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CLINICAL CHARACTERISTICS AND MANAGEMENT OF THE CORONAVIRUS DISEASE (COVID-19)

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THE CORONAVIRUS DISEASE (COVID-19)

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PREFACE

The disease, which emerged on December 1, 2019 in Wuhan, the capital of the Hubei Region of China, was determined to be caused by a new type of coronavirus called SARS-CoV-2, and was first identified as COVID-19 Pandemic Influenza; The global epidemic was declared by the World Health Organization (WHO) on March 11, 2020, after the virus cases began to be reported in various countries in Europe, North America and Asia-Pacific. It has been clearly understood that technology, developments in the quality and quantity of researchers and scientific researches are very important in the detection, control and treatment process of the disease. The fact that the researches carried out during the process are the responsibility of all scientists to add value to scientific developments, national economies and the comfort of life of all humanity has become more evident. Each new scientific and technological field contributes to a more comfortable life in human history. We hope that this book, which includes chapters by valuable scientists, will be useful to Turkey, all our colleagues, dear students and all our people in the COVID-19 pandemic process we have gone through difficult times.

We sincerely thank everyone who contributed to the creation of this book, those who helped convey up-to-date information, our colleagues who were referees, the publishing house and its employees who gave us this opportunity to publish the book.

Regards

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CHAPTER 1

COVID-19: PATHOGENESIS, EPIDEMIOLOGY, CLINICAL FINDINGS & TREATMENT

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PATHOGENESIS

In order to better understand the pathogenesis of COVID-19 disease, it is necessary to know the structure of the SARS-CoV-2 virus. As a result of SARS-CoV-2 replication, non-structural proteins (NSP), structural proteins and other accessory proteins are encoded. The most important structural proteins are spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins.

Each monomer of the S protein, which has a trimeric structure, is approximately 180 kDa and consists of two subunits. As a result of folding the S1 subunit onto itself, independent N-terminal domains (NTD) and C-terminal domains are formed. The N-terminal domain (NTD) and C-terminal domains are involved in the binding of the virus to the receptor on the host cell surface. The S2 subunit mediates the fusion and entry of the virus into the cell. Previously, it has been shown that inhibitory peptides prepared specifically for the S2 subunit domains for SARS-CoV and MERS-CoV infections inhibit the entry of viruses into lung cells.Although these inhibitory peptides are not at

the same level, it has been reported that they may be effective in SARS-CoV-2 infections. The S protein binds to the angiotensin converting enzyme (ACE2) receptor of the host cell, and this complex is subjected to a proteolytic process by the host type II transmembrane serine protease (TMPRSS-2), and the virus enters the cell. ACE2, which is especially expressed in type 2 alveolar epithelial cells, is accepted as the cellular entry receptor of SARS-CoV-2 to humans. Electron microscopy studies have shown that SARS-CoV-2 binds to ACE2 receptors with higher affinity than SARS-CoV. It has been reported that SARS-CoV-2 can enter cells independently of ACE2 in case of high viral load. The D614G mutation detected in the SARS-CoV-2 spike protein occurs in cases identified after April and May 2020 in the COVID-19 outbreak. In this mutation detected at residue 614 of the S protein, glycine replacement occurs instead of aspartic acid. In the SARS-CoV-2 genome, it has been detected in spike mutations accompanied by D614G mutation. It has been found that especially the D614G mutation is critical for infectivity and the presence of this mutation correlates with the high viral load in the nasopharynx of COVID-19 patients. After the SARS-CoV-2 host membrane fusion is achieved, the entry of the virus into the cell is completed and viral genomic RNA is released in the cytoplasm and converted into viral polymerase proteins. Uncoated RNA synthesizes 2 polyproteins (viral replicase polyproteins), pp1a and pp1ab, which encode NSP and form a replication transcription complex (RTC) in the double-membrane vesicle. RTC continuously duplicates and synthesizes a series of subgenomic RNAs that encode helper and structural proteins. Negative (-) polarity genomic RNA is synthesized and used as a template to create subgenomic or genomic positive (+) polarity RNA. While viral RNA and N structural protein are replicated, transcribed or synthesized in the cytoplasm, the S, M, and E protein are transcribed in the endoplasmic reticulum (ER) and transferred to the Golgi. Viral RNA - N complex, S, M and E proteins are assembled in the ER-Golgi spacer (ERGIC) to form a mature virion. This assembled structure is then released from the host cells to the extracellular space by exocytosis. Envelope membrane (E) proteins are relatively small viral structural proteins that assist in the assembly and release of virions. M proteins are 222 amino acid long structural proteins that function together with the E, N and S proteins and play an important role in RNA packaging. Nucleocapsid proteins (N), on the other hand, play an important role in the packaging of viral RNA into the ribonucleocapsid and assist in increasing viral RNA transcription and replication. It contributes to the establishment of order by interacting with the M protein during viral assembly. In

addition to structural proteins, the SARS-CoV-2 genome encodes a large number of NSPs that are involved in the replication and assembly stages of the virus. These proteins contribute to viral pathogenesis by preventing or modifying early transcription regulation, helicase activity, immunomodulation, gene transactivation, and antiviral response.

COVID-19 is a viral respiratory infection. SARS-CoV-2 that causes COVID-19 is a cytopathic virus; It particularly affects the bronchial epithelial cells and causes destruction of the infected cells within 3-5 days through apoptosis. Debris formed by the destruction of the bronchial epithelium and the viral particles released cannot be thrown out because the muco-ciliary activity is impaired and they begin to fill the alveoli. Eventually type II pneumocyte hyperplasia and extensive alveolar damage occurs; If the organized debris cannot be cleaned, fibrosis starts in the lung parenchyma after the second week. On the other hand, as muco-ciliary activity is impaired, upper respiratory tract bacteria also descend into the alveoli with micro-aspirations, causing bronchopneumonia. In post-mortem examinations, bronchopneumonia foci caused by bacteria and sometimes fungi are observed in most of the patients. COVID-19 pathogenesis consists of different stages. It can be divided into three stages from the onset of symptoms. The hallmark of the first seven days is viral activity. Although RT-PCR positivity continues, infective virus cannot be detected after the eighth day of the disease. The peak of the activity of dendritic cells, CD4 and CD8 T lymphocytes as well as the destruction of the cells infected by the virus within 3-5 days plays a role in the end of the viral activity period. T lymphocytes are responsible for the clearance of the virus, and their activities peak at the end of the first week. In post-mortem examinations, two more stages are defined after the end of viral activity. These stages are intertwined and differ from patient to patient. After the end of viral activity, the debris becomes organized and cleared in patients with a severe clinical course, and after about the second week, fibrosis and necrotizing pneumonia draw attention.

As a result; Antiviral therapy should be administered within the first week of viral activity. No significant benefit should be expected from antiviral treatment after viral activity ends. The extent of the damage and the regeneration ability of the host determine the fate of COVID-19. Regeneration ability decreases with age. Therefore, advanced age is among the important parameters that have an effect on the severity of the disease.

EPIDEMIOLOGY

In December 2019, the Chinese Center for Disease Control and Prevention and Wuhan city health authorities reported an outbreak of pneumonia of unknown cause in Wuhan City. On January 7, 2020, the Chinese Center for Disease and Control detected a new coronavirus from patients' lower respiratory tract samples, and announced on January 11 that it showed a genomic sequence. This novel coronavirus was later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) named this infection caused by SARS-CoV-2 identified in 2019 as COVID-19.

