DERLEME / *REVIEW*

Past to Present, Epidemiology of SARS-CoV-2 Infection and Ways of Treatment: A Review

Geçmişten Bugüne, SARS-CoV-2 Enfeksiyonun Epidemiyolojisi ve Tedavi Yolları: Derleme

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ABSTRACT

The rapidly spreading COVID-19 pandemic, which has spread worldwide, emerged at the end of 2019 in Wuhan, Hubei province of China. It has been declared a pandemic by the World Health Organization as of March 12, 2020. The SARS-CoV-2 virus, which caused millions of people to be infected and killed many people worldwide, is a severe public health problem. The average incubation period is 4–5 days (0–14 days). The most common symptoms are fever, dry cough, joint pains, headache, and shortness of breath. The disease can show severe and mortal effects in people with advanced age and different treatments. The disease diagnosis is made by molecular analysis of respiratory samples of suspected cases using special primers. In addition to supportive vitamin and protein support in treatment, specific vaccines are produced, the number of which increases day by day. The absence of close contact, such as handshaking and hugging, and the isolation of possible patients are among the most effective methods to prevent the disease's spread. In addition to personal protective equipment such as masks and gloves, continuous cleaning is essential in the fight against the epidemic.

This study looks at the COVID-19 pandemic from a general perspective, especially with the current advances in vaccines, and evaluates the past pandemic processes worldwide. It is to make inferences by considering the impact of COVID-19 on the world and Turkey.

Key words: *COVID-19; coronavirus; vaccines; pandemics; viruses*

ÖZET

Tüm dünyaya hızla yayılan COVID-19 pandemisi 2019'un sonunda Çin'in Hubei eyaleti Wuhan şehrinde ortaya çıkmıştır. 12 Mart 2020 itibariyle Dünya Sağlık Örgütü tarafından pandemi olarak ilan edilmiştir. Tüm dünyada milyonlarca insanın enfekte olmasına ve çok sayıda kişinin yaşamını kaybetmesine neden olan SARS-CoV-2 virüsü halen daha ciddi bir halk sağlığı problemi olarak etkisini sürdürmektedir. Virüsün yarasa kaynaklı olduğu düşünülmektedir. İnkübasyon süresi ortalaması 4–5 gün (0–14 gün) olarak gösterilmiştir. En yaygın semptomları ateş, kuru öksürük, eklem ağrıları, baş ağrısı ve nefes darlığıdır. Hastalık ileri yaş ve farklı hastalık tedavisi gören kişilerde şiddetli ve mortal etkilerde gösterebilmektedir. Hastalığın teşhisi, şüpheli vakaların solunum yollarından alınan örneklerin özel primerler kullanılarak moleküler analizlerinin yapılmasıyla olur. Temelde tedavide destekleyici vitamin ve protein desteğinin yanında sayıları günden güne artış gösteren spesifik aşılar da üretilmektedir. İnsanların birbirleriyle tokalaşması ve sarılması gibi yakın temasların olmaması ve muhtemel hastaların izolasyonu, hastalığın yayılmasını engellemede en etkin yöntemlerden birisidir. Bulaştan korunmak için maske ve eldiven gibi kişisel koruyucu ekipmanların yanında sürekli bir şekilde temizlik salgın ile mücadelede oldukça büyük öneme sahiptir.

Yapılan bu çalışma; özellikle aşılarda yapılan güncel ilerlemeler ile, COVID-19 pandemisine genel bir perspektifte bakmak ve geçmişte dünyada yaşanan pandemi süreçlerini değerlendirmektir. COVID-19'un dünyada ve Türkiye'de etkisini de dikkate alarak, çıkarımlarda bulunmaktır.

Anahtar kelimeler: *COVID-19; coronavirüs; aşılar; pandemi; virüsler*

Introduction

Although viruses are not cells, they have a nucleic acid genome that encodes functions necessary for the formation and replication of an extracellular form called the virion, which allows the virus to spread from one host cell to another. They are non-living pathogenic agents that live only in the cells of another organism. They are in a structure that is several times smaller than bacteria. Viruses are made up of a protein coat. They contain DNA or RNA as genetic material within this sheath (capsid)[1]. They need a host organism to reproduce. As hosts, they can also infect human cells. The infected adult virus is called a virion and all viruses synthesize their capsid proteins[2]. After viruses infect

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the cell, they inactivate the cell and multiply rapidly by spreading to other cells. Viruses are destroyed in a few hours on non-living surfaces or cells. Antibiotics do not affect viruses. Antiviral drugs are used instead of antibiotics. The most important step in preventing the infection of viruses in the cell is to be vaccinated.

Throughout history, there have been many epidemics caused by viruses. These diseases have affected people negatively. These diseases have been declared a pandemic because they spread in certain geographies. Plague disease, which is called the Black Death, is a disease that started in Central Asia in 1347 and spread to China. It caused the death of 12.5 million people in total[3].

