved and commercialized vaccines are compared. Below is a description of how each type of vaccine works and induces our body to produce antibody against COVID-19 antigens.

9.1. Non-replicating viral vectors vaccines

This type of vaccines is based on SARS-COV proteins expressing on the outer surface of some common viruses like adeno viruses, which are genetically modified. However, the immunity caused by these viruses are neutralized very soon because they are very common and most people come in touch with them. The common cold virus (adenovirus) is weakened and used as a viral vector, which contains the genome of surface S protein of SARS-CoV-2. After inoculating this vaccine, protein is produced and it can attack the corona virus since the immune system of the vaccinated person already has the antibodies specific to this protein. The recombinant adenovirus vector cannot cause a non-stop infection in the body, which received the vaccine because it does not reproduce and it also generates a strong single dose response. This type of vaccine uses type 5 of adenovirus as a vector that delivers the S protein of the coronavirus and teaches the body to detect the S protein corresponding to the coronavirus. This platform is the same as the Ebola virus vaccine (130).

9.2. Whole virus vaccines

Live attenuated vaccines are the most potent immunogenic vaccines. They are made by diminishing the pathogenesis of SARS-CoV-2 with genetic engineering as same as BCG and most antiviral vaccines like polio with live strains, anti-measles, and anti-rubella. There is a risk of mutation that can cause these vaccines to be pathogenic again. This type of vaccines provides the vaccinated person with persistent protection as the natural post-

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infection immunogenicity but it can also cause severe post vaccination reactions. Inactivated viruses are made by inactivating the whole bacteria or virus by heat or formalization. This type has lower side effects but the post vaccine immunity is also less potent than the live attenuated ones (130).

9.3. Protein-based vaccines

Subunit vaccines with antigenic fragments are vaccines based on glycoprotein nanoparticles. This vaccine increases the immune response against the SARS-CoV-2 spike proteins by elevating the levels of neutralizing antibodies using Matrix-M adjuvant. The production of antibodies is triggered by the antigen or antigenic fraction in the vaccine. It can have less side effects since some various components like cellular proteins or nucleic acids, which have no special effects on immunogenicity, are eliminated (130).

9.4. Nucleic acid (RNA and DNA) vaccines

Nucleic-acid vaccines are the fastest type of vaccines to develop because they do not require fermentation or culture. They are made by inserting mRNA or DNA into some cells and forcing them to make immunogenic viral proteins. Sequencing techniques and reverse genetics have a significant role to shorten the development time of a vaccine during the pandemic (133).

DNA vaccines like flu virus vaccine insert a foreign DNA into the cell's genome host and stimulates cellular immunity. Unlike most vaccines that address the humoral immunity, DNA vaccines stimulate cellular immunity. This type of vaccines has both advantages and disadvantages. Introduction of a live virus strain to the human body can be avoided by this type of vaccines but it also may increase oncogenic risks by inhibiting tumor suppressor genes or incorporating DNA into the host cell genome (134).

RNA vaccines are novel and have not been approved yet but they are candidates for COVID-19. This type of vaccines tries to stimulate the production of antibodies against the viral protein that is found on the surface of the virus spike. These antibodies can neutralize and block the cell infecting proteins in the respiratory tract (133).

Currently more than 50 different vaccine candidates are in trials all over the world. So far, two of them have achieved FDA authorization for public vaccination Pfizer-BioNTech and Moderna. There is some information scripted below about these two vaccines (135). Additionally, some remarkable information has been gathered about brand new sort of vaccine for COVID-19.

10. Treatment of SARS-CoV-2

We discuss treatment of this disease in two categories: supportive therapies and antiviral therapy.

10.1. Supportive therapies

Symptomatic and supportive therapy is the mainstay of treatment for SARS-CoV-2 cases (144). Supportive therapy includes different manners which are given to patients with SARS-CoV-2 infection for reaching different curative targets (Table 8). In addition, the plasma of recovering patients with SARS-CoV-2 may be useful for SARS-CoV-2 infection (145).

10.2. Antiviral therapy

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At the present moment, numerous studies are ongoing to manufacture a vaccine against COVID-19. Though, developing vaccine is a long procedure, and the newly produced vaccine will need several safety assessments (146). Based on estimates, human society should wait at least one year to have an available vaccine against COVID-19 (147). Even after preparing an efficient vaccine, human trials will be a major challenge for scientists (Table 9). Now, COVID-19 is being cured with using broad-spectrum antiviral medicines counting remdesivir and Chinese herbal medicine (148, 149).

11. Management of SARS-CoV-2

At the present time that manufactured vaccines need long time to be available for all people around the world, it is important to manage patients with COVID-19. By knowing this fact, some notes should be considered in managing patients with COVID-19. Care ways of COVID-19 should be established at various levels of management including local, regional, and national levels for suspected or confirmed patients with COVID-19. Patients at the first point of contact within the health system should be screened based on case definitions and an assessment of symptoms, and then, suspected or confirmed cases enter into the pathway. Suspected cases should stay in the care pathway of COVID-19 until their lab tests show negative results. Isolating all suspected and confirmed cases in the shortest possible time, implementing local infection prevention and controlling manners are essential. Patients should be triaged by means of a standardized triage tool to evaluate the intensity of malady. patient's values and priorities as well as local and national policy should be considered if accessible and proper judgments according to clinical situation should be utilized in order to steer handle decisions including admission to hospital and to the intensive care unit (150). For better managing of patients, some valuable data have been collected in Figure5.

3. Results

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

3.2. Figures, Tables and Schemes

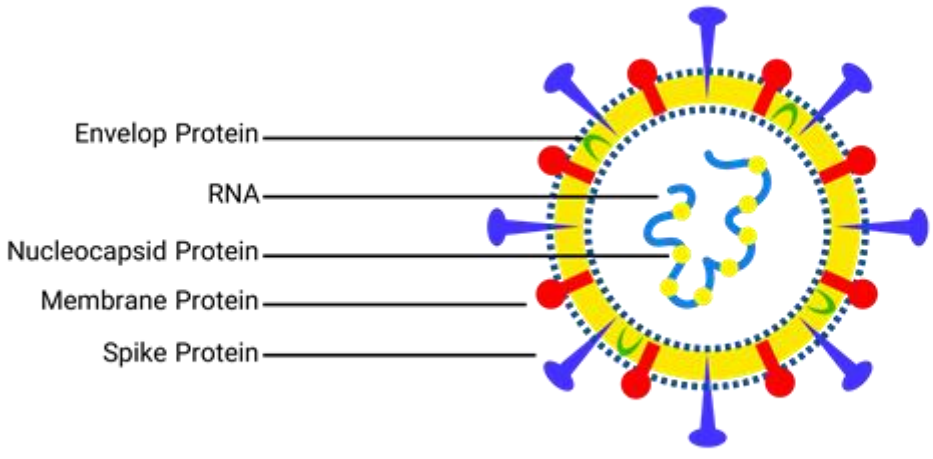

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Figure 1. Structure of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

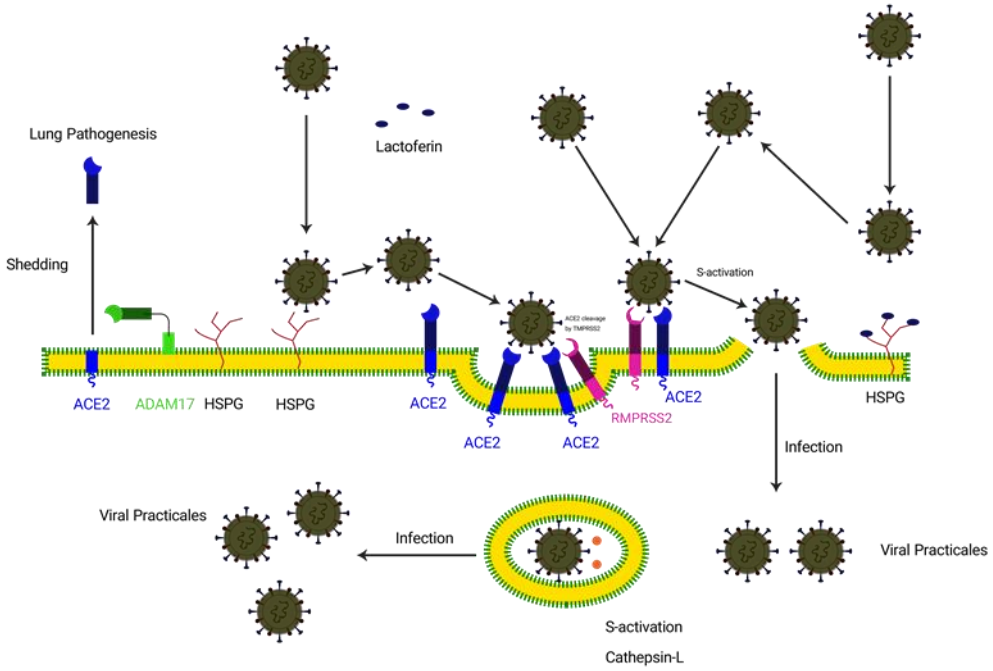

Figure 2. Pathophysiology of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