It has been shown that this disease is transmitted from person to person, especially adults are susceptible to COVID-19 and the severity of the disease is related to age. At the same time, hypertension, diabetes, cardiovascular disease, etc. The disease has been shown to be more severe in people with comorbidities. In a study by Chen et al, examining 99 patients hospitalized in the same hospital with the diagnosis of COVID-19, they showed that older men were more likely to become infected and rapidly entered acute respiratory distress syndrome (ARDS), which created a life-threatening situation. In a study where comorbidities were analyzed, it was shown that approximately 17% of the patients had hypertension, 8% had diabetes, 5% had cardiovascular diseases and 2% had respiratory system diseases.

Many respiratory viruses show seasonal characteristics, the best known of these is influenza. While some scientists think that COVID-19 may have a seasonal characteristic and will decrease with the warming of the weather, some scientists think that this virus is not similar to the influenza virus and will not be affected by the season, presenting the disease as a supporting evidence for the occurrence of the disease in hot regions. There is not enough evidence to say that this virus may show a seasonal characteristic.

CLINICAL FINDINGS & TREATMENT

As a result of the studies carried out during the pandemic process, new information about the natural course of COVID-19 are added. Common symptoms of infection are respiratory symptoms, fever, cough, and dyspnoea. Symptoms such as headache, sore throat, runny nose, muscle and joint pain, extreme weakness, new sense of smell and taste, diarrhea can also be seen. Although the disease can be asymptomatic, in severe cases, pneumonia, severe acute

respiratory tract infection, kidney failure and even death may develop. While the fatality rate was 11% in the SARS epidemic and 35-50% in MERS-CoV, the fatality rate was reported as 3.8% according to the COVID-19 report of the People's Republic of China. This speed is 2.6% in our country as of May 2020.

Asymptomatic infection: In the literature, quantitative RT-PCR (nasopharyngeal swab samples) test positivity has been reported in asymptomatic individuals in community screenings. In most of the asymptomatic cases, some symptoms have developed in the later stage of the infection, but there are also cases who are asymptomatic during the clinical follow-up period.

First Application

Characterized primarily by fever, cough, shortness of breath, and bilateral infiltrates on lung imaging.

Pneumonia is the most common serious symptom of COVID-19. There are no specific clinical features that can reliably distinguish COVID-19 from other respiratory viral infections. In a study examining 138 patients hospitalized with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of the disease were:

- Fever 99%
- Fatigue 70%
- Dry cough 59%
- Anorexia 40%
- Myalgia 35%
- Dyspnea 31%
- Sputum production has been reported to be 27%.

In the study conducted by Li et al on 425 cases, the contagiousness coefficient (R0) was estimated to be 2.2, which means that on average, each patient spread infection to 2.2 people. Generally, an outbreak will increase as long as R0 is greater than 1, and control measures aim to make R0 less than 1.

Other cohort studies from Wuhan with patients with confirmed COVID-19 have reported a similar set of clinical findings. However, fever may not be a universal finding. In one study, fever was reported in almost all patients, but very low-grade fever was <38 ° C in about 20%. Another study on 1099 patients from Wuhan and other regions in China found that fever (axillary temperature measured above 37.5^0 C) was present in only 44 percent of patients at admission, but ultimately at 89 percent during hospitalization. In the first cohort studies from China, smell and taste disturbances (anosmia and dys-

geusia) were also reported as common symptoms in patients with COVID-19. In a survey of 59 patients with COVID-19 in Italy, 34 percent reported loss of either sense of smell or taste, and 19 percent stated that they lost both. Whether this is a hallmark of COVID-19 remains unclear.

Other, less common symptoms include headache, sore throat, and rhinorrhea. In addition to respiratory symptoms, gastrointestinal symptoms (eg. nausea and diarrhea) have also been reported; In some patients, these may also be the application complaint. In a systematic meta-analysis of studies reporting on gastrointestinal symptoms in patients with confirmed COVID-19, the prevalence of gastrointestinal symptoms was 18 percent overall; Diarrhea, nausea / vomiting or abdominal pain were reported in 13, 10, and 9%, respectively.

Dermatological findings in patients with COVID-19 are not well defined. There are rare reports of urticarial rashes and transient livedo reticularis.

TREATMENT

The structure and usage of antiviral drugs used in treatment will be explained under separate headings.

Favipiravir

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is licensed in Japan for the treatment of complicated influenza infections because it inhibits the reproduction of influenza virus (IC50 = 0.022 μg / mL). Favipiravir is 54% bound to serum proteins, metabolized in the liver and excreted in the urine. In in vitro experiments, Ebola is recommended to be used at a dose 50% higher than the recommended dose in phase III studies for influenza treatment in modeling based on the effect of Ebola virus reproduction at a density of 10 μg/mL . In a study conducted with the recommended dose (2x1600mg on the first day, then 2x600mg) in a severe COVID-19 patient, the favipiravir concentration was found to be below the measurement limit of 1 μg/mL, which is well below the lowest EC50 (9.7 μg/mL). Favipiravir recommended in phase III studies A = Early phase viral activity 1-7 days B = Organization of the debris 8-12 days C = Complications organizing pneumonia; necrotizing pneumonia 12 - 1 7 12 A B C 5 dose is for viruses with an IC50 value of ≈3.2 μM. However, IC50 values of favipiravir for SARS-CoV-2 were almost always above the working limits (> 100 μM), so no inhibition could be shown.

Ivermectin

Ivermectin is an anti-parasitic drug widely used in veterinary medicine. The US Food and Drug Administration has confirmed that ivermectin suppresses the replication of SARS-CoV-2 in vitro. However, even with a dose ten times the recommended doses, the desired lung tissue density cannot be achieved. Therefore, it is recommended that inhaler forms be developed and evaluated in clinical studies.

Lopinavir

Lopinavir is a viral protease enzyme inhibitor. In in vitro studies, the lopinavir / ritonavir combination was found to be effective for SARS-CoV and MERS-CoV at accessible doses (SARSCoV EC50, 17.1 μM). Consistent with the in vitro findings, lopinavir / ritonavir has been found to be effective in the treatment of SARS and MERS in clinical studies. In vitro studies show that lopinavir / ritonavir is highly effective on SARS-CoV-2. Pharmacokinetic studies show that a blood density of 10 μg / ml can be achieved with 2 x 400/50 mg lopinavir / ritonavir administration, which includes in vitro EC50 values. A mathematical model study evaluating the very high protein binding capacity of lopinavir / ritonavir has been claimed that the desired density may not be achieved in the lung tissue. In this respect, a loading dose on the first day of clinical use should be considered.

Remdesivir

Remdesivir is an effective nucleoside analogue to Filoviruses (Ebola, Marburg et al.). After parenteral administration, it passes from the blood to the tissues in a very short time and the active compound remains in the cells for a longer time.In vitro studies have shown that it inhibits the proliferation of RSV, MERS-CoV and SARS-Cov-2. When 10 mg / kg is administered parenterally, it reaches a density of 10 μM. There is evidence that the active metabolite accumulated in the cells will reach the effective concentration as a result of administration of remdesivirine as a single daily dose for two hours.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is used in the treatment of malaria. Hydroxychloroquine binds very poorly to proteins, rapidly spreads to tissues, and its half-life is reported to be 32 ± 9 days. Although its anti-viral mechanism

of action is not fully known, it is mainly pointed out that it pre-vents infection when cells are used before they become infected. It has been reported that the effective dose is reached when 2 x 400 mg is used for five days. The most important side effect is QT prolongation. It has been calculated that the daily dose that causes QT prolongation is 2x600 mg and above. QT prolongation occurred in an average of 3.6 ± 1.6 days in patients who received 400 mg on the first day and 200 mg thereafter.