HIV (human immunodeficiency virus), which caused 36 million deaths in 1981, suppresses the immune system of people and reveals the presence of AIDS[4].

The H1N1 virus, which is called the Spanish flu, which surrounds the whole world and causes repercussions with the frequent death of even healthy young people, has caused the death of millions of people[5].

Cholera, the first case of which was detected in 1817 and seen in approximately 2,260,389 patients, is a disease caused by *Vibrio cholerae*, which is transmitted by stale food or water and causes diarrhea in people. These cases resulted in 45,543 human deaths[6].

Typhoid is a disease that causes infection within 7–15 days, transmitted from wastewater caused by *Salmonella typhi*. It is transmitted from person to person with the help of vectors such as lice and fleas. Worldwide, approximately 20 million people suffer from typhoid every year. One out of every 100 people these patients results in death[7].

Ebola, a disease that was first detected in 1976 and lasted until 2014, is the longest-lasting virotic disease. By 2014, more than 1000 people, most of whom were healthcare workers, had died[8]. It was reported that the virus case fatality rate, which increased again on March 21, 2014, was at the level of 59% and in May 2014, the case fatality rate increased to 64%[9]. It has effects such as nausea, vascular rupture, abdominal pain, and bleeding in the gums[10].

Smallpox is the deadliest disease ever. It has continued throughout history. Even the scars on the skin of mummies are reported to be smallpox. It is a disease in which half a million people die today. With the discovery of the vaccine by Dr. Edward Jenner in 1976, humans gained immunity, and deaths decreased[11].

Sars 2003 is a pneumonia-causing disease that originated in southern China. Sars 2003 symptoms are fever and difficulty breathing. In 2003, it spread to other countries and increased its influence[12]. This disease, which can be transmitted to individuals by hanging in the air or by contact, can spread collectively. The World Health Organization announced on March 13, 2003, that it was a global epidemic[12]. In 2003, 8437 cases were recorded and 823 people died.

Influenza A H1N5 is a panzootic disease that can be transmitted from poultry to humans. Bird flu, which poses a great danger to the health of animals and humans, has been accepted as a pandemic[13]. In addition, the infected virus that infects the human respiratory system can cause death[14].

Influenza A H1N1, the causative agent of which is from the Orthomyxoviridae family, emerged in the United States in the spring of 2009 and spread to many regions within a month. It is the most mutated type of influenza among other influenza viruses. This virus, which causes a total of 94,512 cases and 429 deaths in the world, shows the symptoms of headache, sore throat, cough, and runny nose[15].

Mers 2012, known as coronavirus, MERS-CoV is a zoonotic disease that has been proven to exist in the Arabian peninsula[16]. This virus, which caused the death of 858 people in 27 countries in total, can circulate in molecular form in the air and can be transmitted by contact with the surfaces of goods[17].

Influenza A H7N9, which is generally determined to occur after close and long-term contact with bird species, was first detected in March 2013 in China. An (H7N9) virus of avian origin is a serious fatal disease[18].

COVID-19 Epidemiology

In the city of Wuhan, located in the Hubei region of China, cases of pneumonia whose etiology could not be fully determined were recorded by the local representative of the World Health Organization on 31 December 2019. In January 2020, Chinese scientists analyzed the genome of the virus and named it 2019-nCoV. Later, the virus name was changed and given the official name SARS-CoV2. On January 7, 2019, cases were reported to be caused by a new type of coronavirus with no previous evidence that it could infect humans[19]. Research on the disease agent has revealed the similarity of the virus with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). The high rate of spread and reproduction of this new virus, called COVID-19, caused

the severity of the virus-borne disease to be described as a global epidemic on March 11, 2020[20].

The first cases in the world were reported in China in December 2019[21]. Between 18 December and 29 December, 5 cases were detected and one of these cases died[22]. By January 2, 41 patients were diagnosed with COVID-19. It has also been reported that many of these patients have sub-diseases such as hypertension and diabetes[23]. The total number of cases reached 571[24]. The number of cases spread very quickly, reaching 5502 cases on January 24[25]. On January 30, the total number of cases in China was 7734, and a total of 54 cases were detected in Singapore, the USA, India, Canada, France, and Germany outside of China. The total case and total mortality rate were calculated as 2.2%[26]. After the case was seen in the United States, the identification of the virus and disease stages were investigated, and mild symptoms turned into pneumonia on the 9th day. The transmission of the virus from person to person was proven for the first time by the USA[27].

On January 10, 2020, before the case was seen in Turkey, the ministry established the scientific committee, which is the COVID-19 research team. At the beginning of the measures taken, thermal cameras were installed at the airports. On March 13, 2020, a total of 5 cases were seen in Turkey, with the first case. Despite many restrictions, on March 19, 2020, the number of cases was 359, while the number of deaths was reported as 4 people[19].