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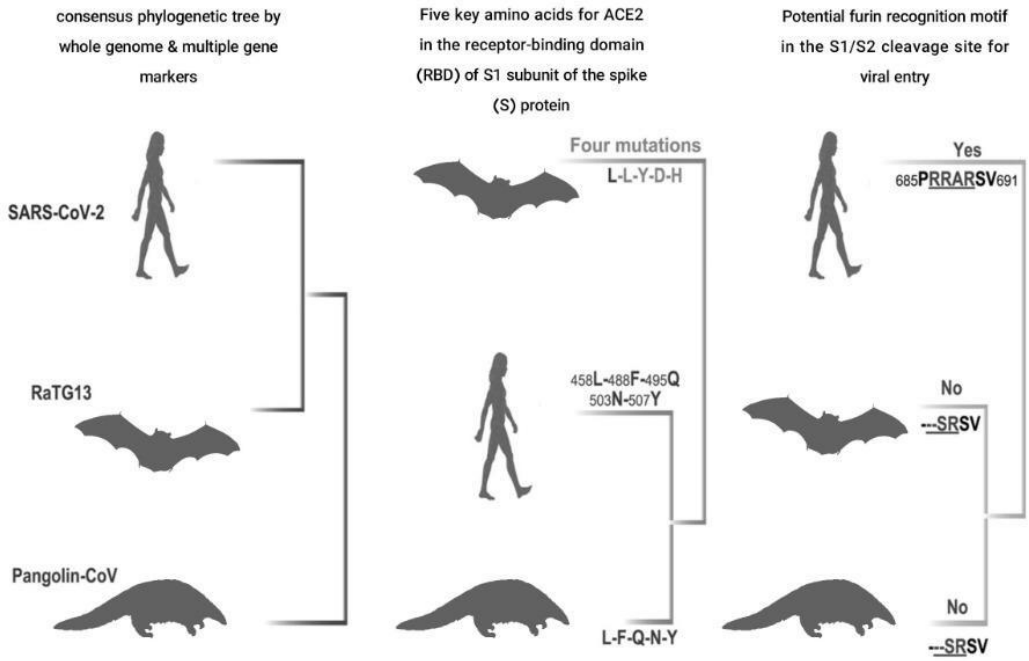

Figure 3. Origin of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

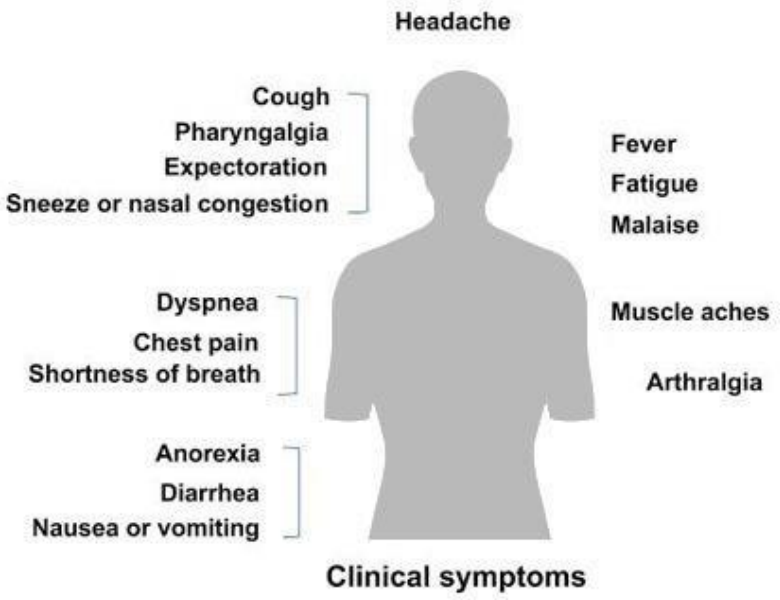

Figure 4. Clinical manifestation of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

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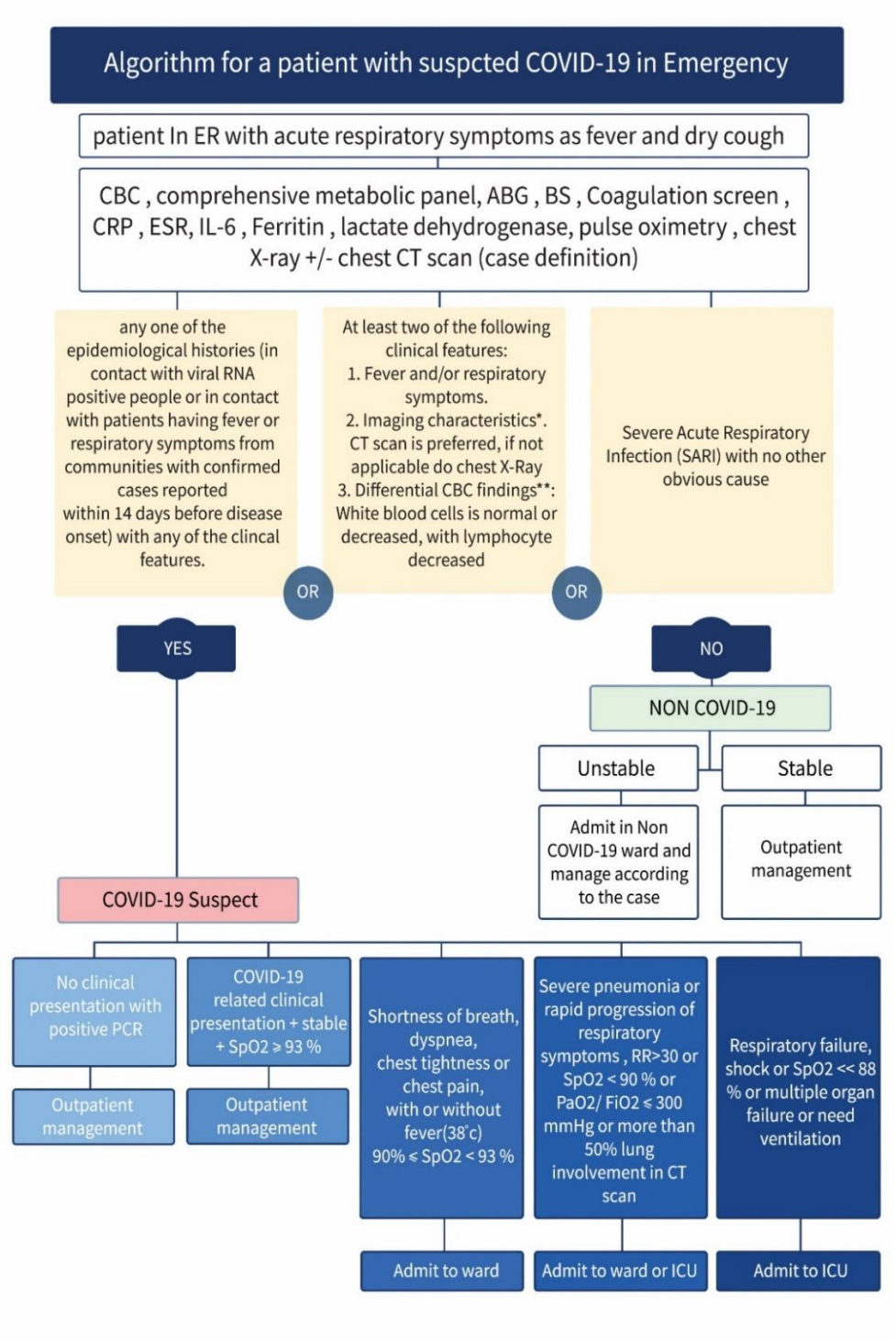

Figure 5. Clinical manifestation of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

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Table 1. The important parts of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

Viral element	Function	References
Genome (RNA)	Transcripting and translating structural and non-structural proteins	(15)
Nonstructural proteins	Block the host innate immune response	(151)
Envelope	Promotes viral assembly and release	(15)
Spear-like structure	Guiding virus to host receptors	(152, 153)
	binding to the ACE-2 receptor in the lungs and other tissues	

Table 2. Clinical manifestations of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) in different surveys.

Clinical manifestations	References
General symptoms:	[39]
Fever	
Cough	
Fatigue	
Fatigue	
Sputum production	
Shortness of breath	
Sore throat	
Headache	
Gastrointestinal symptoms:	[7,49,102,103]
Diarrhea	

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Nausea	
Vomiting	
Abdominal pain	
Hematemesis	
Hematochezia/melena	
Constipation	
Severe symptoms:	[7]
Acute respiratory distress syndrome	
Septic shock	
Severe metabolic acidosis	
Coagulation dysfunction	
Death	
Neurologic symptoms:	[102,104,105]
Headache	
Vision changes	
Altered mental status	
Meningitis signs	
Cranial nerve palsy	
Cardiac signs:	[102,104,105]
Abnormalities on echocardiogram	
Dysrhythmia	

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Scarce symptoms:	[102,104,105]
Rash	
Conjunctivitis	
Strawberry tongue	
Tongue or mouth ulcers	
Tongue enlargement	
Geographical tongue	
Cracked lips	

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Table 3. Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) in pregnant women, neonates and children.