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CHAPTER 2

VIROLOGICAL CHARACTERISTICS OF THE SARS-CoV-2

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INTRODUCTION

Coronaviruses (CoV), which are members of the *Coronaviridae* family, are enveloped, single-stranded viruses with the longest known RNA genome (26-32 kilobases). This virus family takes its name from the crown appearance of the protrusions on the round viral surface (crown, corona in Latin) **(Figure 1)**.

The viral genome encodes non-structural proteins (nsp) and structural proteins (sp): *spike* (S protein) forming the protrusions on the surface, *envelope* (E protein), and *nucleocapsid* (nucleocapsid protein; N). The family is divided into four groups as alpha- (group 1), beta- (group 2), gamma- (group 3), and delta-CoV (group 4). In the 1970s, coronaviruses were detected in many animals (such as dogs, chicks, mice, rats) that cause various diseases, especially the respiratory and gastrointestinal systems. In humans, they mainly cause respiratory and gastrointestinal system complaints, usually mild and rarely more serious diseases such as bronchitis and pneumonia. Currently, six CoVs that cause disease in humans have been identified. While HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 cause mild respiratory infections, especially in children, SARS-CoV-1 and MERS-CoV cause more serious

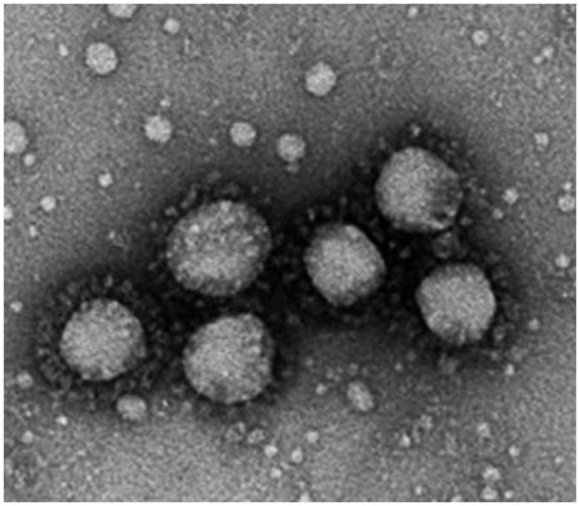

Figure 1. Image of SARS-CoV-2 by electron microscopy (Copyright © 2020 National Institute for Viral Disease Control and Prevention, China CDC).

and fatal diseases. SARS-CoV-1 (Severe Acute Respiratory Syndrome-CoV-1), a beta-CoV, is responsible for the epidemics emerging in China between 2002-2003 and remained partially localized, with a mortality rate of approximately 10%. With a total of 8,273 cases and 775 deaths, this first serious CoV epidemic has reached a mortality rate of 50%, especially in the elderly. MERS-CoV (Middle East Respiratory Syndrome-CoV) was first isolated in Saudi Arabia in 2012, and it causes an infection with a mortality rate of approximately 30%. MERS-CoV-2 is considered one of the most dangerous viruses known since it has been detected in 2494 cases and caused 858 deaths (case/death rate: 34.4%).

SARS-COV-2

On December 31, 2019, 27 cases of pneumonia with none of the known infectious agents responsible were reported in Wuhan city, China. It has been found that almost all of the cases clinically characterized by dry cough, fever, respiratory distress, and bilateral lung findings are associated with the seafood market in Wuhan. On January 7, 2020, a new CoV was detected in throat swab samples taken from patients at the Chinese Center for Disease Control and Prevention. It was named 'Severe Acute Respiratory Syndrome Coronavirus 2', briefly SARS-CoV-2. The World Health Organization (WHO) named the

disease caused by this virus as COVID-19. As the epidemic tends to spread to different countries in a short time, WHO declared on January 30, 2020, that the problem is an international public health concern and declared that it poses a serious threat to the health systems of countries. This important health problem was declared as a pandemic on March 11, 2020, due to its global spread continuing with all its intensity.

SARS-CoV-2, a Beta-CoV subfamily member, is a spherical RNA virus 60-140 nm in diameter. The first 2/3 of the genome that forms its genetic structure consists of a polyprotein encoding 15 non-structural proteins (nsp) that play a role in the replication of the virus. The remaining 1/3 is responsible for encoding four major structural proteins (sp): S, E, M, and N proteins. Of these four structural proteins, the S (spike) protein is used for the attachment of the virus to the target cell. The E (envelope) protein enables the assembly of new viral particles and leaving the host cell. The M (matrix) protein plays a role in establishing the structural integrity of the virus. The N (nucleocapsid) protein, on the other hand, is responsible for protecting the structural features of the virus and providing its relationship with the immune response **(Figure 2)**.

ORIGIN OF CORONAVIRUSES AND THEIR SOURCE IN HUMANS

HCoV-229E, HCoV-NL63, SARS-CoV and MERS-CoV viruses originate from bats, while HCoV-OC43 and HCoV-HKU1 originate from rodents. Nowadays, it is accepted that bats carry many viruses (reservoir), but they do

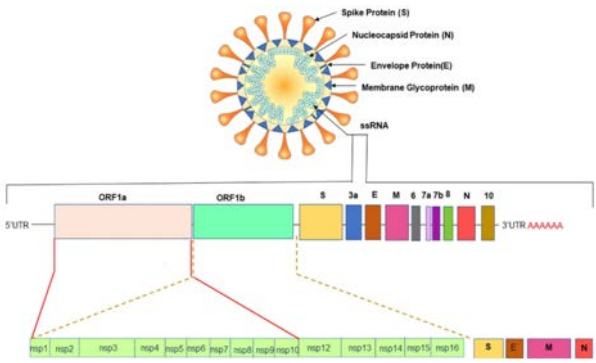

Figure 2. Schematic presentation of the SARS-CoV-2 and its genome. (source: https://respirator research.biomedcentral.com/articles/10.1186/s12931-020-01581 z/figures/2)

not directly transmit these microbes to humans, except for rabies. Generally, viral agents pass from bats to other animals (intermediate hosts) and from there to humans. Indeed, it has been proven that the intermediate host of MERS-CoV is camels, and the intermediate host of SARS-CoV is felines. Genetic analysis of viruses isolated from animals has enabled us to trace coronaviruses detected in different living species. By following this path, it was possible to determine the similarities, differences, and sources of viruses in different living organisms.

In the studies carried out in more than 19,000 animals (bats, rodents, and primates) in different geographies, 98% of the isolated coronaviruses were detected in bats. One or more CoVs were found in 8.6% of the 12,333 bats examined. Phylogenetic studies of the viruses isolated from nine patients in China in the early days of the COVID-19 pandemic have shown a similarity between human and bat coronaviruses and suggested that the virus would be transmitted to humans from bats in the first days of the epidemic. However, research has shown that although the origin of the virus is bats, the transmission does not occur directly from this animal. As a matter of fact, it has been determined that bats, which are mammals, hibernate in December and that bats are not sold in the winter period in the Huanan seafood market where the epidemic occurred. Also, since the genetic similarity is lower than 90%, it has been suggested that the possibility of transmission from bats is low, and even though the reservoir of the agent is bats, the virus was transmitted most likely from an intermediate host as in the MERS and SARS-CoV outbreaks. After that, it was investigated which animal was responsible for the transmission. The opinion that it could be pangolins (scaly mammals from the order Pholidota; anteater-like animals) was accepted. It is known that pangolins are used as food in Far Eastern countries. These animals caught, especially in the African continent, are brought to China illegally and sold in markets.