COVID-19 Etiology

Coronaviruses are from the Orthocoronavirinae family, which originates from animals. The coronavirus, which can make humans and animals sick, is positively charged and has a single chain and enveloped spike-shaped cilia. These viruses, which have 4 different genera, are known as α (Alpha), β (Beta), γ (Gamma), and δ (Delta). The genera that can infect humans are α (Alpha) and β (Beta). As a result of the researches, the SARS-CoV-2 Omicron variant, which was first reported to the World Health Organization in South Africa on November 24, 2021, was detected. They can infect not only humans but also all mammals. Coronavirus strains that can infect poultry are known as γ (Gamma), and δ (Delta)[28,29]. As previously known, six types of coronaviruses (HCoV) that can infect humans have been identified[30]. The coronavirus that emerged in Wuhan was determined as the seventh species with three different strains as a result of research, and it was deemed appropriate to be named coronavirus 2 (SARS-CoV-2) by the International Virus Taxonomy Committee[31].

SARS-CoV-2 shows 59% and 79% similarity to MERS and SARS-CoV, respectively. It has been reported that COVID-19 is less associated with MERS-CoV[32]. However, the receptor-binding gene regions are very similar. The receptors use the same intracellular converter, the ACE2 enzyme[33]. Bats are thought to be the host of SARS-CoV-2. Further work is essential to determine the origin of these virüs[34]. In addition, it has been reported in different studies that there are pangolin, snake, and turtle as creatures that infect different animals as intermediate hosts[35]. The source of the virus is not yet clearly known. Knowing and isolating the source is very important in both vaccine and drug studies and reducing the spread of the virüs[36]. Due to the severe Coronavirus-2 (SARS-CoV-2), the COVID-19 pandemic poses an unprecedented challenge to life on Earth. SARS-CoV-2 can result in death by causing diseases such as asymptomatic acute respiratory distress syndrome (ARDS) and multi-organ involvement. Ethnic origins of people also vary according to the people against the COVID-19 pandemic. The genetic susceptibility of people infected with COVID-19 is increasingly known. For this reason, studies on associating COVID-19 with the genome and related genes are continuing.

Ways to Avoid SARS CoV-2 Infection

The coronavirus group viruses that infect humans are transmitted through droplets from the respiratory tract fluids of sick individuals. However, different modes of transmission have been reported during the SARS-CoV-2 pandemic, such as direct contact with contaminated surfaces, inhalation of aerosol containing viral particles, and fecal contamination (Fig. 1)[37].

Learning the transmission routes has paved the way for taking measures to minimize human contact in society to prevent the spread of the disease. The Chinese government imposed a travel ban by closing the city of Wuhan, where the disease was first seen, on January 23, 2020. However, the disease spread to the whole country in a short time like 3 days, and it was made obligatory to wear masks in public spaces to prevent healthy individuals from being infected by carriers of the disease. Therapeutic antibodies that affect the receptor-binding site of the virus, such as REGN-CoV-2, have been noted to provide substantial protection against SARS-CoV-2 infection. In this field, companies such