Origin	Epidemiology	Sign and symptoms	Diagnosis	Treatment	Other note(s)	Reference
Pregnant women						
Like adults	• Not teratogenic • Does not increases the chance of miscarriage • Pregnancy makes a pregnant women more prone to severe respiratory infections • Risk of severity in pregnant women is lower than normal population	Like adults	• Real-time reverse transcriptase-polymerase chain reaction assay • CT scan	Like adults	• Infected mother and neonate should be physically separated • Infected mother should be isolated from non-infected patients • Assess vital signs • Request laboratory data • Prescribe paracetamol and anticoagulants • Consider ICU admission if situation of patient becomes worsen	[106-127]

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• Preterm birth in an infected mother is much higher than the general population	• Azithromycin is safe during pregnancy and in breastfeeding mothers • Steroid therapy who need mechanical ventilation, oxygen therapy, or both • If glucocorticoids are only for the treatment of COVID-19, prescription of methylprednisolone for 10 days is enough • Prophylaxis for thromboembolism should be given during the pregnancy until 10 days after giving birth • Remdesivir is effective for infected pregnant women

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					• There is no difference between vaginal delivery and caesarean section for infected mothers • Respiratory disease like COVID-19 can exacerbate after giving birth because of pathophysiological changes	
Neonates						
Mother Operation room personnel	Infants less than 1-year-old can presented with more severity than older children	Fever Coughing Sore throat Sneezing Fatigue Nausea Vomiting	Like adults	Oxygen therapy Water Electrolyte maintenance Nutritional support	With acute respiratory distress must treat with surfactant and nitric oxides and ventilation support Cases are presented with bacterial superinfection must treat with antibiotics	[69,128-131]

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		Diarrhea Abdominal pain Poor appetite Poor feeding		Intravenous immunoglobulin Corticosteroids		
Children						
Mostly family	All ages children were presented disposed to COVID-19 There was not expressive sex difference	Cough Fever Breath shortness Nausea Vomiting	Like adults	Like adults	The first way to diagnose infected children Is taking sample from sputum, stool and blood Checking level of bilirubin and hepatic enzymes in children showed severity of the disease Heart problems must be considered	[132-135]

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Clinical display of children's COVID-19 cases were less severe than adult patients The average age of all patients was 7 years The majority of the patients were asymptomatic, mild or moderate symptoms of COVID-19 A few number of pediatric patients observed by sever disease	Diarrhea Fatigue	Patient must hospitalize in isolation negative air pressure room

Table 4. Laboratory finding(s) in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

Laboratory finding(s)	**Changes**	**References**
Early stage		

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Total white blood cell count	Normal or decreased	[15,136,137]
Lymphocyte count	Decreased	[15,136,137]
In severe cases		
Neutrophil count	Increased	[5]
D-dimer	Increased	[5]
Blood urea	Increased	[5]
Creatinine level	Increased	[5]
Lymphocyte count	Decreased	[5]
Interleukins (IL)-6, -2, -7, and -10	Increased	[7,19]
Tumor necrosis factor-α (TNF- α)	Increased	[19]
Lactate dehydrogenase (LDH)	Normal or increased	[15,138]
Muscle enzymes	Normal or increased	[15,138]
C-reactive protein (CRP)	Normal or increased	[15,138]
Myocardial enzymes	Normal	[138]

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ICU patients		
Granulocyte colony-stimulating factor (GCSF)	Increased	[7]
10 kDa interferon-induced gamma protein (IP-10)	Increased	[7]
Monocyte 1 (MCP-1)	Increased	[7]
Macrophage inflammatory protein 1α (MIP-1α)	Increased	[7]
Tumor necrosis factor-α	Increased	[7]

5

Table 5. Pathological finding(s) in infected lung with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) [139-144]. 6

Pathological finding(s)
Intravascular leukocytosis
Anthracosis
Squamous metaplasia
Atypical pneumocytes
Interstitial pneumonitis
Bronchopneumonia

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Diffuse alveolar damage
Hemosiderin-laden macrophages
Immunohistochemistry
Mucus aspiration
Prominent protein edema and exudate
Congestion of arteries
Inflammatory clusters with fibrinoid material
Complex giant cells
Reactive alveolar epithelium hyperplasia
Fibroblastic proliferation (fibroblast branches)
No significant infiltration of neutrophils
Large protein globules
Microthrombi/thrombi in lung

Table 6. Radiological finding(s) in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

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Radiological method	Finding	References
Chest X-ray	Lung consolidation	[145-150]
	Ground glass densities	
	Bilateral lower lobe consolidations	
	Peripheral air space opacities	
	Diffuse air space disease	
	Pleural effusions	
	Lung cavitation	
	Pneumothorax	
	Diffuse chest walls subcutaneous emphysema	
	Pneumomediastinum	
Chest Computed Tomography	Ground-glass opacities	[136,148,151-153]
	Consolidation	
	More than two lobes affected	

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	Opacification distribution and pattern: Rounded morphology, Linear opacities, Crazy-paving pattern	
	Peripheral distribution	
	Reversed halo sign	
	Bilateral patchy shadowing	
	Normal (with no finding)	
Lung Ultrasound	Bilateral involvement	[154-159]
	Irregular pleura	
	Confluent B-lines	
	Small consolidations	
	Spared areas	
	Air bronchograms	
	Nontranslobar and translobar consolidation	
	Multifocal B-lines	
	Confluent B-lines	

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	Pleural thickening/disruption

Table 7. Latest vaccines for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

Vaccine	Type	Injection time	Interval (days)	Dosage (mL)	Injection type	Injection site	Effectivity (%)	Reference
Pfizer/BioNTech	mRNA	2	21-28	0.3	Intra muscular	Deltoid muscle	92	[160,161]
Moderna/NIH	mRNA	2	28 (up to 42)	0.5	Intra muscular	Deltoid muscle	94.1	[162,163]
Sputnik V	Adenoviral vector	2	21	0.5	Intra muscular	Deltoid muscle	91.6	[164-166]

Table 8. Supportive therapy in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

Supportive therapy	Target	References
Oxygen therapy	Control the level of O2 in body	[92]
Maintenance of electrolyte and water balance	Prevent exacerbation of pulmonary edema and decreased oxygen delivery	[92]
Control of basal acid levels	NA	[92]
Zinc	May have antiviral activity	[167]

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Azithromycin	has also been found effective in patients with severe respiratory tract infections suffering from viral infection	[168,169]
Vitamin C (ascorbic acid)	enhancing the host immunity	[168,170]
Corticosteroids	Preventing an extended cytokine response accelerate resolution of pulmonary and systemic inflammation in pneumonia	[170]
Non-steroidal anti-inflammatory drugs (NSAIDs)	May exhibit antiviral activity against SARS-CoV	[170]
Aspirin	Inhibiting virus replication Anti-platelet aggregation (anticoagulant action) Anti-inflammatory Anti-lung injury	[170]

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Table 9. Antiviral drugs in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

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15

Drug	Mechanism of action	Target	FDA-situation	References

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Penciclovir/ Acyclovir	Nucleoside analog	HSV	Approved	[171]
	Interference with viral reproduction	VZV		
Nitazoxanide	Anti-protozoal agent	A vast range of viruses	Approved	[172-174]
	Modulation of survival and proliferation of viruses			
Favipiravir	RNA dependent RNA polymerase inhibitor	Ebola	Investigation	[175-179]
	Cease viral reproduction	Influenza type A		
		SARS-CoV-2		
Lopinavir/ Ritonavir	Protease inhibitors	HIV/AIDS	Approved	[180-182]
	Cause to Produce inactive viruses	SARS		
		MERS		
Darunavir/Umifenovir	Stop virus from merging with target cells	Influenza viruses	Approved	[176,183]
Ganciclovir	Nucleoside analog Inhibitor of the herpes family	CMV	Approved	[184]
		HIV		
Nafamostat	Synthetic serine protease inhibitor	Influenza viruses	Investigation	[185,186]

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	Stop virus from merging with target cells	MERS		
		Ebola		
Remdesivir	Nucleotide analogue	Ebola	Investigation	[187-189]
	Interference after virus entry	SARS		
		MERS		
Glecaprevir	Main protease inhibitor	SARS-CoV-2	Approved	[190]
Maraviroc	Main protease inhibitor	SARS-CoV-2	Approved	[190]
Type 1 interferon (IFN–I)	Prevent the viral egress or membrane fusion	MERS-CoV	Investigation	[191]
	Interfere the replication of virus, indirectly			
Oseltamivir	Neuraminidase inhibitor	Influenza viruses A	Approved	[192,193]
	Inhibition of viral neuraminidase activity germination			
	Prevention of host cell			
	Stop viral replication			
Ribavirin	Synthetic guanosine nucleoside	HCV	Approved	[153,194]

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	Disrupt producing viral mRNA	SARS		
		MERS		
Chloroquine	Enhance the immune system	Malaria	Approved	[12,195-197]
	Increase of autophagy suppressors	Autoimmune diseases		
Hydroxychloroquine	Enhancing the immune system	Malaria	Approved	[198]
	Preventing the viral entry into the cells	Autoimmune diseases		

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12. Conclusions

At present time, SARS-CoV-2 infection has become world-wide concern and causes many social and economic problems. This fact shows the importance of our approach to this infection. Considering this fact that vaccines for SARS-CoV-2 is not accessible for all people around the world because of limitations in producing, financial problems and political issues, best way to prevent from SARS-CoV-2 infection is minimum contact between people in each community. On the other hand, governments should prepare suitable facilities for scientists and researchers to know more about SARS-CoV-2 and its infection to manufacture proper, economical, accessible and beneficial treatments and vaccines for people all around the planet.

