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

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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" but now, it 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 are enveloped positive-stranded RNA viruses. The SARS-CoV-2 has some particular structures for infecting, reproducing and causing damage. 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 both serious and not-serious issues for mankind. 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 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. 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.

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Abbreviations

2019-nCoV, 2019 novel coronavirus; ACE-2, Angiotensin-converting enzyme 2; BCG, Bacillus calmette-guérin; COPD, Chronic obstructive pulmonary disease; COVID-19, Coronavirus disease 2019; E proteins, Envelope proteins; FDA, Food and drug administration; HE, Hemagglutinin-esterase; M proteins, Membrane proteins; MERS, Middle East respiratory syndrome; MERS-COV, Middle east respiratory syndrome coronavirus; mRNA, Messenger RNA; N proteins, Nucleocapsid proteins; NSPs, Non-structural proteins; RBD, Receptor-binding domain; RDS, Respiratory distress syndrome; RTC, Transcription-replication complex; S protein, Spear-like proteins; SARS, Severe acute respiratory syndrome; SARS-COV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome corona virus 2; UK, United Kingdoms; WBC, White blood cell; WHO, World Health Organization

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 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). 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). 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).

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 (4). Symptomatic treatment strategies are recommended for clinical practice (5). In addition, several drugs with potential therapeutic ability such as dexamethasone and remdesivir have been evaluated for the treatment of the SARS-CoV-2 (4). However, as we mentioned before, no antiviral agents have yet been proved to be beneficial for the SARS-CoV-2 infection (6). The aim of the present review was to give a general overview about this new virus considering essential brief for clinicians.

Virology of SARS-CoV-2

Coronaviruses are enveloped positive-stranded RNA viruses (7). Coronaviridae family (order Nidovirales) has a subfamily called Orthocoronavirinae (8). Orthocoronavirinae include four type of CoVs: Alphacoronavirus (alpha-CoV), Betacoronavirus

(beta-CoV), Deltacoronavirus (delta-CoV), and Gammacoronavirus (gamma-CoV) (8). The SARS-CoV-2 belongs to of Betacoronaviruses (9). These viruses are spherical, oval, or pleomorphic with a diameter of about 60-140 nm (10). SARS-CoV-2's structure consists of genome (RNA), nucleocapsid, membrane protein (M) and the envelope (E) protein (2) (Figure 1).
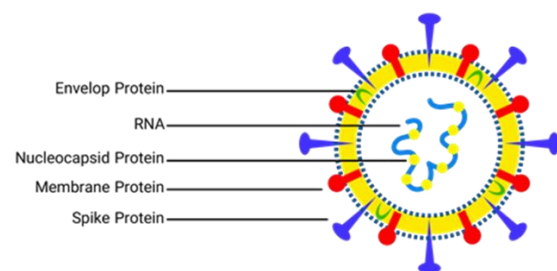

Figure 1. Structure of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

Two-third of viral RNA is finally translated into two polyproteins, pp1a and pp1ab, and 16 non-structural proteins (NSPs), while other parts of the genome encoding subsidiary and structural proteins (11) (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) (11). The SARS-CoV-2 major particles contain genome, spear-like appendages (S protein), non-structural proteins (NSPs), and envelope (10) (Table 1).
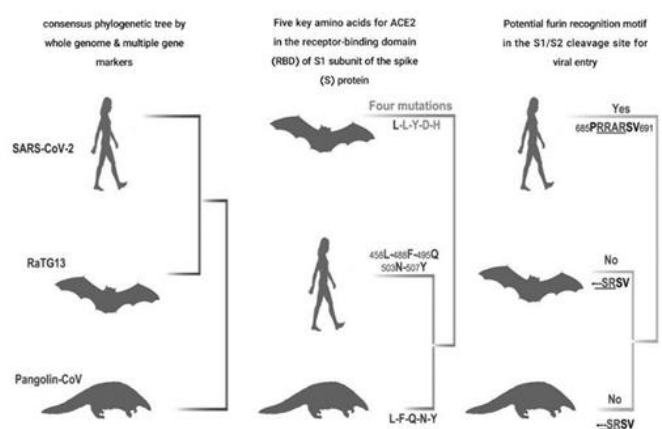

