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REVIEW

COVID-19 (Coronavirus Disease 2019): A New Coronavirus Disease

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Abstract: Coronavirus disease 2019 (COVID-19) is a type of viral pneumonia with an uncommon outbreak in Wuhan, China, in December 2019, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). SARS-CoV-2 is extremely contagious and has resulted in a fast pandemic of COVID-19. Currently, COVID-19 is on the rise around the world, and it poses a severe threat to public health around the world. This review provides an overview about the COVID-19 virus to increase public awareness and understanding of the virus and its consequences in terms of history, epidemiology, structure, genome, clinical symptoms, diagnosis, prevention, and treatment.

Keywords: novel coronavirus, coronavirus disease 2019, COVID-19, SARS-CoV-2

History

The human coronavirus was first diagnosed in 1965 by Tyrrell and Bynoe from the respiratory tract sample of an adult with a common cold cultured on human embryonic trachea.[1] Naming the virus is based on its crown-like appearance on its surface.[2] Coronaviruses (CoVs) are a large family of viruses belonging to the Nidovirales order, which includes Coronaviridae, Arteriviridae, and Roniviridae families.[3] Coronavirus contains an RNA genome and belongs to the Coronaviridae family.[4] This virus is further subdivided into four groups, ie, the α, β, γ, and δ coronaviruses.[5] α- and β-coronavirus can infect mammals, while γ- and δ- coronavirus tend to infect birds.[6] Coronavirus in humans causes a range of disorders, from mild respiratory tract infections, such as the common cold to lethal infections, such as the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and Coronavirus disease 2019 (COVID-19). The coronavirus first appeared in the form of severe acute respiratory syndrome coronavirus (SARS-CoV) in Guangdong province, China, in 2002[7] followed by Middle East respiratory syndrome coronavirus (MERS-CoV) isolated from the sputum of a 60-year-old man who presented symptoms of acute pneumonia and subsequent renal failure in Saudi Arabia in 2012.[8] In December 2019, a β-coronavirus was discovered in Wuhan, China. The World Health Organization (WHO) has named the new disease as Coronavirus disease 2019 (COVID-19), and Coronavirus Study Group (CSG) of the International Committee has named it as SARS-CoV-2.[9,10] Based on the results of sequencing and evolutionary analysis of the viral genome, bats appear to be responsible for transmitting the virus to humans[11] (Figure 1).

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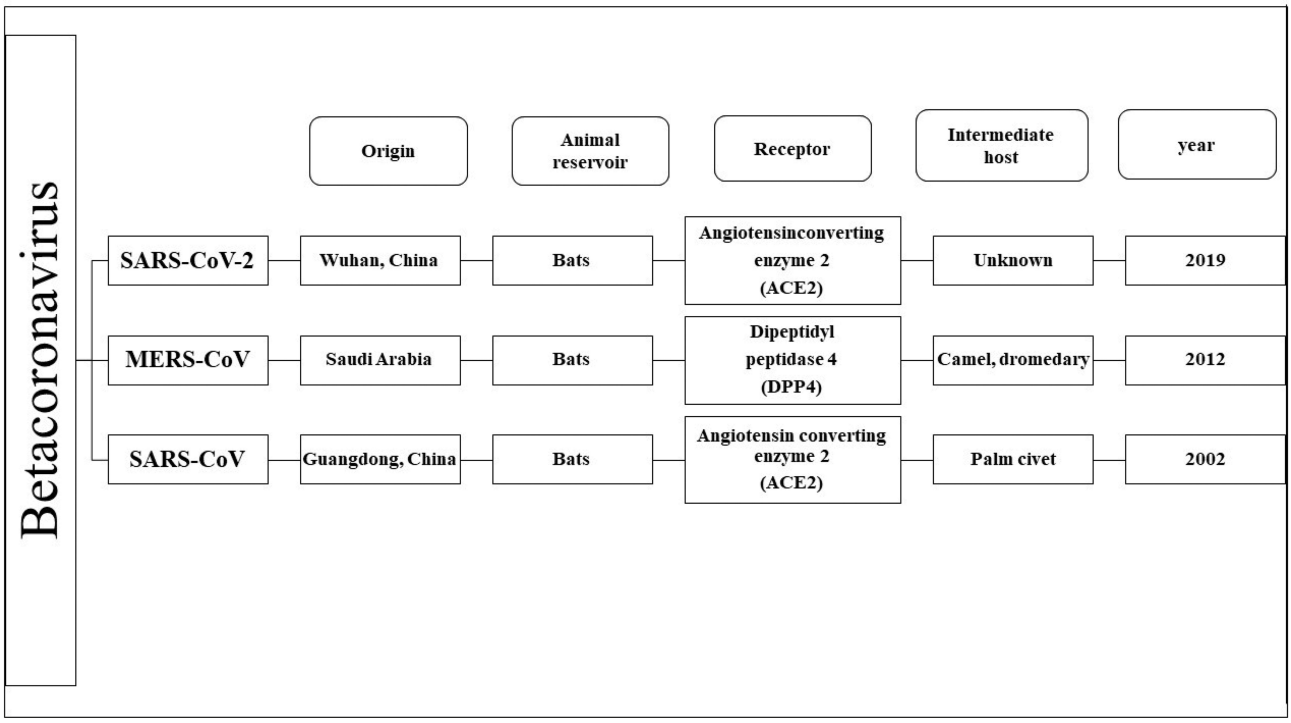