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References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R. A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine* **2020**.
2. Jin, Y.; Yang, H.; Ji, W.; Wu, W.; Chen, S.; Zhang, W.; Duan, G. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses* **2020**, *12*, 372.
3. Wang, C.; Horby, P.W.; Hayden, F.G.; Gao, G.F. A novel coronavirus outbreak of global health concern. *The Lancet* **2020**, *395*, 470-473.
4. Heymann, D.L.; Shindo, N. COVID-19: what is next for public health? *The Lancet* **2020**, *395*, 542-545.
5. Guo, Y.-R.; Cao, Q.-D.; Hong, Z.-S.; Tan, Y.-Y.; Chen, S.-D.; Jin, H.-J.; Tan, K.-S.; Wang, D.-Y.; Yan, Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. *Military Medical Research* **2020**, *7*, 1-10.
6. Lu, Q.; Shi, Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. *Journal of medical virology* **2020**, *92*, 564-567.
7. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet* **2020**, *395*, 497-506.
8. Shereen, M.A.; Khan, S.; Kazmi, A.; Bashir, N.; Siddique, R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research* **2020**.
9. Beigel, J.H.; Tomashek, K.M.; Dodd, L.E.; Mehta, A.K.; Zingman, B.S.; Kalil, A.C.; Hohmann, E.; Chu, H.Y.; Luetkemeyer, A.; Kline, S. Remdesivir for the treatment of Covid-19—preliminary report. *The New England journal of medicine* **2020**.
10. Commission, G.O.o.N.H. General Office of National Administration of Traditional Chinese Medicine. Diagnostic and treatment protocol for Novel Coronavirus Pneumonia. 2020.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

11. Borba, M.G.S.; Val, F.F.A.; Sampaio, V.S.; Alexandre, M.A.A.; Melo, G.C.; Brito, M.; Mourão, M.P.G.; Brito-Sousa, J.D.; Baía-da-Silva, D.; Guerra, M.V.F. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA network open* **2020**, *3*, e208857-e208857.
12. Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research* **2020**, *30*, 269-271.
13. Cao, B.; Wang, Y.; Wen, D.; Liu, W.; Wang, J.; Fan, G.; Ruan, L.; Song, B.; Cai, Y.; Wei, M. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine* **2020**.
14. Cassady, K.A.; Whitley, R.J. Viral infections of the central nervous system. *Clinical Virology* **2016**.
15. Cascella, M.; Rajnik, M.; Cuomo, A.; Dulebohn, S.C.; Di Napoli, R. Features, evaluation and treatment coronavirus (COVID-19). In *Statpearls [internet]*, StatPearls Publishing: 2020.
16. Elfiky, A.A.; Mahdy, S.M.; Elshemey, W.M. Quantitative structure-activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. *Journal of medical virology* **2017**, *89*, 1040-1047.
17. Chan, J.F.; Lau, S.K.; To, K.K.; Cheng, V.C.; Woo, P.C.; Yuen, K.-Y. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clinical microbiology reviews* **2015**, *28*, 465-522.
18. Wu, F.; Zhao, S.; Yu, B.; Chen, Y.-M.; Wang, W.; Song, Z.-G.; Hu, Y.; Tao, Z.-W.; Tian, J.-H.; Pei, Y.-Y. A new coronavirus associated with human respiratory disease in China. *Nature* **2020**, *579*, 265-269.
19. Cui, J.; Li, F.; Shi, Z.-L. Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology* **2019**, *17*, 181-192.
20. Perlman, S.; Netland, J. Coronaviruses post-SARS: update on replication and pathogenesis. *Nature reviews microbiology* **2009**, *7*, 439-450.
21. Wu, F.; Zhao, S.; Yu, B.; Chen, Y.-M.; Wang, W.; Hu, Y.; Song, Z.-G.; Tao, Z.-W.; Tian, J.-H.; Pei, Y.-Y. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. *bioRxiv* **2020**.
22. Tortorici, M.A.; Veesler, D. Structural insights into coronavirus entry. In *Advances in virus research*, Elsevier: 2019; Vol. 105, pp. 93-116.
23. Angeletti, S.; Benvenuto, D.; Bianchi, M.; Giovanetti, M.; Pascarella, S.; Ciccozzi, M. COVID-2019: the role of the nsp2 and nsp3 in its pathogenesis. *Journal of medical virology* **2020**, *92*, 584-588.
24. Hulswit, R.J.; Lang, Y.; Bakkers, M.J.; Li, W.; Li, Z.; Schouten, A.; Ophorst, B.; Van Kuppeveld, F.J.; Boons, G.-J.; Bosch, B.-J. Human coronaviruses OC43 and HKU1 bind to 9-O-acetylated sialic acids via a conserved receptor-binding site in spike protein domain A. *Proceedings of the National Academy of Sciences* **2019**, *116*, 2681-2690.
25. Xia, S.; Zhu, Y.; Liu, M.; Lan, Q.; Xu, W.; Wu, Y.; Ying, T.; Liu, S.; Shi, Z.; Jiang, S. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. *Cellular & molecular immunology* **2020**, 1-3.
26. Yu, F.; Du, L.; Ojcius, D.M.; Pan, C.; Jiang, S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. *Microbes and infection* **2020**.
27. Tripp, R.A.; Tompkins, S.M. *Roles of Host Gene and Non-coding RNA Expression in Virus Infection*; Springer: 2018; Vol. 419.
28. Sawicki, S.; Sawicki, D. Coronavirus transcription: a perspective. In *Coronavirus replication and reverse genetics*, Springer: 2005; pp. 31-55.
29. Hussain, S.; Chen, Y.; Yang, Y.; Xu, J.; Peng, Y.; Wu, Y.; Li, Z.; Zhu, Y.; Tien, P.; Guo, D. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. *Journal of virology* **2005**, *79*, 5288-5295.
30. Perrier, A.; Bonnin, A.; Desmarets, L.; Danneels, A.; Goffard, A.; Rouillé, Y.; Dubuisson, J.; Belouzard, S. The C-terminal domain of the MERS coronavirus M protein contains a trans-Golgi network localization signal. *Journal of Biological Chemistry* **2019**, *294*, 14406-14421.
31. Xiong, C.; Jiang, L.; Chen, Y.; Jiang, Q. Evolution and variation of 2019-novel coronavirus. *Biorxiv* **2020**.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

32. Wen-Bin, Y.; Li, Z.; Richard, T.C. Decoding the evolution and transmissions of the novel pneumonia coronavirus (SARS-CoV-2/HCoV-19) using whole genomic data. *Zoological Research* **2020**, *41*, 247-257.
33. Woo, P.C.; Lau, S.K.; Lam, C.S.; Lau, C.C.; Tsang, A.K.; Lau, J.H.; Bai, R.; Teng, J.L.; Tsang, C.C.; Wang, M. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. *Journal of virology* **2012**, *86*, 3995-4008.
34. Epidemiology, N.C.P.E.R. Team. on behalf of the Chinese Centre for Disease Control and Prevention The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)–China, 2020. *CCDC Weekly* **2020**, *2*, 113-122.
35. Lai, C.-C.; Shih, T.-P.; Ko, W.-C.; Tang, H.-J.; Hsueh, P.-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *International journal of antimicrobial agents* **2020**, 105924.
36. Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *nature* **2020**, *579*, 270-273.
37. Chen, L.; Liu, W.; Zhang, Q.; Xu, K.; Ye, G.; Wu, W.; Sun, Z.; Liu, F.; Wu, K.; Zhong, B. RNA based mNGS approach identifies a novel human coronavirus from two individual pneumonia cases in 2019 Wuhan outbreak. *Emerging microbes & infections* **2020**, *9*, 313-319.
38. Nadeem, M.S.; Zamzami, M.A.; Choudhry, H.; Murtaza, B.N.; Kazmi, I.; Ahmad, H.; Shakoori, A.R. Origin, potential therapeutic targets and treatment for coronavirus disease (COVID-19). *Pathogens* **2020**, *9*, 307.
39. Xiao, K.; Zhai, J.; Feng, Y.; Zhou, N.; Zhang, X.; Zou, J.-J.; Li, N.; Guo, Y.; Li, X.; Shen, X. Isolation and characterization of 2019-nCoV-like coronavirus from Malayan pangolins. *BioRxiv* **2020**.
40. Zhang, H.; Penninger, J.M.; Li, Y.; Zhong, N.; Slutsky, A.S. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive care medicine* **2020**, *46*, 586-590.
41. Yang, L.; Wu, Z.; Ren, X.; Yang, F.; He, G.; Zhang, J.; Dong, J.; Sun, L.; Zhu, Y.; Du, J. Novel SARS-like betacoronaviruses in bats, China, 2011. *Emerging infectious diseases* **2013**, *19*, 989.
42. Hu, B.; Zeng, L.-P.; Yang, X.-L.; Ge, X.-Y.; Zhang, W.; Li, B.; Xie, J.-Z.; Shen, X.-R.; Zhang, Y.-Z.; Wang, N. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLoS pathogens* **2017**, *13*, e1006698.
43. Wan, Y.; Shang, J.; Graham, R.; Baric, R.S.; Li, F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *Journal of virology* **2020**, *94*.
44. Zhang, L.; Shen, F.-m.; Chen, F.; Lin, Z. Origin and evolution of the 2019 novel coronavirus. *Clinical Infectious Diseases* **2020**.
45. Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet* **2020**, *395*, 565-574.
46. Xu, X.; Chen, P.; Wang, J.; Feng, J.; Zhou, H.; Li, X.; Zhong, W.; Hao, P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences* **2020**, *63*, 457-460.
47. Liu, Z.; Xiao, X.; Wei, X.; Li, J.; Yang, J.; Tan, H.; Zhu, J.; Zhang, Q.; Wu, J.; Liu, L. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. *Journal of medical virology* **2020**, *92*, 595-601.
48. Andersen, K.G.; Rambaut, A.; Lipkin, W.I.; Holmes, E.C.; Garry, R.F. The proximal origin of SARS-CoV-2. *Nature medicine* **2020**, *26*, 450-452.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