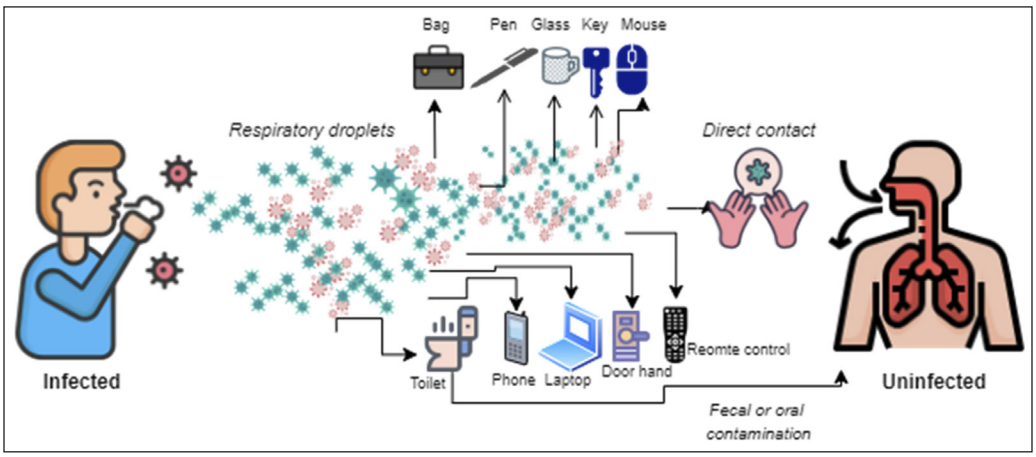

Figure 1. *SARS-CoV-2 transmission routes.*

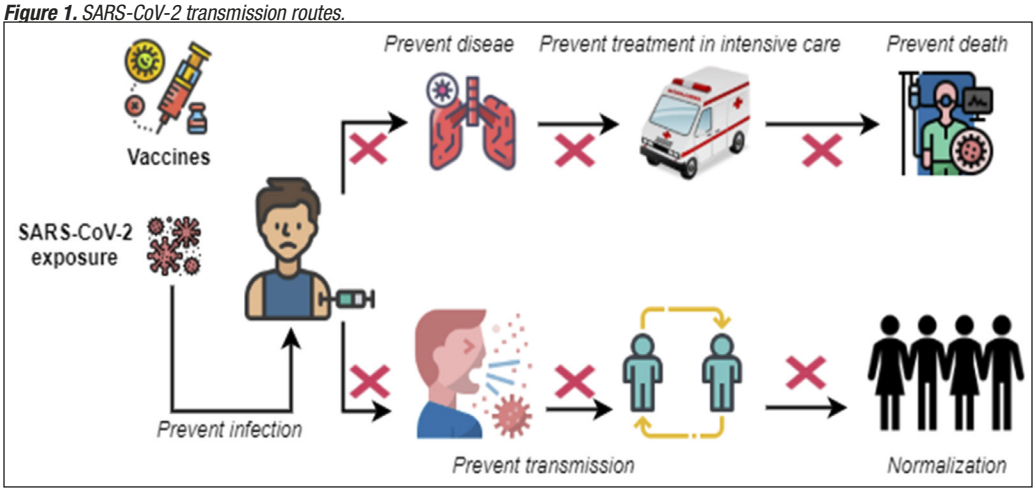

Figure 2. *The possible protection mechanism of Covid-19 vaccines.*

as Regeneron, Eli Lilly, and AbCellera have developed products that have reached the stage of human trials[38].

It is known that vitamin D, an endogenous steroid hormone synthesized in the skin under the influence of UVB rays, plays a role in the prevention of infectious diseases. Since vitamin D deficiency causes immunodeficiency against respiratory diseases, it is thought that supplementing with vitamin D to individuals with vitamin deficiency may be effective in preventing COVID-19[39].

The effect of the herbal mixture called Qingfei Paidu Decoction (QFPD), which is used against pneumonia and viral infections in traditional Chinese medicine, in the prevention and treatment of SARS group viral infections was investigated. Studies have revealed that the product can be effective in the new Coronavirus infection thanks to its anti-viral and anti-inflammatory activity[40,41]

Since the first days of the pandemic, studies have been carried out for the production of vaccines that will be effective on SARS-CoV-2 (Fig. 2). Vaccination aims to prevent the mucosal colonization of the virus and its progression in the lower respiratory tract[42].

Despite many measures taken at the national and international level to prevent the spread of the disease, there are weaknesses in complying with the epidemic measures. In a study conducted with the participation of 4732 people living in Turkey, it was determined that 67% of people with chronic diseases did not comply with epidemic prevention measures[43].

SARS CoV-2 Incubation Time

Angiotensin-converting enzyme 2 (ACE2) is an enzyme that hydrolyzes the hormone angiotensin 2, which causes the narrowing of the vessel walls. This enzyme, which plays a key role in the regulation of the cardiovascular system, is used by viruses of the SARS group as a cell surface receptor that facilitates the entry

of viral RNA into lung cells[44]. Studies have shown that SARS-CoV-2 infection occurs in direct proportion to ACE2 enzyme expression[45]. COVID-19 infection is studied in four stages; The first stage is upper respiratory tract infection. In the second stage, with the progression of the infection, dyspnea (shortness of breath) and pneumonia (pneumonia) are observed. The third stage of infection is characterized by the worsening clinical picture caused by the cytokine storm. In the final stage, death or recovery occurs[46].

In the researche, different results have been reached regarding the incubation period of the virus. In the early stages of the epidemic, it was reported that the number of cases doubled in an average of 7.4 days. In studies on 1099 patients, the estimated incubation period for SARS-CoV-2 was 3.0 days. Symptoms (95%) of the disease began to appear within 10 days of exposure to the virus. In another study conducted on 138 cases, the time elapsed between the onset of the first symptoms and the appearance of the severe acute respiratory syndrome was determined as 5–8 days[47]. Although the incubation period extends to 2–11 days, it is generally accepted as 5–6 days. After the incubation period, the prodormal period begins, in which symptoms begin to appear[37]. Person-to-person transmission of SARS-CoV-2 usually occurs between family members living in the same household, in the hospital, and in public areas. Transmission usually occurs during the incubation period[48].