Figure 1 History of harmful human coronaviruses.

Virion Structure and Structural Proteins

Coronavirus is a medium-sized spherical RNA virus, with a diameter of about 80–160 nm, which can be observed using an electron microscope.[12] This virus has the largest viral RNA (30 kb in length), which is single-stranded, positive in sense, and polyadenylated.[13] The coronavirus genome encodes five protein structures, including the spike (S), membrane (M), envelope (E) glycoproteins, hemagglutinin esterase (HE), and nucleocapsid (N) (Figure 2). N, M, S and E proteins are present in all virions, while, HE is only present in some β-coronaviruses.[14] The S glycoproteins outside of the virions are homotrimers with crown-like structures, accounting for the name of the virus.[15] These homotrimeric glycoproteins belong to class 1 fusion proteins[16] that mediate binding host cell receptors.[17] S protein of betacoronavirus (β-CoV) is critical for cross-species transmission as it mediates virus-receptor recognition and viral pathogenesis. The receptor-binding domain is located on the N-terminal of S protein and is necessary for the penetration of β-CoV into the host cells. Moreover, cross-species transmission and severity of the infection are affected via the mutations in CoV RBD.[18] M glycoproteins have three transmembrane regions[19] leading to the fusion of the virion into the cell and the emergence of antigenic protein that is involved in shaping the viral structure.[20] The N protein is the only protein present in nucleocapsid,[21] which contributes to the formation of a complex structure by binding genomic RNA.[22] E glycoproteins are small proteins comprised of about 76 to 109 amino acids.[23] These glycoproteins play an essential role in the assembly and morphogenesis of virions within the cell.[23] E glycoproteins can act as ion channels which are considered necessary for pathogenesis.[24] The HE acts as a hemagglutinin, binds sialic acids on surface glycoproteins, and has an acetyl-esterase activity.[25] Apparently, these activities enhance S protein-mediated cell entry and virus extension through the mucosa.[26]

Using genomic analysis of coronavirus 2019 isolates from patients COVID-19 in China and the USA, Malik et al[27] reported that the length of the S protein sequence in this new virus was different from that of other β-coronaviruses. The major differences of S protein in novel Coronavirus (nCoV) compared with SARS-CoV include three short insertions at the N-terminal region, and four changes in the receptor-binding motif within the receptor-binding domain.[28] Recent studies have reported that the binding capacity of n-CoV S protein with human angiotensin-converting enzyme 2 (ACE2) is as efficient as SARS-CoV, which further raises the possibility of human-to-human transmission.[27,28]