Figure 2. Pathophysiology of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

Viral element	Function	References
Genome (RNA)	Transcripting and translating structural and non-structural proteins	(8)
NSPs	Block the host innate immune response	(99)
Envelope	Promotes viral assembly and release	(8)
Spear-like structure	Guiding virus to host receptors binding to the ACE-2 receptor in the lungs and other tissues	(100, 101)

ACE-2, Angiotensin-Converting Enzyme 2; NSPs, Non-Structural Proteins.

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 (12). 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 (13). The glycoprotein S contains of two portions, S1 and S2 (14). The S1 divided into three domains, A, B and C (15). 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 (11). The S2 causes modulating of fusion between the virus and the host cell (16).

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 (17). These two polyproteins, pp1a and pp1ab, encode non-structured proteins (NSPs) and form the transcription-replication complex (RTC) within a dual-membrane vesicle (18). The RTC then replicates and transcribes a set of nested RNAs that encode accessory and structural proteins (19). 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 (20).

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 (21). 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 (22).

Coronaviruses, first found in the 1960s, have been found in birds and mammals, including in camels, bats and rats (23). SARS-CoV-2 has a single-stranded positive-sense RNA genome, which has 74 to 99% similarity with coronavirus from the pangolin (Manis javanica) (24). 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 (25). Accordingly, the pangolin is considered as one of the probable intermediate hosts between bat and human (24) (Figure 3).
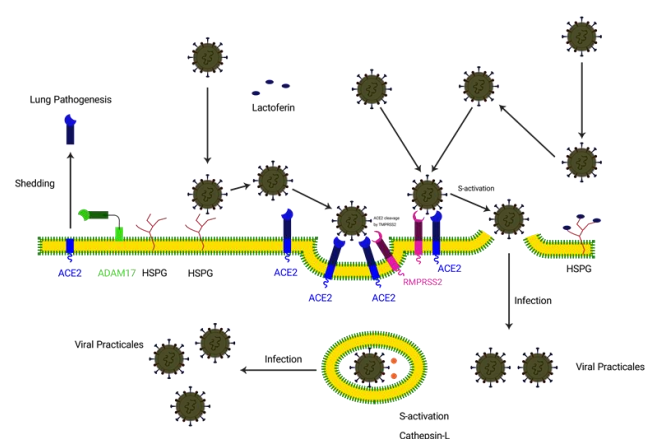

Figure 3. Origin of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

On the other hand, bats have been introduced as the remarkable origin of coronaviruses (26). SARS-CoV-2's genome has 99% similarity with that of horseshoe bat (Rhinolophus sinicus) (Bat-CoVRaTG13) (24). 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 (27). Recently, SARS-CoV-2 has been suggested as a modified coronavirus originated from bat transmitting to humans through zoonotic transmission (28). Other animals were under investigation as the possible intermediate hosts of SARS-CoV-2 like snakes, minks and turtles (29).

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 (30). Different surveys demonstrated that SARS-CoV-2 is an animal virus transmitted to humans through undergoing evolutionary adaptations (31). Analysis of different studies has suggested that SARS-CoV-2 formed by recombining the pangolin-CoV and the bat-CoV-RaTG13-like virus (32). 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 (33).

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 (34). 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 (35).

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 (36). 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 (37). Researches revealed that compared to the initial virus strain, this new class of SARS-CoV-2 has enhanced transmission and infectivity (38). 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 (39).

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 (40). 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 (41). Moreover, origination of SARS-CoV-2 VOC 202012/01 is unclear (40).

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 (42). 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 (43). Furthermore, mutation in this new strain gives ability to stabilize viral bindings with ACE-2 receptor (44) as well as ability to escape from human immune system (45). The severity of infection caused by this new viruses is under investigation (45).

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 (46). 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 (47).

Vertical transmission from mother to infant has been reported (48), but, no intrauterine vertical transmission has been reported for any infant with SARS and MERS in the past (49, 50). 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 (51).