Symptoms of COVID-19

People infected with SARS-CoV-2 usually develop symptoms related to upper respiratory tract infection in the first stage of the disease. The most common symptoms are high fever, sore throat, cough, and shortness of breath. Studies have shown that most of the patients have complaints such as headache, loss of smell and taste, diarrhea, and abdominal pain in addition to these basic symptoms. Neurological symptoms are quite common in COVID-19 patients. Headache (11–34%) reported complaints of SARS-CoV-2 patients admitted to the hospital. These headaches were defined as abrupt onset, throbbing, or pressure-like moderate to mild pain. Headaches have been noted to have poor sensitivity to common analgesics and have been reported to affect the temporoparietal, forehead, or periorbital region. In addition to headache, changes in mental status, impaired consciousness, paresis, hypo-areflexia, encephalopathy, and cerebrovascular events are other common neurological symptoms. In the analysis of cerebrospinal fluid samples taken from SARS-CoV-2 patients by RT-PCR (reverse transcriptase-polymerase chain reaction), it was noted that viral particles were found in a small number of patients[46,49,50]. In some cases, appetite and weight loss have also been shown as symptoms related to COVID-19 infection[37].

Bilateral pneumonia has been observed in the majority of SARS-CoV-2 patients. In blood tests, findings of leukopenia and lymphopenia were found. It was determined that IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα values in the blood plasma of patients treated in intensive care units were higher than in other patients (Wang, 2020). Since COVID-19 symptoms vary according to the course of the disease, patients who do not show symptoms are grouped as asymptomatic and other patients according to their symptoms are grouped as moderate and severe patients. High fever was observed in 98% of patients, cough in 76%, and myalgia (muscle pain) or fatigue in 44%. Atypically, 28% of patients reported sputum, 8% headache, 5% bloody cough, and 3% diarrhea. Lymphopenia was found in 63% of the patients and shortness of breath in 50%. The incidence of lymphopenia is increased in patients with hypertension or chronic lung disease[48]. In elderly patients, pneumonia and organ failure may occur in the later stages of the disease[51]. The neuropsychiatric effects of SARS-CoV-2, on the other hand, remain unclear. The data obtained show that psychotic spectrum disorders occur in 0.9–4% of patients. It is thought that neuropsychiatric disorders such as mild cognitive impairment, mood changes, insomnia, psychosis, encephalopathy, and suicide can be seen with the effect of the disease[52].

Effects of COVID-19 Infection by Age

SARS-CoV-2, like all other infectious group diseases, causes different effects to be observed according to age groups in terms of symptoms and severity of the disease[37]. Early research on COVID-19 infection revealed that children are less affected by the infection. In a study conducted on 72,314 patients, only 1% of the patients were under the age of 10, there were no fatal cases in the patient group under 9 years of age, and the mortality rate was 8.0% in cases aged 70–79; In cases over 80 years of age, the mortality rate was recorded as 14.8%. In another study conducted on 2143 pediatric patients, it was stated that children showed mild upper respiratory tract infection symptoms and more severe symptoms occurred in infants under the age of 1, whose immune

system has not yet completed its development[42,48]. It has been determined that morbidity in SARS-CoV-2 infections is associated with advanced age. Scenarios such as the severity of the disease, the presence of comorbidities such as obesity, diabetes, hypertension, increase in D-dimer and C-reactive protein levels, and decrease in lymphocyte count affect the mortality rate[38,46].

In a study in which data from 23 clinical studies were analyzed, it was reported that smell and taste disorders caused by COVID-19 infection mostly affect young female patients, and complaints of loss of smell persist for longer in younger patients[53]. In statistics on COVID-19 patients in the intensive care unit in Italy, it was determined that the average age of the patients was 63 in 1,591 fatal cases, and 82% of them were male. When the data of 1,300 patients who received respiratory support were examined, it was seen that 88% of the patients were treated in the intensive care unit with mechanical and 11% non-invasive respiratory support, and the mortality in the intensive care unit was 26%[38]. When the rates of re-positive PCR tests of the patients were evaluated, it was determined that the patients under the age of 18 had milder symptoms and complaints, but a higher rate of COVID-19 positive results[54].

Studies by the Chinese Center for Disease Control and Prevention have shown that 86.6% of the cases reported to date include patients aged 30–79 years, with patients over 60 years of age at higher risk compared to late patients who experience milder symptoms or are asymptomatic[47]. Age also affects clinical findings. In the studies, it was revealed that the blood urea nitrogen levels, inflammation indicators, and bilateral lesions were higher in COVID-19 patients over the age of 60[48].

COVID-19 Diagnosis and Treatment Ways

Since SARS-CoV-2 infection is a disease that occurs with flu-like symptoms, it is possible with the use of laboratory instruments and radiological methods to make a definitive diagnosis of COVID-19[37]. Laboratory tests are essential to distinguish pneumonia, which is the most serious sign of the disease, from other viral, mycoplasma, and bacterial infections and pneumonia without infection. COVID-19 tests are carried out by laboratory analysis of nasal swab, nasopharynx, and trachea extracts, sputum, lung tissue, blood, and stool samples. To detect viral RNA molecules in early diagnosis, upper and lower respiratory tract samples are analyzed. For this purpose, RT-PCR (Real-Time Polymerase Chain Reaction) method is used[47].