49. Chen, N.; Zhou, M.; Dong, X.; Qu, J.; Gong, F.; Han, Y.; Qiu, Y.; Wang, J.; Liu, Y.; Wei, Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet* **2020**, *395*, 507-513.
50. Liu, P.; Chen, W.; Chen, J.-P. Viral metagenomics revealed Sendai virus and coronavirus infection of Malayan pangolins (Manis javanica). *Viruses* **2019**, *11*, 979.
51. Li, X.; Zai, J.; Zhao, Q.; Nie, Q.; Li, Y.; Foley, B.T.; Chaillon, A. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. *Journal of medical virology* **2020**, *92*, 602-611.
52. Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K.S.; Lau, E.H.; Wong, J.Y. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England Journal of Medicine* **2020**.
53. Duffy, S. Why are RNA virus mutation rates so damn high? *PLoS biology* **2018**, *16*, e3000003.
54. Domingo, E. Viruses at the edge of adaptation. *Virology* **2000**, *270*, 251-253.
55. Domingo, E. Quasispecies theory in virology. *Journal of Virology* **2002**, *76*, 463-465.
56. Domingo, E.; Holland, J. RNA virus mutations and fitness for survival. *Annual review of microbiology* **1997**, *51*, 151-178.
57. Pachetti, M.; Marini, B.; Benedetti, F.; Giudici, F.; Mauro, E.; Storici, P.; Masciovecchio, C.; Angeletti, S.; Ciccozzi, M.; Gallo, R.C. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. *Journal of Translational Medicine* **2020**, *18*, 1-9.
58. World Health Organization. SARS-CoV-2 Variants. Availabe online: https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/ (accessed on
59. Li, Q.; Wu, J.; Nie, J.; Zhang, L.; Hao, H.; Liu, S.; Zhao, C.; Zhang, Q.; Liu, H.; Nie, L. The impact of mutations in SARS-CoV-2 spike on viral infectivity and antigenicity. *Cell* **2020**, *182*, 1284-1294. e1289.
60. Daniloski, Z.; Jordan, T.X.; Ilmain, J.K.; Guo, X.; Bhabha, G.; Sanjana, N.E. The Spike D614G mutation increases SARS-CoV-2 infection of multiple human cell types. *BioRxiv* **2020**.
61. Leung, K.; Shum, M.H.; Leung, G.M.; Lam, T.T.; Wu, J.T. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. *Eurosurveillance* **2021**, *26*, 2002106.
62. Davies, N.G.; Barnard, R.C.; Jarvis, C.I.; Kucharski, A.J.; Munday, J.; Pearson, C.A.; Russell, T.W.; Tully, D.C.; Abbott, S.; Gimma, A. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. *medRxiv* **2020**.
63. Starr, T.N.; Greaney, A.J.; Hilton, S.K.; Ellis, D.; Crawford, K.H.; Dingens, A.S.; Navarro, M.J.; Bowen, J.E.; Tortorici, M.A.; Walls, A.C. Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. *Cell* **2020**, *182*, 1295-1310. e1220.
64. Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* **2020**, *581*, 215-220.
65. Yi, C.; Sun, X.; Ye, J.; Ding, L.; Liu, M.; Yang, Z.; Lu, X.; Zhang, Y.; Ma, L.; Gu, W. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. *Cellular & Molecular Immunology* **2020**, 1-10.
66. Shang, J.; Ye, G.; Shi, K.; Wan, Y.; Luo, C.; Aihara, H.; Geng, Q.; Auerbach, A.; Li, F. Structural basis of receptor recognition by SARS-CoV-2. *Nature* **2020**, *581*, 221-224.
67. Tegally, H.; Wilkinson, E.; Giovanetti, M.; Iranzadeh, A.; Fonseca, V.; Giandhari, J.; Doolabh, D.; Pillay, S.; San, E.J.; Msomi, N. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. *medRxiv* **2020**.
68. Zhang, W.; Du, R.-H.; Li, B.; Zheng, X.-S.; Yang, X.-L.; Hu, B.; Wang, Y.-Y.; Xiao, G.-F.; Yan, B.; Shi, Z.-L. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerging microbes & infections* **2020**, *9*, 386-389.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

69. Bordbar, A.; Kashaki, M.; Rezaei, F.; Jafari, R. Vertical transmission of COVID-19 in a 1-day-old neonate. *Travel Medicine and Infectious Disease* **2020**.
70. Principi, N.; Bosis, S.; Esposito, S. Effects of coronavirus infections in children. *Emerging infectious diseases* **2010**, *16*, 183.
71. Zumla, A.; Hui, D.S.; Perlman, S. Middle East respiratory syndrome. *The Lancet* **2015**, *386*, 995-1007.
72. Chen, H.; Guo, J.; Wang, C.; Luo, F.; Yu, X.; Zhang, W.; Li, J.; Zhao, D.; Xu, D.; Gong, Q. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet* **2020**, *395*, 809-815.
73. Ran, L.; Chen, X.; Wang, Y.; Wu, W.; Zhang, L.; Tan, X. Risk factors of healthcare workers with corona virus disease 2019: a retrospective cohort study in a designated hospital of Wuhan in China. *Clinical Infectious Diseases* **2020**.
74. Zhao, Y.; Zhao, Z.; Wang, Y.; Zhou, Y.; Ma, Y.; Zuo, W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. *BioRxiv* **2020**.
75. Zhang, Q.; Cong, M.; Wang, N.; Li, X.; Zhang, H.; Zhang, K.; Jin, M.; Wu, N.; Qiu, C.; Li, J. Association of angiotensin-converting enzyme 2 gene polymorphism and enzymatic activity with essential hypertension in different gender: A case–control study. *Medicine* **2018**, *97*.
76. Hoffmann, M.; Kleine-Weber, H.; Krüger, N.; Mueller, M.A.; Drosten, C.; Pöhlmann, S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *BioRxiv* **2020**.
77. Zhang, H.; Kang, Z.; Gong, H.; Xu, D.; Wang, J.; Li, Z.; Cui, X.; Xiao, J.; Meng, T.; Zhou, W. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *BioRxiv* **2020**.
78. Jia, H.P.; Look, D.C.; Shi, L.; Hickey, M.; Pewe, L.; Netland, J.; Farzan, M.; Wohlford-Lenane, C.; Perlman, S.; McCray, P.B. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *Journal of virology* **2005**, *79*, 14614-14621.
79. Gao, Z. Efficient management of novel coronavirus pneumonia by efficient prevention and control in scientific manner. *Zhonghua jie he he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases* **2020**, *43*, E001-E001.
80. Qin, J.; You, C.; Lin, Q.; Hu, T.; Yu, S.; Zhou, X.-H. Estimation of incubation period distribution of COVID-19 using disease onset forward time: A novel cross-sectional and forward follow-up study. *Science Advances* **2020**, *6*, eabc1202, doi:10.1126/sciadv.abc1202.
81. Luo, W.; Yu, H.; Gou, J.; Li, X.; Sun, Y.; Li, J.; Liu, L. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints* **2020**, *2020*, 2020020407.
82. Tabary, M.; Khanmohammadi, S.; Araghi, F.; Dadkhahfar, S.; Tavangar, S.M. Pathologic features of COVID-19: A concise review. *Pathology-Research and Practice* **2020**, 153097.
83. Menter, T.; Haslbauer, J.D.; Nienhold, R.; Savic, S.; Hopfer, H.; Deigendesch, N.; Frank, S.; Turek, D.; Willi, N.; Pargger, H. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology* **2020**, *77*, 198-209.
84. Ou, F.; Wu, H.; Yang, Y.; Tan, W.; Zhang, J.; Gu, J. Countermeasures for rapid spread of new coronavirus pneumonia in Wuhan. *Chinese General Practicing Nursing* **2020**.
85. Calisher, C.; Carroll, D.; Colwell, R.; Corley, R.B.; Daszak, P.; Drosten, C.; Enjuanes, L.; Farrar, J.; Field, H.; Golding, J. Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19. *The Lancet* **2020**, *395*, e42-e43.
86. Calina, D.; Sarkar, C.; Arsene, A.L.; Salehi, B.; Docea, A.O.; Mondal, M.; Islam, M.T.; Zali, A.; Sharifi-Rad, J. Recent advances, approaches and challenges in targeting pathways for potential COVID-19 vaccines development. *Immunologic research* **2020**, 1-10.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