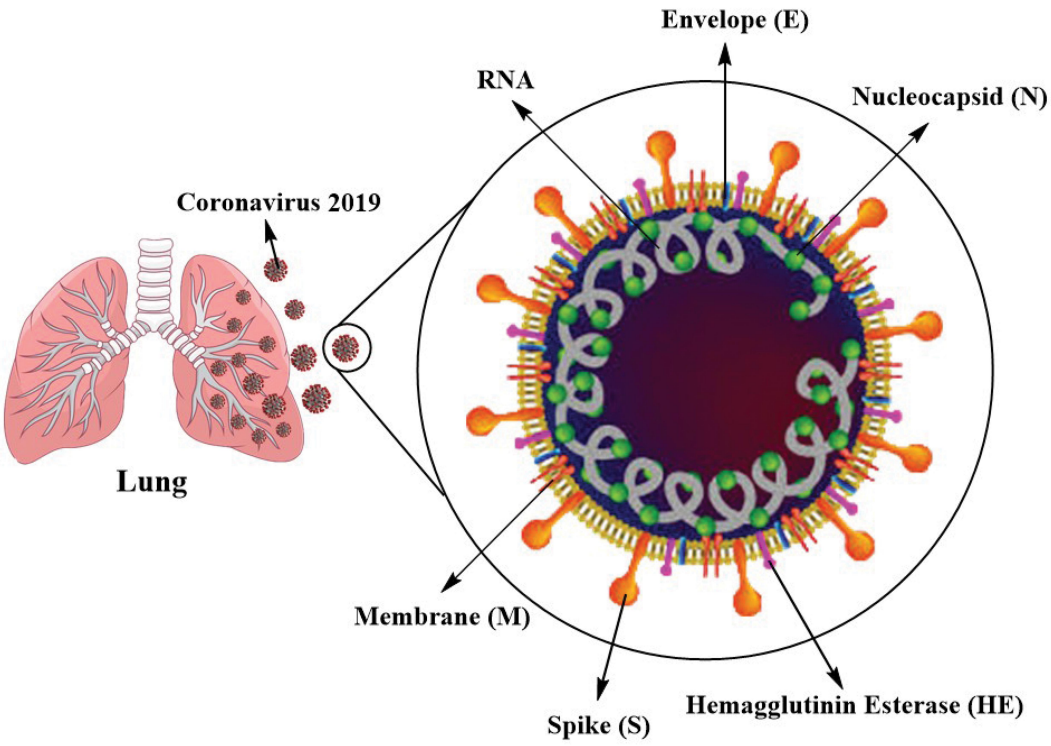

Figure 2 SARS-CoV-2 virus structure.

Epidemiology

Coronaviruses are disseminated widely among humans, other mammals, and birds, further causing acute respiratory diseases.[29] The epidemics of unknown acute respiratory tract infection at the first time on December 29th 2019, in Wuhan, China, was very likely associated with a seafood market.[30,31] Many studies have reported that bats may be the primary reservoirs of the disease.[29,31-33] Currently, COVID-19 is a pandemic that according to the latest WHO report, until July 08, 2020, a total of 11,635,939 cases were infected in more than 216 countries around the world, and 539,026 cases died.[34]

Respiratory droplets are the major transmission route of this disease,[31] and transmission among people occurs through direct (cough, sneeze, and droplet inhalation) and indirect (contact with oral, nasal, and eye mucous membranes) routes.[35] Human-to-human transmission of this infection occurs mostly among family members, including relatives and friends who are in close contact with patients or carriers.[36,37] Furthermore, occupational exposure to health-care workers is another concern.[38]

Older people with underlying diseases such as asthma, heart failure, diabetes, and Immunodeficiency diseases are at a higher risk of a more severe COVID-19 disease.[39]

New evidence demonstrated that the SARS-CoV-2 may also be an enteric virus that can spread through the fecal-oral route. According to initial papers from Wuhan, 2–10% of patients with COVID-19 showed gastrointestinal (GI) symptoms, such as nausea, abdominal pain, vomiting, and diarrhea. A current meta-analysis article on >4000 East Asian COVID-19 cases illustrated that up to 20% of cases showed GI signs, and viral RNA was detected in the stool of approximately 50% of cases.[40]

Dental patients and professionals are at a high risk of contracting COVID-19 infection due to exposure to blood and saliva as well as face-to-face interaction, and handling of sharp tools.[41]

Smoking is harmful to the immune system and causes smokers to be more vulnerable to infectious diseases.[42] Verdavas et al[43] reported that the smokers are 1.4 times more at risk of showing severe signs of COVID-19, and are almost 2.4 times more likely to be admitted to an ICU, require mechanical ventilation or die compared with non-smokers.