Although RT-PCR is the most actively used analysis method for detecting the SARS-CoV-2 virus, the sensitivity of PCR analysis is affected by variables such as viral load, sample type, and time from sample collection to analysis. Even patients with all symptoms can sometimes be negative due to errors in sampling. In order to minimize these erroneous results, genomic points such as ORF1a and ORF1b nucleocapsid genes and spike protein genes are targeted in RT-PCR[47]. Before the COVID-19 epidemic turned into a pandemic, studies were carried out to develop PCR-based rapid diagnostic kits in January 2020, and these kits began to be used all over the world. In addition to virological tests, it is also diagnosed with serological tests. Pneumonia findings are also evaluated in radiological examinations, and MR and tomography images are used to support positivity in the diagnosis of COVID-19[38].

Favipiravir, Lopinavir, Ritonavir, Hydroxychloroquine sulfate, and Oseltamivir drugs are used in the treatment of COVID-19 in Turkey. Information on the use, dosage, and preparation recommendations of these drugs, as well as possible drug interactions, have been announced by the official authorities and the documents have been uploaded to the relevant websites in a way that can be accessed by everyone.

Hand Hygiene

Hand hygiene is of great importance as the virus is transmitted through contact. Proper cleaning and hygiene of hands are very important. Hands should be washed for at least 20 seconds. When soap and water are not available, hand hygiene can be provided with disinfectants containing at least 60% alcohol. The correct use of disinfectants is very important in terms of hygiene[55].

Mask

It is the barrier that prevents the virus transmitted through airborne droplets from entering the body. Hand hygiene and social distance protection should not be neglected when using masks, gloves and rules should not be forgotten when wearing masks, and hands must be cleaned before wearing a mask. The mask should be worn in such a way that the mouth and nose are completely covered. Moistened masks should be changed while changing the mask, they should be changed by holding the ropes, and then the hands should be cleaned. It is not appropriate to use disposable masks more than once[56]. When medical masks are not available, fabric masks should be used and washed at high temperatures[57].

Social Distancing and Isolation

The virus spreads to a distance of two meters in the air, so it is very important to maintain social distance. We know that people who do not show COVID-19 symptoms are carriers, and they should not go out of the house unless necessary. Public vehicles should not be used unless it is very necessary for transportation. Meetings and events that will require crowded should be postponed or canceled. In this process, the continuity of remote working and distance education systems is also important to prevent the spread of the virüs[58].

Villages, neighborhoods, apartments, etc., where a virus case has been detected. areas should be quarantined immediately. The quarantine application determined by WHO should be followed for people who have contact with the sick person or have symptoms during the trip[59]. Quarantine applications are as follows; stay away from the house for 14 days and at least two meters away from the individuals in the house. Contact should not be made with anyone other than the quarantined individuals in the household. In case of any symptoms that will develop within two days, they should not contact anyone and apply to health institutions.

Protection of Healthcare Workers

High-level measures should be taken to prevent the health workers, who are in the highest risk occupational group in the society, from contracting the epidemic. Isolation rooms should be created for patients with symptoms and the number of personnel working in these rooms should be limited. Masks should be worn everywhere in the hospital. Employees who circulate with patients need to take extra precautions. Ventilation in all waiting areas should work actively, and areas, where verbal conversations with patients are made, should be limited with glass barriers. Cleaning of glass barriers should be done routinely, and employee rotation and working times should be shortened. A new section should be opened for COVID-19 patients and people with symptoms, and they should be prevented from sharing the same environment with other patients. It should be preferred that those who need to go to hospitals for prescriptions and drugs should get help by making phone calls as much as possible. Personnel reinforcement should be provided to intensively working hospital units and departments[60].

Environmental Cleaning

Since the disease is transmitted by contact, routine cleaning of contacted surfaces will greatly reduce the rate of viruses infecting people. Places such as door handles and electrical switches in public areas should be wiped and ventilated at regular intervals. Bleach (1/100 ratio) or alcohol (at least 60%) should be preferred for cleaning. Animal products used in meals should not be preferred raw or undercooked. Vegetables or fruits should be washed with vinegar or plenty of water[61].

Drugs

Favipiravir

Favipiravir, which is effective in reducing mild and moderate complaints of COVID-19 patients in early clinical studies; is a commercial drug that has an inhibitory effect on the RNA polymerase enzyme[62]. Favipiravir is currently used in the inhibition of various influenza group viruses (H5N1, H7N9, H1N1)[63]. There are also studies showing that it is an effective antiviral agent in the Ebola epidemic[64]. In studies on COVID-19 patients who had previously been treated with Lopinavir/Ritonavir, it was determined that the use of Favipiravir was more effective in reducing the symptoms of the disease[62].