87. Locht, C. Vaccines against COVID-19. *Anaesthesia, critical care & pain medicine* **2020**.
88. Krammer, F. SARS-CoV-2 vaccines in development. *Nature* **2020**, *586*, 516-527.
89. de Queiroz, N.M.G.P.; Marinho, F.V.; Chagas, M.A.; Leite, L.C.C.; Homan, E.J.; de Magalhães, M.T.Q.; Oliveira, S.C. Vaccines for COVID-19: perspectives from nucleic acid vaccines to BCG as delivery vector system. *Microbes Infect* **2020**, *22*, 515-524, doi:10.1016/j.micinf.2020.09.004.
90. Silveira, M.M.; Moreira, G.M.S.G.; Mendonça, M. DNA vaccines against COVID-19: Perspectives and challenges. *Life Sci* **2021**, *267*, 118919-118919, doi:10.1016/j.lfs.2020.118919.
91. Centers for Disease Control and Prevention. Different COVID-19 Vaccines. Availabe online: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html (accessed on
92. Wang, L.; Shi, Y.; Xiao, T.; Fu, J.; Feng, X.; Mu, D.; Feng, Q.; Hei, M.; Hu, X.; Li, Z. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection. *Annals of translational medicine* **2020**, *8*.
93. Mair-Jenkins, J.; Saavedra-Campos, M.; Baillie, J.K.; Cleary, P.; Khaw, F.-M.; Lim, W.S.; Makki, S.; Rooney, K.D.; Group, C.P.S.; Nguyen-Van-Tam, J.S. 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. *The Journal of infectious diseases* **2015**, *211*, 80-90.
94. Chen, D.; Xu, W.; Lei, Z.; Huang, Z.; Liu, J.; Gao, Z.; Peng, L. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. *International Journal of Infectious Diseases* **2020**.
95. Jiang, F.; Deng, L.; Zhang, L.; Cai, Y.; Cheung, C.W.; Xia, Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *Journal of general internal medicine* **2020**, 1-5.
96. Li, G.; De Clercq, E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature Publishing Group: 2020.
97. Luo, H.; Tang, Q.-l.; Shang, Y.-x.; Liang, S.-b.; Yang, M.; Robinson, N.; Liu, J.-p. Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. *Chinese journal of integrative medicine* **2020**, 1-8.
98. World Health Organization. COVID-19 Clinical management: living guidance. Availabe online: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1 (accessed on
99. Lei, J.; Kusov, Y.; Hilgenfeld, R. Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. *Antiviral research* **2018**, *149*, 58-74.
100. Song, W.; Gui, M.; Wang, X.; Xiang, Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS pathogens* **2018**, *14*, e1007236.
101. de Abajo, F.J.; Rodríguez-Martín, S.; Lerma, V.; Mejía-Abril, G.; Aguilar, M.; García-Luque, A.; Laredo, L.; Laosa, O.; Centeno-Soto, G.A.; Gálvez, M.Á. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *The Lancet* **2020**.
102. Miller, J.; Cantor, A.; Zachariah, P.; Ahn, D.; Martinez, M.; Margolis, K.G. Gastrointestinal Symptoms as a Major Presentation Component of a Novel Multisystem Inflammatory Syndrome in Children That Is Related to Coronavirus Disease 2019: A Single Center Experience of 44 Cases. *Gastroenterology* **2020**.
103. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama* **2020**, *323*, 1061-1069.
104. Euronews. 'COVID tongue': Mouth ulcers or rashes likely a coronavirus symptom, says expert. Availabe online: https://www.euronews.com/2021/02/01/covid-tongue-mouth-ulcers-or-rashes-likely-a-coronavirus-symptom-says-expert (accessed on
105. WEBMD HEALTH NEWS. 'COVID Tongue' May Be a Symptom, Professor Says. Availabe online: https://www.webmd.com/lung/news/20210129/covid-tongue-may-be-a-symptom-professor-says (accessed on

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

106. Yu, N.; Li, W.; Kang, Q.; Xiong, Z.; Wang, S.; Lin, X.; Liu, Y.; Xiao, J.; Liu, H.; Deng, D. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. *The Lancet Infectious Diseases* **2020**.
107. Zhu, H.; Wang, L.; Fang, C.; Peng, S.; Zhang, L.; Chang, G.; Xia, S.; Zhou, W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Translational pediatrics* **2020**, *9*, 51.
108. Ryean, G.A.; Purandare, N.C.; McAuliffe, F.M.; Hod, M.; Purandare, C.N. Clinical update on COVID-19 in pregnancy: A review article. *Journal of Obstetrics and Gynaecology Research* **2020**.
109. De Bernardo, G.; Giordano, M.; Zollo, G.; Chiatto, F.; Sordino, D.; De Santis, R.; Perrone, S. The clinical course of SARS-CoV-2 positive neonates. *Journal of Perinatology* **2020**, *40*, 1462-1469.
110. Ryan, G.A.; Purandare, N.C.; McAuliffe, F.M.; Hod, M.; Purandare, C.N. Clinical update on COVID-19 in pregnancy: A review article. *Journal of Obstetrics and Gynaecology Research* **2020**, *46*, 1235-1245.
111. Zaigham, M.; Andersson, O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta obstetricia et gynecologica Scandinavica* **2020**.
112. Karami, P.; Naghavi, M.; Feyzi, A.; Aghamohammadi, M.; Novin, M.S.; Mobaien, A.; Qorbanisani, M.; Karami, A.; Norooznezhad, A.H. Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings. *Travel medicine and infectious disease* **2020**.
113. Hantoushzadeh, S.; Shamshirsaz, A.A.; Aleyasin, A.; Seferovic, M.D.; Aski, S.K.; Arian, S.E.; Pooransari, P.; Ghotbizadeh, F.; Aalipour, S.; Soleimani, Z. Maternal death due to COVID-19 disease. *American journal of obstetrics and gynecology* **2020**.
114. Ferrazzi, E.M.; Frigerio, L.; Cetin, I.; Vergani, P.; Spinillo, A.; Prefumo, F.; Pellegrini, E.; Gargantini, G. COVID-19 Obstetrics Task Force, Lombardy, Italy: executive management summary and short report of outcome. *International Journal of Gynecology & Obstetrics* **2020**, *149*, 377-378.
115. Browne, P.C.; Linfert, J.B.; Perez-Jorge, E. Successful treatment of preterm labor in association with acute COVID-19 infection. *American journal of perinatology* **2020**, *37*, 866.
116. Bajpai, D.; Shah, S. COVID-19 pandemic and pregnancy in kidney disease. *Advances in chronic kidney disease* **2020**.
117. Silasi, M.; Cardenas, I.; Kwon, J.Y.; Racicot, K.; Aldo, P.; Mor, G. Viral infections during pregnancy. *American journal of reproductive immunology* **2015**, *73*, 199-213.
118. Wastnedge, E.A.; Reynolds, R.M.; van Boeckel, S.R.; Stock, S.J.; Denison, F.C.; Maybin, J.A.; Critchley, H.O. Pregnancy and COVID-19. *Physiological reviews* **2021**, *101*, 303-318.
119. Alhazzani, W.; Møller, M.; Arabi, Y.; Loeb, M.; Gong, M.; Fan, E. & Du, B.(2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive care medicine*, 1-34.
120. Chen, L.; Li, Q.; Zheng, D.; Jiang, H.; Wei, Y.; Zou, L.; Feng, L.; Xiong, G.; Sun, G.; Wang, H. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. *New England Journal of Medicine* **2020**.
121. Dashraath, P.; Jeslyn, W.J.L.; Karen, L.M.X.; Min, L.L.; Sarah, L.; Biswas, A.; Choolani, M.A.; Mattar, C.; Lin, S.L. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *American journal of obstetrics and gynecology* **2020**.
122. IoOaG, R. COVID-19 Infection Guidance for Maternity Services. *Institute of Obstetricians and Gynaecologists-Royal College of Physicians Ireland (RCPI)* **2020**, *21*.
123. Burwick, R.M.; Yawetz, S.; Stephenson, K.E.; Collier, A.-R.Y.; Sen, P.; Blackburn, B.G.; Kojic, E.M.; Hirshberg, A.; Suarez, J.F.; Sobieszczyk, M.E. Compassionate use of remdesivir in pregnant women with severe coronavirus disease 2019. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* **2020**.
124. Saad, A.F.; Chappell, L.; Saade, G.R.; Pacheco, L.D. Corticosteroids in the management of pregnant patients with coronavirus disease (COVID-19). *Obstetrics & Gynecology* **2020**, *136*, 823-826.
125. Di Renzo, G.C.; Giardina, I. Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and thromboprophylaxis. *American Journal of Obstetrics & Gynecology* **2020**.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