During the pandemic, several conspiracy theories on the subject have been put forward, and the opinion that the virus was produced in laboratories and spread to the public, either deliberately or accidentally, was frequently voiced. However, it has been scientifically demonstrated by genetic analysis of the isolated viruses that it is impossible to produce SARS-CoV-2 in the laboratory. Based on the fact that 75% of infectious diseases are zoonoses today, it is a scientific fact that SARS-CoV-2 originates from bats, is transmitted to humans through pangolins. It is one of many viruses that spread to humans by jumping species due to close contact with animals.

MECHANISM OF SARS-COV-2 INFECTION

For the infection to begin, the causative virus must enter sensitive cells, and to do so; it must bind to the receptor on the cell surface. It has been shown that SARS-CoV-2 infects epithelial cells in the nose and bronchi at the first stage and binds to a receptor on these cells, called ACE-2 (angiotensin-converting enzyme 2), via the S protein on its surface. After this attachment, the contribution of the enzyme called TMPRSS2 (type 2 transmembrane serine protease), which is also found on the host cell membrane, is required for the virus to be taken into the cell. With the help of this enzyme, the virus attached to the cell is taken inside. Thereafter, the viral RNA passes into the cytoplasm of the infected cell, and the replication process of the virus begins. As a result, numerous new SARS-CoV-2 production takes place inside the cell, which is like a virus factory, and these viruses spread around and infect new cells with the destruction of the host cell **(Figure 3).**

Interestingly, unlike viruses that cause other respiratory infections such as influenza, ACE2, the receptor specific for SARS-CoV-2, is not only found on respiratory tract cells. The presence of this receptor on almost all tissues and organs in the body, such as the digestive, urogenital and nervous systems, outside of the respiratory system, causes SARS-CoV-2 to infect the whole body. The virus can bind to other receptors besides ACE2. It has been suggested that binding to the CD147 (basigin = EMMPRIN) receptor, which is among these and is also found in cells involved in the immune response, may trigger an abnormal immune response. In addition, the Neuropilin-1 receptor

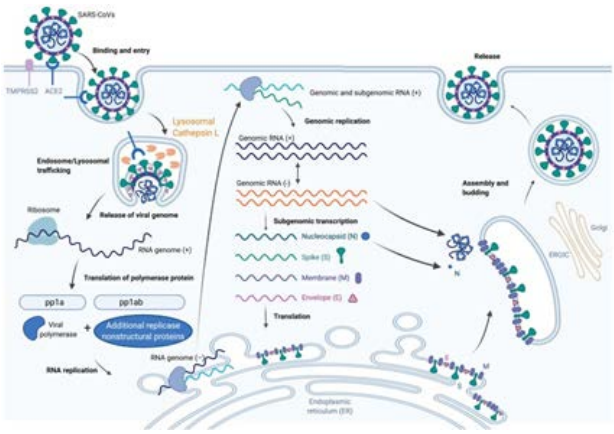

Figure 3. Mechanism of SARS-CoV-2 infection (source: https://www.cell.com/trends/immunology/fulltext/S1471-4906(20)30233-7).

has also been shown to facilitate the entry of SARS-CoV-2 into cells, especially in the nasal cavity.

SARS-COV-2 AND MUTATIONS

Since SARS-CoV-2 spread continues, mutations in the viral genome are inevitable. The evolutionary rate of SARS-CoV-2 is calculated as approximately $6x10^{-4}$ nucleotides/genome/year. This rate means that SARS-CoV-2, which has a genome of approximately 30 kb, will change approximately 20 nucleotides per year. Mutations in and around the receptor binding domain (RBD) can significantly alter the structure of the S protein. Thus, they should be constantly monitored in terms of their effect on the disease's transmission and severity. GISAID (Global initiative on sharing all influenza data; http://gisaid.org/) is continuously monitoring the new mutations of SARS-CoV-2 during the pandemic. Many of the variants appeared in late 2020 and early 2021 (Hodcroft E.M. 2021. CoVariants: SARS-CoV-2 Mutations and Variants of Interest. https://covariants.org/). However, mutations that cause altered function are particularly dangerous, as they increase transmissibility and disease severity. D614G is the most detected variant in all SARS-CoV-2 infections to date and is attributed to increasing transmission. The D614G variant is more infectious because the functional change in the structure of the S protein facilitates the binding of RBD to the receptor. Three new variants have recently emerged: 501Y.V1/B.1.1.7 from United Kingdom, 501Y.V2/B.1.351 from South Africa, and 501Y.V2/P.1 from Brazil. Lately, a new variant (B.1.429) suspected of causing a rapid increase in cases has been identified in the United States of America. The spread of these strains worldwide is of concern, as transmission may increase and the effect of vaccine/therapeutic neutralizing antibodies reduce. Variants B.1.1.7 and B.1.351 are partially resistant to antibody neutralization. In addition to being resistant to many monoclonal neutralizing antibodies, the Brazil variant P.1 is also more resistant to the plasma of convalescent and vaccinated individuals. Existing vaccines can achieve partial protection against the P1 variant. In studies conducted with Pfizer/BioNTech, Moderna, and Novavax vaccines, antibody titres did not change against B.1.1.7, but lower efficacy was observed against B.1.351 variant. The E484K mutation, found in both South African and Brazilian variants with reduced neutralization of some convalescent serum antibodies, is thought to contribute to resistance. Another variant found in the UK, South Africa, and

Brazil, N501Y, is thought to increase the transmission of SARS-CoV-2 by enhancing binding to the ACE2 receptor. These emerging variants have been shown to reduce the efficacy of existing antibody treatments used against COVID-19, in addition to vaccination.

TRANSMISSION CHARACTERISTICS OF SARS-COV-2

SARS-CoV-2 is transmitted from person to person through virus-containing particles scattered by coughing, sneezing, or even speech. At the beginning of the pandemic, only symptomatic patients were considered to spread the virus. However, it was later found out that asymptomatic individuals also disseminate the virus. It has been found that asymptomatic cases spread the virus for a long period of at least 19 days and the same amount as symptomatic patients. Some asymptomatic people start to show symptoms for a while, but a few (about 6.2%) continue to spread the virus without symptoms.

Classically, respiratory viruses are transmitted by droplets of infected individuals. Particles >5 μm in diameter fall to the ground quickly due to gravity's effect before they can go 1-2 m away. On the other hand, particles <5 μm in diameter can remain hanging in the air, and the virus is transmitted to humans from the air in environments that contain such particles. The main transmission route for SARS-CoV-2 is close and long-term contact in closed environments. As a matter of fact, the virus spreads rapidly in closed environments (cruise ships, restaurants, sports halls, religious ceremonies, choral work, celebrations, etc.). For this reason, it is necessary to comply with the physical distance rules besides using masks in preventing the spread. On the other hand, it is claimed that there are people defined as super spreaders in the transmission of infection in the community and spread a great number of viruses around. However, these individuals' characteristics, why, and how they spread viruses over a long time are not yet clear.

SARS-CoV-2 has also been detected in other body fluids such as feces, blood, and semen. However, the role of the isolation of the virus in these body fluids to the dynamics of the spread has not yet been clearly elucidated.