According to the Information Guide on Drugs to be Used in the Treatment of COVID-19 (SARS-CoV2 Infection) published by the Ministry of Health of the Republic of Turkey, it is recommended to use Favipiravir 200 mg tablet (2×1600 mg for 5 days). Favipiravir is a drug in tablet form that can be swallowed with water. If the drug cannot be used as recommended for various reasons, it can be prepared in liquid dosage form by hospital pharmacists.

It has been determined that the use of favipiravir during pregnancy may cause fetal anomalies and its interactions with various drugs have been recorded. An increase in exposure to Favipiravir has been observed when Alcuronium from the anesthetic/muscle relaxant group, Moxonidine, and Treprostinil from antihypertensive group drugs, Ipratropium bromide from bronchodilators, and paracetamol derivatives from analgesics are used together with Favipiravir. Similarly; Antibacterials, antidiabetics, contraceptives, and hormone replacement therapy agents can also show overexposure when used with Favipiravir. Although no significant interactions of favipiravir with other antiviral drugs have been reported, concomitant use with Oseltamivir is not recommended.

Hydroxychloroquine Sulfate

Hydroxychloroquine is an immunomodulator used in the treatment of rheumatic diseases and malaria.

Prophylactic use of contacts and healthcare workers in the risk group in the COVID-19 pandemic has been recommended. In a study in which the prophylactic effect of hydroxychloroquine sulfate was observed, 821 asymptomatic volunteers were studied. It was noted that 87.6% of the participants were contacted in the high-risk group. Some of the participants were given hydroxychloroquine and some were given a placebo and were followed for 14 days. No significant prophylaxis was observed in subjects receiving hydroxychloroquine supplementation after 14 days[65].

According to the Information Guide on Drugs to be Used in the Treatment of COVID-19 (SARS-CoV2 Infection) published by the Ministry of Health of the Republic of Turkey, the prescribed use of Hydroxychloroquine is 2 x 200 mg tablets for 5 days in outpatients with mild pneumonia symptoms. Since side effects such as ventricular tachycardia and QT prolongation may occur, it is recommended that patients with cardiovascular disorders should be followed up with ECG. The usual method of use is to swallow the tablet with food or milk, without crushing and chewing. In cases where oral use is not possible, the tablets can be crushed and mixed with liquid/semi-liquid foods and used.

The most common side effect of hydroxychloroquine has been noted as QT prolongation. It should be used with caution because of the possibility of cardiotoxicity and retinotoxicity. Since it is predicted that the use of hydroxychloroquine with analgesics, antiarrhythmics, anticonvulsants, and some antipsychotics may cause serious interactions, it is not recommended to be used together with drugs from this group. However, it is generally in the safe group for patients on hormone replacement therapy, using lipid-lowering, inotropes, or vasopressors.

Lopinavir/Ritonavir

Lopinavir/Ritonavir drug combination is an antiviral used in the treatment of SARS and AIDS prophylaxis[66]. It has common side effects such as gastrointestinal system disorders, headache, fatigue, and QT prolongation. The lopinavir/Ritonavir combination is not recommended for use in neonates. *In vitro* and *in vivo* studies have confirmed the inhibitory effect of Lopinavir and Ritanovir on SARS CoV[66]. In the Information Guide on Drugs to be Used in the Treatment of COVID-19 (SARS-CoV2 Infection) published by the Ministry of Health of the Republic of Turkey, the use of 200 mg Lopinavir and 50 mg Ritonavir combination in the form of 2×2 tablets for 10–14 days is recommended for pregnant women with signs of COVID-19. In infants and pediatric patients older than 14 days, 16 mg of Lopinavir per body mass is recommended depending on the progression of the disease course. QT/PR prolongation has been reported when lopinavir and ritonavir are co-administered with some anesthetics/muscle relaxants, antiarrhythmics, antibacterials, antidepressants, antipsychotics/neuroleptics, antiemetic drugs, beta-blockers, and calcium channel blockers. If these drugs are used together, it is recommended to monitor the patient with ECG.

Oseltamivir

Oseltamivir is an antiviral agent widely used in the treatment and prophylaxis of influenza-related infectious diseases. Its success in shortening the duration of the disease and preventing aggravation of the course has been proven[67]. It is recommended to be used especially in pediatric cases with the severe course and accompanying other diseases[68].

Oseltamivir is used in cases showing signs of viral pneumonia associated with influenza. Its use is not recommended for COVID-19. Since the findings of COVID-19 are very similar to seasonal flu and influenza group diseases, and COVID-19 can be detected in patients who are currently using Oseltamivir, interactions with other drugs used in the treatment have been investigated. It has been noted that exposure to Oseltamivir may be increased by 14% when used with favipiravir.