Diverse maternal physiological adaptations in the immune (immunosuppression) and cardiorespiratory (such as diaphragm elevation and physiologic anemia) systems are observed in pregnant women leading to poor outcomes of viral respiratory infections.[44] It is unknown whether the

COVID-19 can be transferred by breast milk, but it is clear that an infected mother can transfer the COVID-19 by respiratory droplets to her child.[45,46] Wang et al[47] reported a neonatal case with COVID-19 36 hours after birth whose pharyngeal swabs tested positive with real-time reverse-transcription polymerase chain reaction assay in China. However, whether this was a vertical transmission case from mother to neonate remains to be confirmed[47] (Figure 3).

Clinical Symptoms and Diagnosis

Clinical signs of COVID-19 disease appear after an incubation period of about 5.2 days[48] which takes about 6–41 days (average of 14 days) until death depending on the age of the patient or the patient's immune status.[49,50] Generally, the clinical symptoms of COVID-19 are nonspecific and common symptoms include fever, cough, and fatigue.[51] Fever is considered as the dominant symptom, however, it is not always the initial symptom of infection.[52] Other symptoms include headache, sputum production, diarrhoea, dyspnoea, and lymphopenia.[53,54] At the beginning, infection rapidly advances to organs resulting in symptoms such as acute respiratory distress syndrome (ARDS), shock, acute kidney failure, acute cardiac failure, and even death in severe cases. Patients may demonstrate normal or lowered white blood cell counts, lymphopenia, thrombocytopenia with greater thromboplastin activation time, and raised C-reactive protein level[55] (Table 1).

Fever, reduction in lymphocytes and white blood cells (WBC), new pulmonary infiltrates on chest radiography, and no improvement in symptoms after three days of antibiotics treatment are common ways of diagnosing patients with COVID-19 infection.[48] For patients suspected with COVID-