VIROLOGICAL DIAGNOSIS IN SARS-COV-2 INFECTIONS

Different laboratory methods are used at different stages in the diagnosis of virus infections. To detect acute cases in the early stages of SARS-CoV infec-

tions, virus propagation in cell culture, antigen detection, or nucleic acid detection methods is used. Specific antibodies are detected in the late period and especially in seroprevalence studies.

The most common method used in the early period is polymerase chain reaction (PCR). PCR detects the RNA of the virus. It should be kept in mind that not every PCR positivity necessarily indicates that the virus is replicated; that is, it is alive. The sensitivity limit for the detection of SARS-CoV-2 RNA was determined by the CDC as 4-10 RNA copies/µl. Primers targeting one or more genes of the RNA-dependent RNA polymerase (RdRp), N, and E genes of the virus are used. However, PCR, which has high sensitivity in diagnosing many infectious diseases such as viral hepatitis, influenza, or HIV infection, does not give similar results in detecting SARS-CoV-2 infections. The sensitivity of the PCR method varies between 58-96%, especially depending on the sample. In this context, where and how to get the sample is important. Bronchoalveolar lavage or sputum samples are particularly convenient for this virus that affects the lower respiratory tract. Depending on the dynamics of the virus, some unexpected results may occur in the detection of SARS-CoV-2 by PCR. For example, cases that give positive results in the convalescence phase or, as in asymptomatic cases, positivity in recovering cases. As a result, it should be kept in mind that a positive SARS-CoV-2 PCR test result is not always an indicator of active replication, and false negativity may be observed due to unsuitable sampling. Also, according to the tomography results, a large number of patients (on average 40%) who are thought to have COVID-19 patients but whose PCR tests are negative are encountered. Since SARS-CoV-2 infects other tissues and organs besides the respiratory system, the virus can also be detected in samples other than the respiratory tract. The virus can be detected in stool and serum for approximately 17 days. Viral shedding from the respiratory tract and stool may be prolonged. However, (except for immunosuppressive patients) no live virus was detected since the ninth day of the disease.

Many studies are carried out on the development of antigen detection tests. These tests, which are generally produced with "lateral flow" technology, can be used as Point-of-Care tests when they have high sensitivity and specificity. However, the most important problem with these tests is that they can't reach sufficient sensitivity. Therefore, antigen detection tests may not detect infected cases, especially with low viral load.

Serological tests detect SARS-CoV-2 specific antibodies as an indirect indicator of contact with the virus. However, antibody kinetics specific to COVID-19 are in contradiction. Antibodies do not become positive in all cases. It is not known whether they will cross-react with other coronaviruses and how long they will be found. Antibody levels are different in mild and severe cases.

HOST IMMUNE RESPONSE IN SARS-COV-2 INFECTION

As in other infectious diseases, in COVID-19, the immune system steps in, and a virus-specific response occurs. It is expected that the virus is inactivated in the immune response. However, it is seen that the immune response creates problems rather than benefits, especially in severe COVID-19 patients.

SARS-CoV-2 prevents the effect of interferon by disrupting or downregulating its synthesis. On the other hand, interferons that should work for the benefit of the host increase the number of ACE2 in some cases and allow more viruses to enter the cells. Furthermore, the p53 gene stimulated by interferons suppresses the differentiation of epithelial cells, leading to a more severe course of the disease and susceptibility to bacterial superinfections.

In some severe cases of COVID-19, the so-called cytokine storm is encountered. The activation of a large number of immune system cells causes an exaggerated cytokine production by these cells. This resulting abundance of cytokines causes damage through inflammation and an even more severe disease course. Exaggerated activation of cells resulting in excessive production of cytokines such as IL-1, TNF-α, IL-6 intensely stimulates new cells. Thus, it causes tissue damage, vascular destruction, multiple organ failure, and the clinical picture's aggravation.

Another feature of the immune system observed in COVID-19 cases is the numerical and functional decrease, especially in T cells. Since T cells play an important role in the immune response's formation and functioning, lymphopenia disrupts the entire system.

Specific antibodies are synthesized during SARS-CoV-2 infection. However, it has been suggested that these antibodies will only be useful when they are neutralizing the virus. Otherwise, they may be harmful by taking a role in carrying the virus into some cells.

CONCLUSION

As a result, the different parameters of the immune response that exist to protect the body are disrupted by SARS-CoV-2; multiple organ deterioration, vascular damage, coagulation disorder, and respiratory distress occurs.

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CHAPTER 3

THE ORGANIZATION AND TRIAGE OF COVID-19 PATIENTS APPLYING TO EMERGENCY SERVICE

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INTRODUCTION

Cases of coronavirus disease 2019 (COVID-19) have emerged in Hubei, Wuhan, and many parts of China since December 2019. The disease spread rapidly to other countries, and the World Health Organization (WHO) reported the infection as a global pandemic. Despite the implementation of comprehensive control measures, the impact of COVID-19 has gradually increased. According to the data of the World Health Organization, 108.006.680 confirmed cases and 2.378.115 deaths occurred all over the world as of February 14, 2021. Despite the progress in vaccination studies, these numbers are increasing day by day.

COVID-19 has placed an unexpected and unforeseen burden on emergency services and health care systems that are at the forefront of any pandemic. Emergency services that are already crowded outside of pandemic conditions were overwhelmed. The organization was greatly disrupted by the

devastating epidemic. While other departments can regulate patient flow and volume with scheduled interviews and operating room allocations, emergency services must respond efficiently and effectively to any patient fluctuations.

Critical and supportive care of patients with suspected COVID-19 should focus on early detection and forthwith isolation, as well as convenient infection prevention. Limiting the dissemination of the infection, determining whole cases, and predicting the seriousness of the disease are very important in the emergency room management of COVID-19.

INFECTION PREVENTION AND CONTROL MEASURES

Apart from patients affected by this epidemic, emergency services are usually full of other patients seeking care for other diseases. If an infected person comes to a busy emergency room, they are likely to spread the virus and potentially contaminate others. Telling people not to come to the emergency room unless they are very sick definitely reduces emergency room visits. However, this method can cause an increase in morbidity and mortality rates in the period. Limiting the number of face-to-face interactions in the emergency room can be achieved by the use of telehealth and teletriage.

Telehealth and Teletriage

Telehealth is generally defined as the usage of electronic data and telecommunication technologies to support health care services. While telehealth services can be used in a counseling model where clinicians communicate with each other using digital health tools, it is more commonly used to support communication between clinicians and patients through both live video and remote monitoring devices and mobile technology.

The least complex and most cost-effective platforms are required to quickly and successfully implement a teletriage program during the pandemic. Platforms that are already in use in your hospital and familiar to the staff for teleconferencing, such as Apple, Facebook Messenger video chat, Zoom, and Skype can be preferred

Doctors who do not have experience in telehealth, especially those who can not work actively for medical reasons, can be trained (eg quarantined but asymptomatic, immunocompromised, pregnant, elderly doctors, or those with underlying medical conditions). They can continue working with minimal or no exposure in this way. Thus, the impact on personal problems during this

critical period can be minimized. Many patients with COVID-19 signs and symptoms can be managed from home via telehealth and they do not need to go to healthcare. This model could potentially eliminate face-to-face interac-tions as long as evaluations are made by an experienced provider. Besides, it can reduce the usage of personal protective equipment (PPE) and other risks to hospital functioning and hospital staff.