126. Knight, M.; Bunch, K.; Vousden, N.; Morris, E.; Simpson, N.; Gale, C.; O'Brien, P.; Quigley, M.; Brocklehurst, P.; Kurinczuk, J.J. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *bmj* **2020**, *369*.
127. Reynolds-Wright, J.J.; Fletcher, J. Troublesome bleeding following early medical abortion. *BMJ Sexual & Reproductive Health* **2020**.
128. Centers for Disease Control and Prevention. Care for Newborns. Availabe online: https://www.cdc.gov/coronavirus/2019-ncov/hcp/caring-for-newborns.html (accessed on
129. Yu, Y.; Chen, P. Coronavirus disease 2019 (COVID-19) in neonates and children from China: a review. *Frontiers in pediatrics* **2020**, *8*, 287.
130. The Times of India. Coronavirus: Can newborns catch COVID-19? What symptoms should you lookout for. Availabe online: https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/coronavirus-symptoms-in-newborns-can-newborns-catch-covid-19-what-symptoms-should-you-lookout-for/photostory/80265894.cms (accessed on
131. Saeedi, M.; Sangsari, R.; Mirnia, K. COVID-19 in Neonates: A Review. *Iranian Journal of Pediatrics* **2021**, *31*.
132. Covid, C.; Team, R.; Covid, C.; Team, R.; COVID, C.; Team, R.; Bialek, S.; Gierke, R.; Hughes, M.; McNamara, L.A. Coronavirus disease 2019 in children—United States, february 12–april 2, 2020. *Morbidity and Mortality Weekly Report* **2020**, *69*, 422.
133. Dong, Y.; Mo, X.; Hu, Y.; Qi, X.; Jiang, F.; Jiang, Z.; Tong, S. Epidemiology of COVID-19 among children in China. *Pediatrics* **2020**, *145*.
134. Zare-Zardini, H.; Soltaninejad, H.; Ferdosian, F.; Hamidieh, A.A.; Memarpoor-Yazdi, M. Coronavirus disease 2019 (COVID-19) in children: prevalence, diagnosis, clinical symptoms, and treatment. *International Journal of General Medicine* **2020**, *13*, 477.
135. Karimi, A.; Rafiei Tabatabaei, S.; Rajabnejad, M.; Pourmoghaddas, Z.; Rahimi, H.; Armin, S.; Mansour Ghanaie, R.; Kadivar, M.R.; Fahimzad, S.A.; Sedighi, I. An algorithmic approach to diagnosis and treatment of coronavirus disease 2019 (COVID-19) in children: Iranian expert's consensus statement. *Archives of Pediatric Infectious Diseases* **2020**, *8*.
136. Guan, W.-j.; Ni, Z.-y.; Hu, Y.; Liang, W.-h.; Ou, C.-q.; He, J.-x.; Liu, L.; Shan, H.; Lei, C.-l.; Hui, D.S. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine* **2020**, *382*, 1708-1720.
137. Liu, K.; Fang, Y.-Y.; Deng, Y.; Liu, W.; Wang, M.-F.; Ma, J.-P.; Xiao, W.; Wang, Y.-N.; Zhong, M.-H.; Li, C.-H. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chinese medical journal* **2020**.
138. Jin, R. Recommendation for the diagnosis and treatment of novel coronavirus infection in children in Hubei (Trial version 1). *Chinese Journal of Contemporary Pediatrics* **2020**, *22*.
139. Martines, R.B.; Ritter, J.M.; Matkovic, E.; Gary, J.; Bollweg, B.C.; Bullock, H.; Goldsmith, C.S.; Silva-Flannery, L.; Seixas, J.N.; Reagan-Steiner, S. Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. *Emerging infectious diseases* **2020**, *26*, 2005.
140. Tian, S.; Hu, W.; Niu, L.; Liu, H.; Xu, H.; Xiao, S.-Y. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *Journal of Thoracic Oncology* **2020**.
141. Bryce, C.; Grimes, Z.; Pujadas, E.; Ahuja, S.; Beasley, M.B.; Albrecht, R.; Hernandez, T.; Stock, A.; Zhao, Z.; Al Rasheed, M. Pathophysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience. *medRxiv* **2020**.
142. Carsana, L.; Sonzogni, A.; Nasr, A.; Rossi, R.S.; Pellegrinelli, A.; Zerbi, P.; Rech, R.; Colombo, R.; Antinori, S.; Corbellino, M. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *The Lancet Infectious Diseases* **2020**.
143. Schaller, T.; Hirschbühl, K.; Burkhardt, K.; Braun, G.; Trepel, M.; Märkl, B.; Claus, R. Postmortem examination of patients with COVID-19. *JAMA* **2020**.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

144. Remmelink, M.; De Mendoca, R.; D'Haene, N.; De Clercq, S.; Verocq, C.; Lebrun, L.; Lavis, P.; Racu, M.L.; Trepant, A.L.; Maris, C. Unspecific post-mortem findings despite multiorgan 1 viral spread in COVID-19 patients. *medRxiv* **2020**.
145. Zhou, S.; Wang, Y.; Zhu, T.; Xia, L. CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. *American Journal of Roentgenology* **2020**, *214*, 1287-1294.
146. Littrup, P.J.; Freeman-Gibb, L.; Andea, A.; White, M.; Amerikia, K.C.; Bouwman, D.; Harb, T.; Sakr, W. Cryotherapy for breast fibroadenomas. *Radiology* **2005**, *234*, 63-72.
147. Wong, H.Y.F.; Lam, H.Y.S.; Fong, A.H.-T.; Leung, S.T.; Chin, T.W.-Y.; Lo, C.S.Y.; Lui, M.M.-S.; Lee, J.C.Y.; Chiu, K.W.-H.; Chung, T. Frequency and distribution of chest radiographic findings in COVID-19 positive patients. *Radiology* **2020**, 201160.
148. Bernheim, A.; Mei, X.; Huang, M.; Yang, Y.; Fayad, Z.A.; Zhang, N.; Diao, K.; Lin, B.; Zhu, X.; Li, K. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology* **2020**, 200463.
149. Gozansky, E.K.; Moore, W.H. SARS-CoV-2 from the trenches: a perspective from New York City. *American Journal of Roentgenology* **2020**, 1-2.
150. Sun, R.; Liu, H.; Wang, X. Mediastinal emphysema, giant bulla, and pneumothorax developed during the course of COVID-19 pneumonia. *Korean Journal of Radiology* **2020**, *21*, 541.
151. Lei, J.; Li, J.; Li, X.; Qi, X. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology* **2020**, *295*, 18-18.
152. Kong, W.; Agarwal, P.P. Chest imaging appearance of COVID-19 infection. *Radiology: Cardiothoracic Imaging* **2020**, *2*, e200028.
153. Chung, M.; Bernheim, A.; Mei, X.; Zhang, N.; Huang, M.; Zeng, X.; Cui, J.; Xu, W.; Yang, Y.; Fayad, Z.A. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* **2020**, *295*, 202-207.
154. Huang, Y.; Wang, S.; Liu, Y.; Zhang, Y.; Zheng, C.; Zheng, Y.; Zhang, C.; Min, W.; Zhou, H.; Yu, M. A preliminary study on the ultrasonic manifestations of peripulmonary lesions of non-critical novel coronavirus pneumonia (COVID-19). *Available at SSRN 3544750* **2020**.
155. Buonsenso, D.; Piano, A.; Raffaelli, F.; Bonadia, N.; Donati, K.D.G.; Franceschi, F. novel coronavirus disease-19 pnemoniae: a case report and potential applications during COVID-19 outbreak. *European review for medical and pharmacological sciences* **2020**, *24*, 2776-2780.
156. Moro, F.; Buonsenso, D.; Moruzzi, M.; Inchingolo, R.; Smargiassi, A.; Demi, L.; Larici, A.; Scambia, G.; Lanzone, A.; Testa, A. How to perform lung ultrasound in pregnant women with suspected COVID-19. *Ultrasound in Obstetrics & Gynecology* **2020**, *55*, 593-598.
157. Penga, Q.-Y.; Wangb, X.-T. Findings of lung ultrasonography of novel corona virus pneumonia during the.
158. Thomas, A.; Haljan, G.; Mitra, A. Lung ultrasound findings in a 64-year-old woman with COVID-19. *CMAJ* **2020**, *192*, E399-E399.
159. Vetrugno, L.; Bove, T.; Orso, D.; Barbariol, F.; Bassi, F.; Boero, E.; Ferrari, G.; Kong, R. Our Italian experience using lung ultrasound for identification, grading and serial follow-up of severity of lung involvement for management of patients with COVID-19. *Echocardiography* **2020**, *37*, 625-627.
160. Centers for Disease Control and Prevention. Pfizer-BioNTech COVID-19 Vaccine