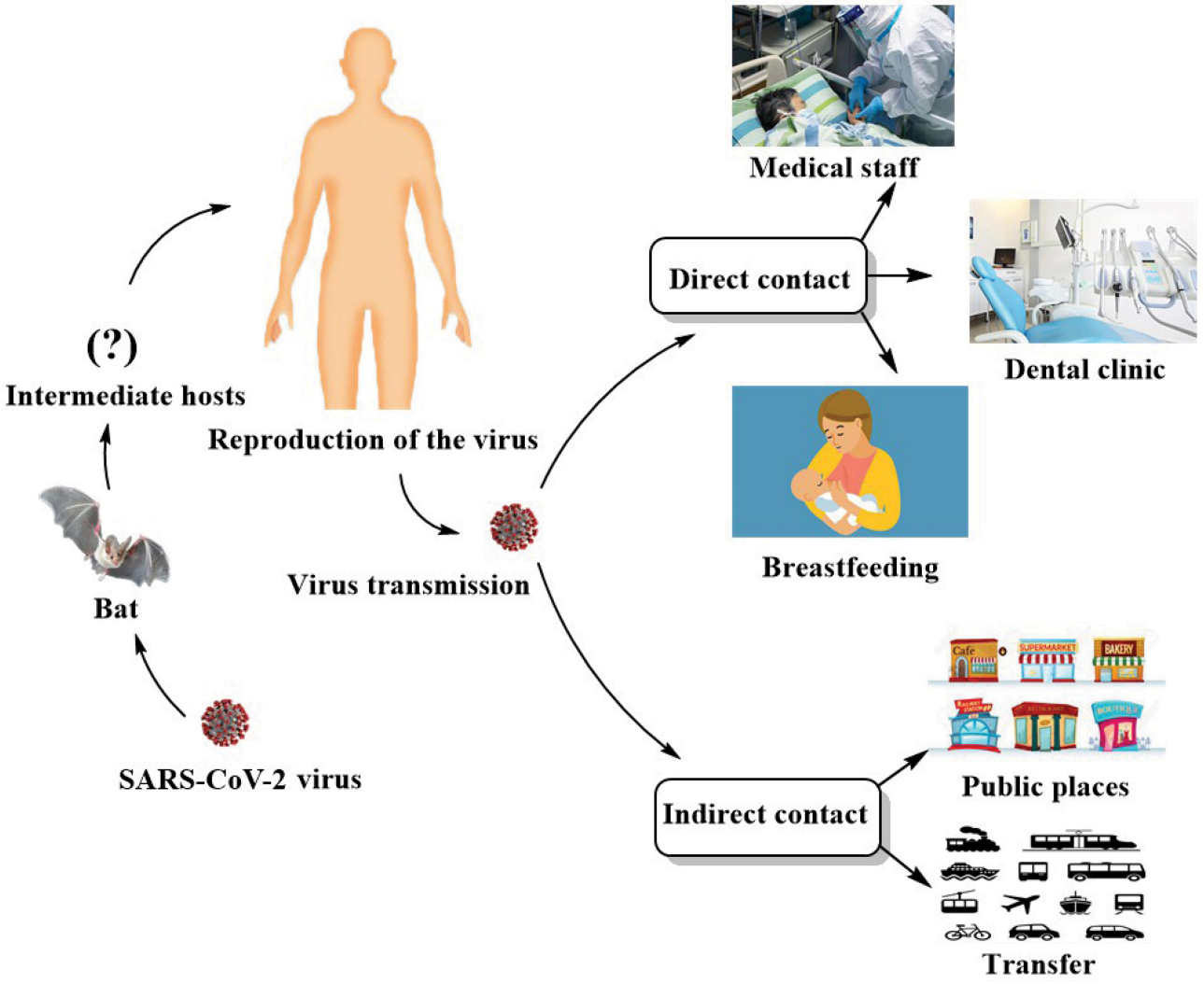

Figure 3 SARS-CoV-2 virus transmission.

Table 1 Difference Between Clinical Symptoms of the Common Cold and Flu Diseases with COVID-19

Symptoms	COVID-19	FLU	COLD
Cough	Common (usually dry and severe)	Common (usually dry)	Mild
Fever	Common	Common	Rare
Sneezing	Rare	Rare	Common
Diarrhea	Occasional	Occasional	No
Headache	Occasional	Common	Rare
Shortness of Breath	With mild/moderate infection	Rare	NO

19, real-time PCR on nasopharyngeal and/or pharyngeal swabs, sputum, and secretions of the lower respiratory tract samples has been suggested for the detection of COVID-19 DNA.[56,57]

Testing for antibody response to infection is usually based on measuring immunoglobulin M (IgM) and immunoglobulin G (IgG). In serological studies immunoglobulin A (IgA) and total antibodies may also be measured. Most tests evaluate both IgM and IgG. IgM usually increases rapidly with infection and decreases soon after the clearance of infection. IgG is thought to increase more slowly and may even remain stable thereby representing longer-term immunity. Antibody assays are likely to be available in laboratories in the form of enzyme-linked immunosorbent assay (ELISA), or point-of-care tests by a disposable device using one or two blood drops from thumb prick upon a testing strip, which takes about 10 minutes.[58]

The sensitivity of chest radiography or chest X-ray (CXR) in the primary stages can be low as ground glass lesions are not observed, however, in severe cases, bilateral multifocal consolidation and even advancement to the white lung can be seen.[59]