In the United Kingdom, pre-existing emergency phone lines have been used to reduce emergency room visits or ambulance dispatches. An online clinic was set up to ease patient triage in a study conducted in China. Hospitals first decided on the urgency of treatment through free online consultation and recommended that non-urgent patients postpone their hospital appointments or refer to non-epidemic hospitals. They gave treatment instructions to low-suspect patients by isolating themselves at home and invited patients with highly suspicions to the fever clinic. The online clinic effectively alleviated the workload of the emergency department and eased the early determination of possible cases.

Prehospital Evaluation

Patients can be transferred by the pre-hospital emergency medical service or come immediately to the emergency room. The case, acquaintances, or medical practitioner can call the emergency number to indicate that a possible case of COVID-19 infection with symptoms is seeking care. In this case, the pre-hospital team will meet with the patient by wearing PPE and assess the clinical condition. They analyze whether family individuals or other people in contact are likely contaminated and organize the transport to the hospital or the isola-tion of whole likely infected people at home. This suggested way to assist the health care system may prevent the dangerous passage of an infected patient into the public space of the emergency room. If the patient is brought to the hospital by ambulance, emergency medical services (EMS) staff should inform the emergency department of the hospital to prepare the treatment center for the infected patient. In this context, a protocol should be designed between EMS and hospital emergency service.

Organization of Emergency Department

When a patient directly admits to the emergency room, the patient's rapid triage is mandatory. All patients admitted to the emergency department should be screened for symptoms of COVID-19. Efforts should be made to place patients with suspected COVID-19 in single examination rooms as soon as possible, and these rooms should be disinfected after each visit.

each visit. If an examina-tion room is not immediately available, such patients should not wait among other patients. It is more appropriate to keep these patients in a personal vehicle or in a well-ventilated area where they can easily access respiratory hygiene materials and be separated by at least six feet. If there is not enough space in the hospital for this, tents can be used for this purpose (Figure 1

Figure 1. Waiting tent area for patients with suspected COVID-19

Immediate recognition of cases with COVID-19 presenting with asymptomatic or atypical complaints is a challenge. Therefore, general practices to control infection throughout an epidemic are even more critical. Hand and respiratory hygiene, and contact prevention precautions are essential. The Center for Disease Control and Prevention (CDC) recommends installing ample non-contact hand sanitizer stations and easy-to-dispense face mask boxes at the entrances of the emergency room and hospital. Besides, everyone entering the facility should immediately wear a mask and not take it off as long as they are in the facility, cover their mouth/nose when coughing or sneezing, use and dispose of tissue paper carefully and do hand hygiene after contact with secretions. Banners should be placed suggesting all these protec-tive measures.

Suspected cases of COVID-19 should be isolated by minimizing movement in the emergency room, x-ray unit, toilets, or other parts. Combining plural potentially infected patients into one group is an appropriate precaution. Keeping these in mind, facility changes are inevitable for emergency services. Creating staging areas such as tents, split flow and split cohort models may be preferred to safely reduce and manage the number of patient spikes and minimize infection in the hospital. The purpose here is to separate low, medium, and high-risk areas in the emergency department. These areas should have physical barriers (Figure 2) between the mand have visual cues

appropri-ate to the levels of attention needed. If the building permits, adequate ventila-tion should be provided in all areas. A plan of the emergency department is shown in Figure 3

Clean area (Lower risk):

It is the area that hosts patients other than COVID-19. These patients have no history, suspected exposures, signs, or symptoms related to COVID-19. Since asymptomatic carriers can also be found in this space, suitable protection measures and guidance should be followed.

Figure 2. Physical barriers between the different risk areas

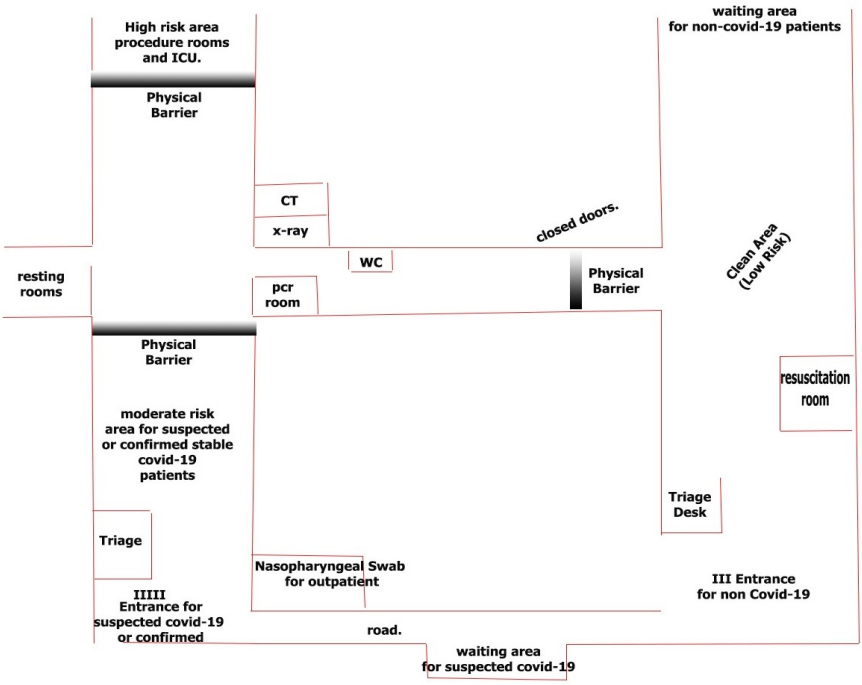


Figure 3: The scheme showing the rearrangement of the emergency department of our hospital after Covid 19.

Area with suspicion (Moderate risk):

It is the area that hosts clinically stable patients with suspected or confirmed COVID-19, such as screening and triage clinics. Patients in this category are those with a respiratory rate of <20 breaths per minute with ≥90% oxygen saturation at room air. If the disease is not suspected to be related to COVID-19, higher levels of care, including resuscitation, may be offered at this position.

Contaminated area (High risk) :

All patients in this area are highly susceptible to COVID-19. These patients appear sick. They respond positively to one or more disease triage questions. These patients are tachypneic (RR> 20), tachycardic (HR> 120), or hypoten-sive (BP <90/60) with an oxygen saturation of <90% in room air. These patients need additional evaluation and stabilization. There is a high risk of exposure to aerosolized viral particles in this area. This area should be equipped for high levels of care, have negative pressure rooms, and optimally have rooms splitted by walls and doors. If possible, negative pressure chambers should be used for procedures that cause aerosol generation.

Work Safety and PPE Use

Providing health care personnel with qualified PPE plays an important role in avoiding occupational exposure and infection. The U.S. CDC recommends gowns, gloves, surgical masks, and eye protection as standard PPE to health care professionals for COVID-19 infection control. While PPE provides some protection, CDC recommends the use of plexiglass physical barriers in the field of office workers and triage as the best protection method against droplets.

In cases where the patient undergoes aerosol-generating processes such as cardiopulmonary resuscitation, manual ventilation before intubation, tra-cheal intubation, open aspiration of airways, bronchoscopy, tracheotomy, non-invasive ventilation, high-flow oxygen, and nebulizer treatments, airborne precautions (apron, gloves, N-95 and eye protection) are recommended. The PPE box is a barrier made of transparent material that can be disinfected quickly. The PPE box, with cutouts for the neck used for the patient's neck, is placed on the head of an unconscious patient. There are two holes on one side of the box for access to intubation or aspiration (Figure 4).