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 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 (52).

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) (47). 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 (47).

Pathophysiology of SARS-CoV-2

SARS-CoV-2 uses ACE-2 receptors to transport itself to human cells (53). 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 (31). 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 (53). Different organs of human body can be affected by SARS-CoV-2 infection (8). 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 (54).

Diagnosis of SARS-CoV-2

SARS-COV-2 is diagnosed based on history taking, radiographic images, and detailed laboratory tests (55). Current diagnostic tools include nucleic acid testing or virus genome detection (55). Samples included nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, and feces (55). The nasopharyngeal swab is the most common example; however, the number of positive cases is less than 50% (55). Repeated diagnostic testing is necessary to increase diagnostic accuracy (55). 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 (55).

Clinical manifestations

The incubation period of COVID-19 has been estimated 1 to 14 days and the average of 8 days (56). 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 (57).

SARS-CoV-2 infection can cause various sorts of clinical manifestations depends on patient situation (Table 2 and Figure 4).
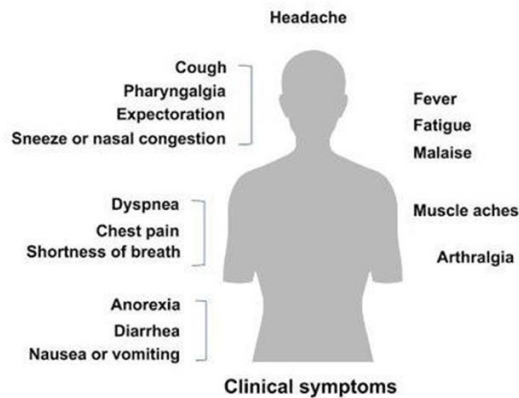

Figure 4. Clinical manifestation of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

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

Clinical manifestations	References
General symptoms:	(102)
Fever	
Cough	
Fatigue	
Sputum production	
Shortness of breath	
Sore throat	
Headache	
Gastrointestinal symptoms:	(103)
Diarrhea	
Nausea	
Vomiting	
Abdominal pain	
Hematemesis	
Hematochezia/melena	
Constipation	
Severe symptoms:	(21)
Acute respiratory distress syndrome	
Septic shock	
Severe metabolic acidosis	
Coagulation dysfunction	
Death	
Neurologic symptoms:	(104)
Headache	
Vision changes	
Altered mental status	
Meningitis signs	
Cranial nerve palsy	
Cardiac signs:	(105)
Abnormalities on echocardiogram	
Dysrhythmia	
Scarce symptoms:	(106)
Rash	
Conjunctivitis	
Strawberry tongue	
Tongue or mouth ulcers	
Tongue enlargement	
Geographical tongue	
Cracked lips	

SARS-CoV-2 in pregnant woman

COVID-19 has been spreading rapidly since 2019, and we have had many cases since then, but our knowledge about the clinical manifestations and treatment of COVID-19 in pregnant woman is very limited (58). Pregnant women are a high-risk group during an infectious disease epidemic (59).The exact infected maternal mortality rate dose not determined yet (60). According to a research on 118 infected pregnant woman in Wuhan, fever and cough are the most common symptom of COVID-19 in pregnancy (presented in %75 of patients) (61). Forty-four percent of patient presented lymphopenia. Ninety-three pecent of patients gave birth by cesarean section most of them was due to concern about COVID-19. The study on six patients was negative for transmission of the virus through breast milk but we are worried about transmission of virus by respiratory secretions and droplets in close contact that infected mother and neonate have during the breast feeding (62). Severe respiratory disease in infected neonate is rare and if it happen, it's unclear that infection occurred in utero or after the birth (63). According to researches on vertical corona virus transition in two small clinical series research there is no evidence that COVID-19 can transfer vertically from mother to fetus (62). Researches show that, delaying in clamping of umbilical cord doesn't increase risk of COVID-19 transition (62).