Recent chest CT scan findings of COVID-19 pneumonia show as multifocal unilateral or bilateral ground glass opacity (GGO) or mixed GGO and consolidation mostly peripherally located. GGO is generally seen in the primary days and advance to the consolidation in the following days. Generally, lymphadenopathy is not seen, and pleural effusion is rare and mild. Generally, a normal chest CT scan may be useful in ruling out COVID-19.[60,61]

In the complete blood count-differential (CBC-Diff) test shows leukopenia or lymphocytopenia less than normal rates based on age (an absolute lymphocyte count <3000/microliter in infants (1 month to 12 months), <2000/microliters in Childs 1–5 years of age and <1100/microliters are older than 5 years).[62,63]

Among four structural proteins (S, M, E, and N) in the coronavirus family, S and M proteins seem to contain antigenic sites for the development of serological tests for COVID-19 detection. Serological tests have focused on detecting serum antibodies for S proteins of the coronavirus spike. S proteins are determined with the S gene and are functionally divided into S1 and S2 subunits. Another protein that seems to be a significant antigenic site for the development of serological tests for COVID-19 detection is the N protein, which is a structural constituent of the helical nucleocapsid.[64]

The commonly used nucleic acid diagnosis technique for this disease is real-time semi-quantitative polymerase chain reaction (RT-qPCR). The authoritative identification approach for SARS-CoV-2 is virus blood culture and high-throughput whole genome sequencing. Nonetheless, the use of high-throughput sequencing technology in clinical diagnosis is limited due to high price and equipment dependency.[65] Thus, RT-qPCR is the most common and efficient method for detecting pathogenic viruses in respiratory secretions and blood.[66,67]

Treatment and Prevention

To date, there have been no specific antiviral drugs or vaccines to combat COVID-19, and treatment is merely provided as supportive and palliative approaches, as well as several antiviral and anti-inflammatory drugs care at the clinic. However, WHO has announced that the COVID-19 vaccine is expected to be launched in the next 18 months.[68] Supportive therapy for patients with coronavirus is one of the most important principles along with other treatments for patient management, including oxygen therapy, fluid retention, and the use of antibiotics to avoid secondary bacterial infections.[65] The use of antiviral drugs is another treatment for COVID-19. In one study, remdesivir has been used to treat COVID-19 patients and favorable results have been achieved in vitro.[69] It is also possible that antiviral agents such as ribavirin, galidesivir, and favipiravir, which are nucleoside analogues, could be clinically used to treat coronaviruses.[70,71] EIDD-2801 (β -D-N4-hydroxycytidine-5′-isopropyl ester) can be considered as a drug for the treatment of COVID-19 infection due to its high efficacy properties against respiratory infections such as seasonal influenza virus and pandemic influenza.[72] Arbidol is another antiviral drug used against some viruses such as influenza A and B, hepatitis C and SARS-CoV viruses. For