Vaccines for the COVID-19 Pandemic

To end the pandemic caused by SARS-CoV-2 infection, vaccine, and drug development studies have been carried out since the first days of the epidemic. To create an effective treatment and prevention method, the mechanism of action of the virus has been investigated, and the vaccines and drugs produced have been started to be tested on human and animal models. The effects of the developed vaccines were observed on genetically modified BALB/c mice and human experiments were conducted with products that showed successful results[37].

The main purpose of vaccination; is to protect people from SARS-CoV-2 infection, signs of disease caused by infection, and transmission. For this reason, safety and efficacy principles are observed in the formulation of vaccines. However, the examination of candidate vaccines in different countries within the scope of changing parameters such as duration of protection, immunological response, and cost necessitated the

production of vaccine alternatives that could meet different expectations in vaccine development. It has been suggested by the US Food and Drug Administration (FDA) that vaccines can be considered successful if their effectiveness is at least 50%. In vaccine studies, 3 clinical trials are required to prevent severe illness and death from possible side effects. In these studies, controlled infection studies are carried out on volunteers as well as animal subjects[69].

All known vaccine types have been tested in preclinical studies, including attenuated virus, inactivated virus, DNA, mRNA, virus-like particle, and subunit vaccines against the SARS-CoV-2 virus. In attenuated and inactivated virus vaccines, the genes encoding the replication regions of the virus are removed from the genome or inactivated by physical and chemical processes. As another method, viruses other than SARS-CoV are modified by recombinant methods to synthesize the causative compounds of the SARS-CoV virus. Vaccines derived from virus-like particles are vaccines designed to produce an effect similar to that of the virus in the vaccinated organism[51]. The working mechanism of mRNA vaccines, which stands out as a fast and easily modifiable method during the pandemic process, is based on the principle of transferring the gene fragments encoding the metabolites of the virus to the organism in the form of mRNA by modifying it. In studies conducted on 30,420 volunteers, it was found that the mRNA-based mRNA-1273 vaccine caused regional, transient, or systemic reactions in some participants; however, it was found to be effective at a rate of 94.1%[70].

The biggest concerns in vaccine studies are that the vaccine causes an immune response or that vaccines containing viral particles multiply in the body after vaccination and lead to infection. The fact that the vaccines developed to prevent the H1N1 swine flu epidemic that emerged in 1976 caused autoimmune reactions, especially in children, made it necessary to produce the vaccine meticulously and to launch the products after the clinical trials were completed[71]. Another concern with vaccines is vaccine hypersensitivity. Animal studies have found that vaccines containing viral antigens treated with formalin elicit an immune response that leads to Th2 polarization and deficiency of cytotoxic T cells[72].

When the results are observed, according to covid19. trackvaccines. org data, as of end of August 2022, there are 222 vaccine candidates developed against the SARS-CoV-2 virus worldwide. Trials (774) of these vaccines have been made and 41 of them have been approved. The Pfizer/BioNTech vaccine approved in 149 countries and the Moderna Spikevax vaccines approved in 88 countries are RNA-based; Oxford/AstraZeneca AZD1222 approved in 149 countries, Gamaleya Sputnik V approved in 74 countries, Serum Institute of India Covidshield approved in 49 countries, CanSino Ad5-nCoV approved in 10 countries, Janssen Ad26. COV2. S non-replicating virus-based approved in 113 countries; Sinopharm BBIBP-CorV approved in 93 countries, Sinovac CoronaVac approved in 56 countries, Sinopharm Inactivated approved in 2 countries and Bharat Biotech Covaxin approved in 14 countries are inactive and FBRI EpiVacCorona protein subunit based vaccines approved in 4 countries (https://covid19.trackvaccines.org/). Vaccine studies in Turkey started with the Ministry of Health approved Sinovac and Pfizer/BioNTech BNT162b2. Clinical studies of ERUCOV-VAC vaccines developed by CoronaVac and Erciyes University have been finalized and approved.

Conclusion

The COVID-19 outbreak broke out in Wuhan, China's Hubei province in December 2019 and was recognized as a pandemic by the World Health Organization in March 2020. More than 605 million people around the world have been sick so far due to the disease. In addition, approximately 6.48 million people died from these cases. Along with COVID-19, in addition to epidemics such as Ebola, which are limited and effective only in certain regions, in the developing and constantly circulating the world, a pandemic that has affected the whole world has been encountered for the first time. In the face of this unexpected situation, some circles thought that the disease would only be temporary. Other people, on the other hand, were not given the possibility that such a situation could be real at this time. The realistic view of the citizens on this issue has started to become more believable with the loss of their lives as a result of this disease, such as family members, and friends around them. As a result, when we look at it today, it seems that our most powerful weapon, after vaccinations, is cleanliness and social distance.

Authors' Contribution

Study Conception: OU; Study Design: OU, EU, UA; Supervision: AG; Data Collection and/or Processing: OU, EU, UA; Literature Review: OU, EU, UA; Manuscript Preparation: OU; and Critical Review: OU, AG

Conflict of Interest

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