Although we are not concern about vertical transmission COVID-19 to fetus, but neonate could be infected via respiratory secretion of infected mother, because of that infected mother and neonate should be physically separated. Factors like prematurity and fatal distress should be considered during the separation (64). Maternal illness can cause other clinical findings (respiratory distress, thrombocytopenia, death and etc.) in neonates, for example in one clinical series research approximately 60% of neonates with infected mother have abnormal clinical findings in their early life (62). The rate of preterm birth in an infected mother is much higher than the general population, and most were iatrogenic due to the maternal condition (65). There is no difference between vaginal delivery and caesarean section for infected mothers and decision should be based on the individualized basis (60). There is no evidence that COVID-19 is teratogenic or increases the chance of miscarriage (60). Changes in the immune system allow the allogeneic fetus to grow during pregnancy (63). The immune system of pregnant women is modulated. This modulation may affect how the immune system responds to the virus (66). Pregnancy causes changes in lung functions and a decrease in total lung capacity. These factors make a pregnant women more prone to severe respiratory infections (63). According to research on 118 pregnant woman risk of severity of COVID-19 in pregnant women is lower than normal population but respiratory disease like COVID-19 can exacerbate after giving birth because of pathophysiological changes (67). Current gold standard for detecting SARS-CoV-2 is real-time reverse transcriptase-polymerase chain reaction assay (60). If necessary, a CT scan should be performed on the pregnant woman (60).

Treating a pregnant woman has too many challenges. For example, mechanical ventilation, experimental treatment, prescribing certain drugs and early termination of pregnancy due to maternal condition (60). If a pregnant COVID-19 patient needs to be admitted, the infected mother should be isolated from non-infected patients and then assess vital signs, request laboratory data, and prescribe paracetamol and anticoagulants (60). Evaluate patient's condition, if it's worsens, consider ICU admission, IV fluid therapy, oxygen therapy, empirical antibiotics for pneumonia and invasive ventilation (60). Azithromycin is safe during pregnancy and could be prescribed to breastfeeding mothers (68).

Remdesivir is currently used to treat COVID-19, but our information about its effects on pregnancy is limited, a research on an 86 infected pregnant and postpartum women shows that Remdesivir can be effective and increase rate of recovery (69). Treatment with methylprednisolone is recommended in recent guidelines in non-pregnant patients with moderate acute respiratory distress syndrome (70). A study of 454 non-pregnant women with COVID-19 infection treated with corticosteroids revealed that giving dexamethasone to non-pregnant women significantly reduced mortality, need for mechanical ventilation and oxygen support (70). It is best to administer corticosteroids that have lowest rate of placental transfer and minimal mineralocorticoid effects and highest lung tissue penetration, like Methylprednisolone (70). Numerous studies have shown that giving corticosteroids for preterm labor significantly reduces complications and mortality of neonates by inducing fetal lung maturation (70). Steroid therapy should be given to pregnant women with COVID-19 who need mechanical ventilation or oxygen therapy, or both (70). If glucocorticoids are not required for fetus lung maturation and are prescribed only for the treatment of COVID-19, prescription of methylprednisolone for 10 days is enough. When we want to prescribe corticosteroids for fetal lungs maturation and treatment of COVID-19, it is best to start with a two days course of dexamethasone and then give the patient a 10-days course of prednisolone (70). Patients with COVID-19 infection are at higher risk for thromboembolic events compare to normal population and pregnancy is a hypercoagulable state because of that guidelines recommend that prophylaxis for thromboembolism should be given during the pregnancy until 10 days after giving birth (71).

SARS-CoV-2 in neonates

Infants and neonates are affected by COVID-19 less than adults. Although major passages for infecting neonates like intrauterine or perinatal ways remains unclear and vertical transmission should be examined more, but some surveys demonstrated infection by COVID-19 via vertical transmission and respiratory droplets at the time of exposing newborn contact with mother and operation room personnel (48). Symptoms in infants similar to others like: fever, coughing, sore throat, sneezing, fatigue, gastrointestinal problems like nausea vomiting Diarrhea abdominal pain, the have poor appetite and poor feeding (72).