this reason, in a study, Arbidol and Kaletra (lopinavir/ritonavir) were used against COVID-19, and according to the results, Arbidol had a better therapeutic effect and was able to reduce the prevalence of severe cases. Oral administration of ritonavir, lopinavir, oseltamivir, and intravenous administration of ganciclovir for 3–14 days were also helpful in 75 patients.[73] In addition, chloroquine has been shown to have an immune-suppressive activity and is effective in vitro and in the treatment of patients with COVID-19.[74,75] In Chinese medicine, it has been suggested that the use of a decoction such as Shuanghuanglian oral liquid (Sol) can inhibit COVID-19 by lung detoxification and clearance.[76] Sol contains active ingredients such as forsythin, baicalin, and chlorogenic acid with inhibitory properties against a variety of viruses and bacteria by reducing inflammatory responses.[77,78] Natural herbal medicine Lianhuaqingwen capsule has also antiviral properties, regulates immune responses, and reduces inflammatory factors in the early stages of infection.[79] Natural compounds such as flavonoids, Glycyrrhizin, diarylheptanoids, and cinanserin, which inhibit main coronavirus enzymes involved in replication, can be considered as attractive options for COVID-19 treatment.[80,81] Immunoenhancement therapy is one of the treatment methods that employs recombinant interferon, thymosin alpha-1 (Ta1), Thymopentin, Levamisole, Cyclosporine A, and intravenous immunoglobulin against viral infections.[82] Previous studies have shown that recombinant interferon-alpha affects MERS, suggesting its possible effectiveness against COVID-19.[83] Intravenous immunoglobulin is an immunomodulator used for all ages that enhances the production of anti-inflammatory mediators and inhibits the production of pro-inflammatory cytokines.[84] Ta1 is also an immune system booster that has been effectively used in SARS outbreaks.[85] Intravenous immunoglobulin and Ta1 may be considered as an effective treatment for COVID-19.[82] Combining thalidomide (an immunomodulatory and anti-inflammatory agent) with a low-dose of glucocorticoids in the treatment of COVID-19 pneumonia showed immune-regulating effects, inhibited inflammatory cytokines, relieved vomiting, and reduced anxiety, oxygen consumption, as well as lung exudation.[86] In the lack of specific vaccines and antiviral drugs for COVID-19, convalescent plasma therapy is an appropriate way to reduce the severe form of the disease.[87] In previous studies, plasma therapy against SARS and influenza resulted in reduced mortality and shorter hospital stay.[88,89] Most patients recovered from COVID-19 produce specific antibodies against the virus that can limit COVID-19 reinfection. Therefore, plasma of recovered patients can be considered as a potential treatment option.[82] Another treatment option is extracorporeal blood purification, which can be used to treat severe n-CoV pneumonia cases,[90] which can eliminate cytokine storms as well as inflammatory agents, and maintain acid-base balance in patients with COVID-19.[91] The recombinant monoclonal antibody is another important treatment option against respiratory viruses such as SARS-CoV. Various recombinant monoclonal antibodies, including CR3022, m396, and CR3014, have been used against human coronavirus that can be considered as therapeutic candidates for SARS-CoV-2 infection.[65] The WHO recommends that steroids and methylprednisolone can be used for patients with COVID-19 only in the acute stage of respiratory distress syndrome as they prolong viral shedding in patients.[92]

Although there is no vaccine available yet, COVID-19 is an RNA virus, and present RNA virus vaccines (measles, polio, influenza, and Japanese encephalitis virus) can offer a promising option to prevent person-to-person transmission, immunization of health-care workers and non-infected people.[68] The use of decoctions for one week (not long) is one of the principles of COVID-19 prevention by fortifying the body's strength.[93] Previous studies have suggested the use of vitamins such as vitamins A, B, C, D, and E and the use of Omega-3 polyunsaturated fatty acids, Zinc, Selenium, and iron supplementation as a good solution to prevent and control low respiratory tract infections such coronavirus infection, especially in people with underlying conditions (diabetes, high blood pressure, tumors, and heart disease) as they have low systemic immunity.[94,95] As a result, strengthening the immune system and creating individual resistance is very important to combat COVID-19 and the most important approach for boosting personal immunity include maintaining personal health, following a healthy lifestyle, and maintaining adequate food intake.[96] Also, taking protective measures such as improving personal hygiene, washing hands frequently, keeping a distance from others (at least one meter), avoiding unnecessary gatherings, wearing masks, getting enough rest, covering the face when sneezing and coughing, avoiding touching the face with contaminated hands and proper ventilation can prevent COVID-19.[97]

Conclusion

According to the pandemic, COVID-19 is a life-threatening infectious disease, especially in immunocompromised individuals. The main symptoms of this

respiratory disease are fever, cough and fatigue. The primary source of these infections is not yet known, but the disease can be transmitted through droplets and close contact. After several months of the spread of this dangerous virus, there are still no specific drugs and definitive treatments for the virus. Definitive and timely diagnosis of this disease and isolating patients can be helpful in treating patients and preventing the spread of the disease. The onset and progression of COVID-19 depend on the interaction between the virus and the immune system. Therefore, the best way to control this disease is disruption of the transmission route, using decoction and vitamins to strengthen the immune system and using drugs to control the progression of the disease. Following recommendations of WHO should be a priority for everyone.

Disclosure

The authors report no conflicts of interest in this work.

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