Endotracheal intubation of patients with COVID-19 should be applied by health care professionals experienced in airway management to minimize the

Figure 4: A view of the PPE box

number of attempts and the risk of transmission. Video laryngoscopy with a C-MAC (Karl Storz SE and Co. KG, Tuttlingen, Germany) or a GlideScope (Verathon, Inc., Bothell, WA) device is suggested as the first choice for endotracheal intubation. Viral and bacterial filters are placed in the circuit after intubation. The use of automatic CPR devices for patients requiring cardiopulmonary resuscitation is beneficial in reducing the number of staff in the resuscitation room.

Triage of COVID-19 Patients

Rapid diagnosis and effective triage are necessary for the emergency department, to prevent the spread of the virus among patients and health care professionals, delays in guiding patients to other services or intensive care, and if necessary, to provide rational and efficient use of the limited resources. To make effective and appropriate triage of patients with COVID-19, it is necessary to recognize the symptoms of the disease, determine the severity of the disease, and identify the risk factors for rapid deterioration in the clinical condition of the patient, severe disease, and/or increased mortality.

Screening and diagnosis of COVID-19 patients

Signs and symptoms of COVID-19 may vary. Most patients experience one or more of the following:

- Fever or chills
- Cough (with o or without sputum production)
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle aches
- Headache
- New loss of taste or smell
- Congestion or runny nose
- Nausea or vomiting
- Abdominal pain/diarrhea

Anorexia, sore throat, confusion, chest pain, dizziness, syncope, and hemoptysis, ocular manifestations such as conjunctival hyperemia, chemosis, epiphora, or increased secretions have also been indicated. Elderly people and immunosuppressed patients especially may present with atypical symptoms such as fatigue, reduced alertness, diarrhea, loss of appetite, and absence of fever.

Adverse pregnancy events such as shortness of breath, fever, fatigue, and gastrointestinal (GI) symptoms due to physiological adaptations in pregnant women, or other regional disease symptoms may overlap with the symptoms of COVID-19. There are no specific clinical features that dependable distinguish COVID-19 from other respiratory viral infections. Dyspnea that develops a few days after the onset of the first symptoms is thought-provoking in terms of COVID-19. A definitive diagnosis can not be made without microbiological tests.

Whom to test

- People with symptoms of COVID-19.
- People in close contact with someone with confirmed COVID-19 (15 minutes or more within 6 feet).
- People who participate in activities that pose a higher risk to COVID-19, where social distancing can not be maintained, such as traveling, attending large mass gatherings, or being in crowded interiors.

Limited capacity may prevent all patients with suspected COVID-19 from being tested in some locations. Local health departments can set specific criteria for testing.

In some patients, the baseline test may be negative, false-negative nucleic acid amplification tests (eg RT-PCR) taken from upper respiratory tract samples are well documented. If a patient appears to have COVID-19 disease, they should be treated like COVID-19 in isolation and a second test performed within 3 days. When the two tests are negative and there is a high suspicion for COVID-19 (for example, a patient with consistent clinical symptoms and a history of contact with a person with known or suspected COVID-19), infection control measures should be continued. If possible such patients should be managed with an infectious disease specialist to assist in the evaluation of alternative etiologies. For screening purposes, patients with fever should be tested according to routine protocols in areas with other endemic infections such as malaria, dengue fever, and tuberculosis (TB) that cause fever. These infections may coexist with COVID-19. Throughout the influenza season, whole patients with acute respiratory symptoms in hospitals and other health care settings should be tested for SARS-CoV-2 and influenza in parallel to monitor incidence and trends over time.

Due to the probability of false-negative test results for SARS-CoV-2 RNA, chest CT is of great importance in the screening and diagnosis of patients who do not have an exact epidemiological history or who may have a history of occult contact in the epidemic region. Lung CT shows multiple small irregular shadows and changes, especially in the peripheral lungs at an early stage, followed by multiple ground-glass opacities in both lungs. Serious patients may present with signs of pulmonary consolidation, but pleural effusions are infrequent. Lung ultrasound is very useful in the initial evaluation of patients in the emergency room. It is more sensitive than a chest X-ray with a diffuse B-line pattern and is associated with a good response to PEEP. (For detailed information, see Chapter 16 the imaging and radiological diagnosis methods in a patient with COVID-19).

SEVERITY OF DISEASE

While most people develop the mild and moderate disease (80%), approximately 15% develop severe disease, and 5% have critical disease. According to the classification of the world health organization;

- Mild disease: symptomatic disease matching COVID-19 case definition without evidence of pneumonia or hypoxia.
- Moderate disease: clinical signs of pneumonia (fever, cough, dyspnoea, rapid breathing) but no sign of severe pneumonia, with SpO2 ≥90% in room air

- Severe disease: clinical signs of pneumonia (fever, cough, dyspnoea, rapid breathing) plus one of the following: respiratory rate> 30 breaths/minute; severe respiratory distress; or SpO2 <90% in room air
- Critical disease: complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury.

RISK FACTORS FOR SEVERE DISEASE AND MORTALITY

Patients with the following conditions are at risk of serious sickness and increased mortality; age more than 60 years, cancer, chronic kidney disease, chronic obstructive pulmonary disease, down syndrome, immunodeficiency condition due to organ transplant, obesity (body mass index [BMI] ≥30 kg/m^2), severe cardiovascular disease (eg, heart failure, coronary artery disease, cardiomyopathy), smoking, sickle cell anemia, type 2 diabetes mellitus, pregnancy.

Patients with the following conditions may be at high risk for serious sickness and increased mortality; asthma (moderate to severe), cerebrovascular disease, cystic fibrosis, hypertension, immunodeficiency condition (eg, from hematopoietic cell transplant, HIV infection, use of corticosteroids, or other immunosuppressants, other immunodeficiencies), liver disease, neurologic conditions (eg, dementia), overweight (BMI ≥25 but <30 kg/m^2), pulmonary fibrosis, thalassemia and type I diabetes mellitus.

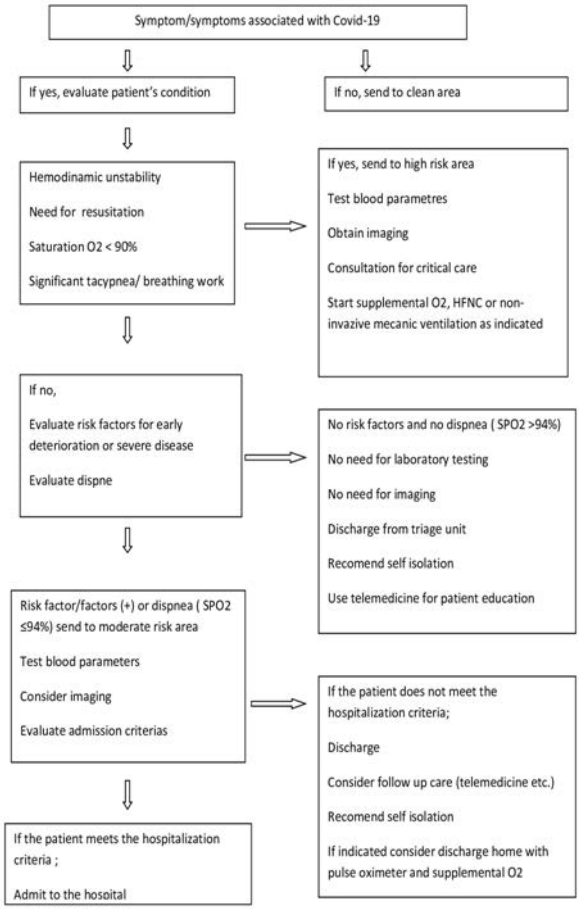
Some patients with mild to moderate sickness may be discharged home directly by the physician in the triage. However, isolation is required for whole suspected or confirmed cases, and follow-up care and monitoring should be arranged. The decision to monitor a suspected case in a health care facility, community facility, or home should be made on a case-by-case basis. This decision will depend on clinical presentation, the need for supportive care, potential risk factors for severe illness, and conditions in the home. This may also apply to pregnant and postpartum women with pre-existing or preg-nancy-related comorbidities (eg pregnancy-induced hypertension, gestational diabetes).