First line of treatment is oxygen therapy, water and electrolyte maintenance, nutritional support. Newborn with acute respiratory distress must treat with surfactant and nitric oxides and ventilation support. Intravenous immunoglobulin, corticosteroids and for those case who are presented with bacterial superinfection must treat with antibiotics (73).

SARS-CoV-2 in children

Based on study was performed in 2020, the average age of all patients was 7 years and 56.6% of all patients were boys. About 90% of the patients were asymptomatic, mild or moderate symptoms of COVID-19. The average time from sickness onset to recognize were 2days. Only 4.4% of pediatric patients observed by sever disease. All ages children were presented disposed to COVID-19 and there was not expressive sex difference. Despite the fact clinical display of children's COVID-19 cases were chiefly less severe than adult patients. The dispensation of children's COVID-19 cases was different in time and space. Additionally, according to this study strong averment of human to human transmission. Most of infected children were transmitted by their family (74). About sign and symptoms, some surveys have showed that cough, fever, fatigue and breath shortness were the most common between patients and some of pediatric patients detected with digestive symptoms like nausea, vomiting and diarrhea (75). 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. Also increase level of lymphocytes in blood known as severe symptoms in children. Lung imaging also is important to confirm the diagnosis. In some articles reported that symptoms of COVID-19 in children like Kawasaki's disease then heart problems must be considered (74). Patient must hospitalize in isolation negative air pressure room. First line of treatment is supportive care like fluid therapy and electrolyte management, antiviral drugs and respiratory care. Treatment for the patient in ICU include first line of treatment and combination of immunomodulator and anti-viral drugs such as oseltamivir and hydroxychloroquine and based on the patient's situation Antibiotics can be added (76).

Laboratory examinations

Laboratory examinations along with taking history and radiographic analysis are three bases for finding and curing COVID-19 sufferers (77).

Studies show different laboratory finding and we gathered different laboratory findings in Table 3.

Table 3. Laboratory finding(s) in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2)

Laboratory finding(s)	Changes	References
Early stage		
Total WBC	Normal or significantly decreased	(8, 107, 108)
Lymphocyte count	Significantly decreased	(8, 107, 108)
In severe cases		
Neutrophil count	Significantly increased	(47)
D-dimer	Significantly increased	(47)
Blood urea	Significantly increased	(47)
Creatinine level	Significantly increased	(47)
Lymphocyte count	Significantly decreased	(47)
IL-6, -2, -7, and -10	Significantly increased	(11, 21)
TNF-α	Significantly increased	(11)
LDH	Normal or significantly increased	(8, 109)
Muscle enzymes	Normal or significantly increased	(8, 109)
CRP	Normal or significantly increased	(8, 109)
Myocardial enzymes	Normal	(109)
ICU patients		
GCSF	Significantly increased	(21)
IP-10	Significantly increased	(21)
MCP-1	Significantly increased	(21)
MIP-1α	Significantly increased	(21)
TNF-α	Significantly increased	(21)

WBC, White blood cell count; IL, Interleukin; Tumor necrosis factor-α; LDH, Lactate dehydrogenase; CRP, C-reactive protein; GCSF, Granulocyte colony-stimulating factor; IP-10, 10 kDa interferon-induced gamma protein; MCP-1, Monocyte 1; MIP-1α, Macrophage

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 (78).

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 (77). In Table 4, we discussed histopathologic changes in lung tissues after being infected by SARS-CoV-2.

Table 4. Pathological finding(s) in infected lung with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) (110-114)

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

Radiological findings

Radiological findings in this disease are varied. These findings have been presented in Table 5. 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 (47).

Table 5. Radiological finding(s) in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2)

Radiological method	Finding	References
Chest X-ray	Lung consolidation	(115-120)
	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	(107, 118,
	Consolidation	121-123)
	More than two lobes affected	
	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	(124-128)
	Irregular pleura	
	Confluent B-lines	
	Small consolidations	
	Spared areas	
	Air bronchograms	
	Nontranslobar and translobar - consolidation	
	Multifocal B-lines	
	Confluent B-lines	
	Pleural thickening/disruption	

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 (79). 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 (80).