Vaccine Preparation and Administration Summary. Availabe online: https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/downloads/prep-and-admin-summary.pdf (accessed on
161. Centers for Disease Control and Prevention. Information about the Pfizer-BioNTech COVID-19 Vaccine. Availabe online: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Pfizer-BioNTech.html (accessed on
162. Centers for Disease Control and Prevention. Moderna COVID-19 Vaccine

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

Vaccine Preparation and Administration Summary. Availabe online: https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/downloads/prep-and-admin-summary.pdf (accessed on

163. Centers for Disease Control and Prevention. Information about the Moderna COVID-19 Vaccine. Availabe online: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Moderna.html (accessed on
164. British Broadcasting Channel. Russia's Sputnik V vaccine has 92% efficacy in trial. Availabe online: https://www.bbc.com/news/health-55900622 (accessed on
165. Sputnik V. General Information. Availabe online: https://sputnikvaccine.com/about-vaccine/ (accessed on
166. Logunov, D.Y.; Dolzhikova, I.V.; Shcheblyakov, D.V.; Tukhvatulin, A.I.; Zubkova, O.V.; Dzharullaeva, A.S.; Kovyrshina, A.V.; Lubenets, N.L.; Grousova, D.M.; Erokhova, A.S. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *The Lancet* **2021**.
167. Sarma, P.; Prajapat, M.; Avti, P.; Kaur, H.; Kumar, S.; Medhi, B. Therapeutic options for the treatment of 2019-novel coronavirus: An evidence-based approach. *Indian journal of pharmacology* **2020**, *52*, 1.
168. Wu, R.; Wang, L.; Kuo, H.-C.D.; Shannar, A.; Peter, R.; Chou, P.J.; Li, S.; Hudlikar, R.; Liu, X.; Liu, Z. An update on current therapeutic drugs treating COVID-19. *Current Pharmacology Reports* **2020**, 1.
169. Asai, A.; Konno, M.; Ozaki, M.; Otsuka, C.; Vecchione, A.; Arai, T.; Kitagawa, T.; Ofusa, K.; Yabumoto, M.; Hirotsu, T. COVID-19 drug discovery using intensive approaches. *International journal of molecular sciences* **2020**, *21*, 2839.
170. Rudrapal, M.; Khairnar, S.J.; Borse, L.B.; Jadhav, A.G. Coronavirus Disease-2019 (COVID-19): An Updated Review. *Drug research* **2020**, *70*, 389.
171. Shiraki, K. Antiviral drugs against alphaherpesvirus. In *Human Herpesviruses*, Springer: 2018; pp. 103-122.
172. Cao, J.; Forrest, J.C.; Zhang, X. A screen of the NIH Clinical Collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral research* **2015**, *114*, 1-10.
173. Rossignol, J.-F. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral research* **2014**, *110*, 94-103.
174. Rossignol, J.-F. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. *Journal of infection and public health* **2016**, *9*, 227-230.
175. Cardile, A.P.; Warren, T.K.; Martins, K.A.; Reisler, R.B.; Bavari, S. Will there be a cure for Ebola? *Annual review of pharmacology and toxicology* **2017**, *57*, 329-348.
176. Dong, L.; Hu, S.; Gao, J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug discoveries & therapeutics* **2020**, *14*, 58-60.
177. Furuta, Y.; Gowen, B.B.; Takahashi, K.; Shiraki, K.; Smee, D.F.; Barnard, D.L. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral research* **2013**, *100*, 446-454.
178. Goldhill, D.H.; Te Velthuis, A.J.; Fletcher, R.A.; Langat, P.; Zambon, M.; Lackenby, A.; Barclay, W.S. The mechanism of resistance to favipiravir in influenza. *Proceedings of the National Academy of Sciences* **2018**, *115*, 11613-11618.
179. Nagata, T.; Lefor, A.K.; Hasegawa, M.; Ishii, M. Favipiravir: a new medication for the Ebola virus disease pandemic. *Disaster medicine and public health preparedness* **2015**, *9*, 79-81.
180. Arabi, Y.M.; Asiri, A.Y.; Assiri, A.M.; Jokhdar, H.A.A.; Alothman, A.; Balkhy, H.H.; AlJohani, S.; Al Harbi, S.; Kojan, S.; Al Jeraisy, M. Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. *Trials* **2020**, *21*, 1-8.
181. Chu, C.; Cheng, V.; Hung, I.; Wong, M.; Chan, K.; Chan, K.; Kao, R.; Poon, L.; Wong, C.; Guan, Y. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* **2004**, *59*, 252-256.
182. Cvetkovic, R.S.; Goa, K.L. Lopinavir/ritonavir. *Drugs* **2003**, *63*, 769-802.
183. Kadam, R.U.; Wilson, I.A. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proceedings of the National Academy of Sciences* **2017**, *114*, 206-214.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2021 doi:10.20944/preprints202102.0530.v1

184. Al-Badr, A.A.; Ajarim, T.D. Ganciclovir. *Profiles of Drug Substances, Excipients and Related Methodology* **2018**, *43*, 1-208.
185. Hsieh, H.-P.; Hsu, J.T.-A. Strategies of development of antiviral agents directed against influenza virus replication. *Current pharmaceutical design* **2007**, *13*, 3531-3542.
186. Nishimura, H.; Yamaya, M. A synthetic serine protease inhibitor, Nafamostat Mesilate, is a drug potentially applicable to the treatment of ebola virus disease. *The Tohoku journal of experimental medicine* **2015**, *237*, 45-50.
187. Agostini, M.L.; Andres, E.L.; Sims, A.C.; Graham, R.L.; Sheahan, T.P.; Lu, X.; Smith, E.C.; Case, J.B.; Feng, J.Y.; Jordan, R. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *MBio* **2018**, *9*.
188. Lo, M.K.; Feldmann, F.; Gary, J.M.; Jordan, R.; Bannister, R.; Cronin, J.; Patel, N.R.; Klena, J.D.; Nichol, S.T.; Cihlar, T. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Science translational medicine* **2019**, *11*, eaau9242.
189. Tchesnokov, E.P.; Feng, J.Y.; Porter, D.P.; Götte, M. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses* **2019**, *11*, 326.
190. Shamsi, A.; Mohammad, T.; Anwar, S.; AlAjmi, M.F.; Hussain, A.; Rehman, M.; Islam, A.; Hassan, M. Glecaprevir and Maraviroc are high-affinity inhibitors of SARS-CoV-2 main protease: possible implication in COVID-19 therapy. *Bioscience Reports* **2020**, *40*.
191. Sallard, E.; Lescure, F.-X.; Yazdanpanah, Y.; Mentre, F.; Peiffer-Smadja, N. Type 1 interferons as a potential treatment against COVID-19. *Antiviral Res* **2020**, *178*, 104791-104791, doi:10.1016/j.antiviral.2020.104791.
192. Jefferson, T.; Jones, M.; Doshi, P.; Spencer, E.A.; Onakpoya, I.; Heneghan, C.J. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *Bmj* **2014**, *348*, g2545.
193. McQuade, B.; Blair, M. Influenza treatment with oseltamivir outside of labeled recommendations. *American Journal of Health-System Pharmacy* **2015**, *72*, 112-116.
194. Arabi, Y.M.; Shalhoub, S.; Mandourah, Y.; Al-Hameed, F.; Al-Omari, A.; Al Qasim, E.; Jose, J.; Alraddadi, B.; Almotairi, A.; Al Khatib, K. Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study. *Clinical infectious diseases* **2020**, *70*, 1837-1844.
195. Golden, E.B.; Cho, H.-Y.; Hofman, F.M.; Louie, S.G.; Schönthal, A.H.; Chen, T.C. Quinoline-based antimalarial drugs: a novel class of autophagy inhibitors. *Neurosurgical focus* **2015**, *38*, E12.
196. Savarino, A.; Boelaert, J.R.; Cassone, A.; Majori, G.; Cauda, R. Effects of chloroquine on viral infections: an old drug against today's diseases. *The Lancet infectious diseases* **2003**, *3*, 722-727.
197. Vincent, M.J.; Bergeron, E.; Benjannet, S.; Erickson, B.R.; Rollin, P.E.; Ksiazek, T.G.; Seidah, N.G.; Nichol, S.T. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology journal* **2005**, *2*, 1-10.
198. Pastick, K.A.; Okafor, E.C.; Wang, F.; Lofgren, S.M.; Skipper, C.P.; Nicol, M.R.; Pullen, M.F.; Rajasingham, R.; McDonald, E.G.; Lee, T.C. Hydroxychloroquine and chloroquine for treatment of SARS-CoV-2 (COVID-19). In Proceedings of Open Forum Infectious Diseases; p. ofaa130.