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 (81). 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 (82). 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 (82).

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 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 (83). 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 (81).

Currently, there are four main types of COVID-19 vaccines that are going to large scale clinical trials. In Table 6 clinically approved (passed Phase III) 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.

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 (81).

Table. 6. Latest vaccines for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) that passed phase III of clinical trials before July 2021

Vaccine	Pfizer/ BioNTech	Moderna/ NIH	Oxford/ AstraZeneca	Johnson & Johnson
Type	mRNA	mRNA	Adenoviral vector	Adenoviral vector
Injection time	2	2	2	1
Interval (days)	21-28	28 (up to 42)	8 to 12 weeks	NA
Dosage (mL)	0.3	0.5	0.5	0.5
Injection type	Intra muscular	Intra muscular	Intra muscular	Intra muscular
Injection site	Deltoid muscle	Deltoid muscle	Deltoid muscle	Deltoid muscle
Effectivity (%)	92	94.1	63.09	66.3
Reference	(129)	(87)	(130)	(131)

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-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 (81).

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 (81).

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 (84).

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 (85).

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 (84).

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 (86, 87). Other companies are also developing various types of COVID-19 vaccines (88).

Treatment of SARS-CoV-2

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

Supportive therapies

Symptomatic and supportive therapy is the mainstay of treatment for SARS-CoV-2 cases (89). Supportive therapy includes different manners which are given to patients with SARS-CoV-2 infection for reaching different curative targets (Table 7). In addition, the plasma of recovering patients with SARS-CoV-2 may be useful for SARS-CoV-2 infection (90). New therapeutic approaches are developing including gene therapy (91), exosome therapy (92) and stem cell therapy (93) of COVID-19.

Table 7. Supportive therapy in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2)

Supportive therapy	Target	References
Oxygen therapy	Control the level of O_2 in body	(89)
Maintenance of electrolyte and water balance	Prevent exacerbation of pulmonary edema and decreased oxygen delivery	(89)
Control of basal acid-levels	NA	(89)
Zinc	May have antiviral activity	(132)
Azithromycin	Effective in patients with severe respiratory tract infections suffering from viral infection	(133, 134)
Vitamin C (ascorbic-acid)	Enhancing the host immunity	(133, 135)
Corticosteroids	Preventing an extended cytokine response accelerate resolution of pulmonary and systemic inflammation in pneumonia	(135)
NSAIDs	May exhibit antiviral activity against SARS-CoV	(135)
Aspirin	Inhibiting virus replication Anti-platelet aggregation (anticoagulant action) Anti-inflammatory Anti-lung injury	(135)

NA, not applicable; NSAIDs, Non-steroidal anti-inflammatory drugs; SARS-CoV, Severe Acute Respiratory Syndrome Corona Virus.

Antiviral therapy

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 (94). Based on estimates, human society should wait at least one year to have an available vaccine against COVID-19 (95). Even after preparing an efficient vaccine, human trials will be a major challenge for scientists (Table 8). Now, COVID-19 is being cured with using broad-spectrum antiviral medicines counting remdesivir and Chinese herbal medicine (96, 97).

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 (98). 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. For better managing of patients, some valuable data have been collected in Figure 5.

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

Drug	Mechanism of action	Target	FDA	References
Penciclovir/ Acyclovir	Nucleoside analog Interference with viral reproduction	HSV VZV	Approved	(136)
Nitazoxanide	Anti-protozoal agent Modulation of survival and proliferation of viruses	A vast range of viruses	Approved	(137-139)
Favipiravir	RNA dependent RNA polymerase inhibitor Cease viral reproduction	Ebola Influenza type A SARS-CoV-2	Investigation	(140-144)
Lopinavir/ Ritonavir	Protease inhibitors Cause to Produce inactive viruses	HIV/ AIDS SARS MERS	Approved	(145-147)
Darunavir/ Umifenovir	Stop virus from merging with target cells	Influenza viruses	Approved	(141, 148)
Ganciclovir	Nucleoside analog Inhibitor of the herpes family	CMV HIV	Approved	(149)
Nafamostat	Synthetic serine protease inhibitor Stop virus from merging with target cells	Influenza viruses MERS Ebola	Investigation	(150, 151)
Remdesivir	Nucleotide analogue Interference after virus entry	Ebola SARS MERS	Investigation	(152-154)
Glecaprevir	Main protease inhibitor	SARS-CoV-2	Approved	(155)
Maraviroc	Main protease inhibitor	SARS-CoV-2	Approved	(155)
IFN–I	Prevent the viral egress or membrane fusion Interfere the replication of virus, indirectly	MERS-CoV	Investigation	(156)
Oseltamivir	Neuraminidase inhibitor Inhibition of viral neuraminidase activity germination Prevention of host cell Stop viral replication	Influenza viruses A	Approved	(157, 158)
Ribavirin	Synthetic guanosine nucleoside	HCV SARS	Approved	(123, 159)
	Disrupt producing viral mRNA	MERS		
Chloroquine	Enhance the immune system Increase of autophagy suppressors	Malaria Autoimmune diseases	Approved	(160-163)
Hydroxy-chloroquine	Enhancing the immune system Preventing the viral entry into the cells	Malaria Autoimmune diseases	Approved	(164)

AIDS, Acquired immunodeficiency syndrome; CMV, Cytomegalovirus; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; HSV, Herpes simplex virus; MERS-CoV, Middle East respiratory syndrome coronavirus; MERS, Middle East respiratory syndrome; SARS, Severe acute respiratory syndrome; IFN-1, Type 1 interferon; VZV, Varicella zoster virus
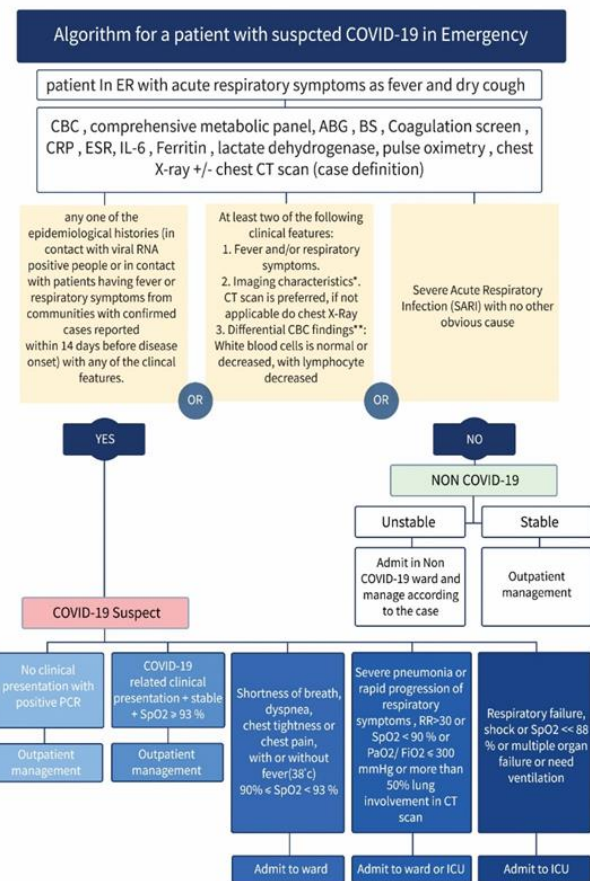

Figure 5. Management of patient with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection.

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.

Declarations

Conflicts of interest
Author Mohammad Amin Behzadi was employed by the company Auro Vaccines LLC. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions
A.Z., M.A.B., S.A., I.N., and A.T. conceived and designed the format of the manuscript. A.Z., S.F.S., A.M., N.P., Z.H., N.B., and A.K. drafted and edited the manuscript. M.A.B., S.A. and A.T. reviewed the manuscript. All authors contributed to the critical reading and discussion of the manuscript. All authors have read and agreed to the published version of the manuscript.

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