Patients without risk factors for severe sickness (identified or probable) and shortness of breath are discharged to home self-care. They receive instruc-tions to contact their clinicians with any worsening symptoms. Patients with one or more known risk factors for severe disease should be closely monitored for deterioration (outpatient pulse oximeters, close telehealth follow-up, out-patient clinic, and calling EMS if any worsening of clinical status). The use of home oximetry monitoring is being evaluated for patients seen in the emer-gency room setting and discharged home. However, there is no high-quality evidence that patient outcomes are improved using this approach. In the outpatient setting, patients are asked to check their oximeters twice a day and inform their doctor if the value falls below 95 percent.

Critters for transfer to the emergency department are;

- Patients appear toxic and in distress
- Resting O2 saturation <94% on room air
- Desaturation on ambulation or requires bronchodilator treatment or any following criteria
- Change in mentation (eg, confusion, change in behavior, difficulty in rousing) or other signs and symptoms of hypoperfusion or hypoxia (eg, falls, cyanosis, hypotension, anuria, chest pain suggestive of an acute coronary syndrome)
- RR >20/min
- Pulse>120 bpm or
- Systolic BP< 90 mm Hg and diastolic BP<60 mm Hg.
- Criters for hospitalization and likely admission are; Having <94% oxygen saturation in room air, > 30 breaths/minute respiratory rate, PaO2/FiO2 <300 mmHg or >50% lung infiltration.

Triage algorithm of Covid-19 patients applied to the emergency department



CONCLUSIONS

Emergency services, which are at the forefront of the health care system in any pandemic, have to identify and manage patients with suspected COVID-19 and continue to provide emergency health care to other patients who present with emergencies other than COVID-19, as in non-pandemic periods. Emergency services should play a main role not only in patient management but also in the rapid identification of COVID-19 by helping with surveillance and spread control. This situation required a massive reorganization of emergency services to face the significant increase in patients with suspected COVID-19 around the world. Emergency services should be prepared to separate the "clean" flow from the "dirty" flow, adjusting areas and resources to the flow of incoming patients. Fast and effective triage is essential for early

diagnosis of patients, preventing delays in treatment, ensuring rational and efficient use of limited resources, and protecting health care personnel and patients from contamination.

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CHAPTER 4

THE SKIN FINDINGS ASSOCIATED WITH COVID-19

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INTRODUCTION

Because of the rod-like protrusions on the surfaces of corona viruses, these viruses are named as crowned virus (corona virus) due to the meaning of "crown", that is, "corona" in Latin. In December 2019 in Wuhan, China, the corona virus disease, which was defined as an unexplained viral pneumonia factor, was named **Co**rona **Vi**rus **D**isase-2019 (COVID-19).

The virus can be transmitted from animal to human and from human to human. The most common form of transmission among humans is through the respiratory system via droplets. Other routes of transmission are fecal-oral and mother-to-child. The first entry point of the virus is the respiratory system, but it can also infect the urinary, digestive, hematological and neurological systems. The incubation period is five days on average and may vary between 2-14 days.

Typical symptoms of COVID-19 disease are respiratory system symptoms such as fever, cough, fatigue, myalgia, and shortness of breath. However, it is

known that COVID-19 has symptoms such as decrease in smell and taste, headache, vomiting, diarrhea and hemoptysis, and can cause multisystemic involvement that can result in organ failure or even death. COVID-19 disease remains at mild or moderate level in most patients and symptoms resolve within a week. It was reported that no symptoms were observed in some patients.

Some of the dermatological manifestations related to COVID-19 may start before other manifestations of the disease, some may start at the same time with other manifestations or after other manifestations. The most frequently reported areas for the dermatological manifestations of COVID-19 are hands and feet. Besides, lesions in one or more parts of the body have been reported.

Skin lesions in patients with COVID-19 infection have been reported in the literature with a rate of 0.2-20%. While the incidence was 0.2% in a case study of 1099 positive patients in China, it was reported as 20.4% in a case series of 88 patients in Italy.

PATHOGENESIS OF COVID-19 SKIN MANIFESTATIONS

The pathophysiology of skin lesions in COVID-19 is unclear. COVID-19 not only affects the respiratory system but also the erythrocytes. Damage to erythrocytes can cause vascular changes and damage all tissues and organs. This situation may explain the emergence of vascular changes seen in the skin.

In the case where the first COVID-19 skin manifestation was reported outside of China, the patient with petechial skin rash in Thailand was considered as dengue fever, which is common in this country. However, when respiratory symptoms began, COVID-19 was diagnosed by using polymerase chain reaction.

Case reports and studies on the skin manifestations of COVID-19 were reported from all over the world, and the data on the skin manifestations caused by the disease are increasing day by day. As per these data, we can divide the skin manifestations of COVID-19 into three groups. These findings are summarized in **Table 1**.

MUCOCUTANEOUS MANIFESTATIONS ASSOCIATED WITH COVID-19

Skin manifestation associated with COVID-19 are divided into seven subgroups according to the morphology of the lesions: They can be classified as maculopapular lesions, vesicular lesions, urticaria, pernio-like (acroischemic) lesions, livedoid/necrotic lesions, purpuric lesions and other lesions.

The most common lesions are maculopapular lesions. Pernio-like (acroischemic) lesions are generally observed in mildly severe cases, vesicular lesions in moderate cases, urticarial lesions and maculopapular lesions in severe cases, livedoid and purpuric lesions in the most severe cases.

a) Maculopapular lesions

Maculopapular lesions are nonspecific cutaneous manifestations in COVID-19 patients and are the most frequently reported skin lesions. It is similar to measles, often symmetrical erythematous macules and papules are observed. Maculopapular lesions usually start from the body and then spread to the extremities. As with other viral exanthems, involvement of the oral mucosa and palmoplantar areas has not been reported. The lesions are usually itchy and heal within 10 to 14 days. Symptoms usually occur at the same time as other symptoms of COVID-19, and can be seen in the early or later stages of the disease.

Perifollicular may appear as erythema multiforme-like, pityriasis rosea-like, erythema elevatum-like, purpuric, Dengue-like petechial eruption, itchy purpuric flexural eruption.

Treatment: Oral antihistamines and topical corticosteroids are used for symptomatic control of itching. Systemic corticosteroids may be given in more severe cases.

b) Vesicular lesions

These lesions initially begin as erythematous papules and then turn into vesicles. It can sometimes be seen as bullous or hemorrhagic. Lesions are not polymorphic like varicella but consist of monomorphic vesicles. It can be distributed as localized or generalized. Vesicular lesions generally start at the same time as systemic symptoms or after three days and heal without a trace within an average of 10 days. Lesions are usually located on the body, but can also be seen in the extremities. Those located in the feet are more severe and may show bulla, bruising and superficial necrosis. It is usually itchy and is more common in the middle age group. It was also been reported in asymptomatic children.

Treatment: Treatment is not necessary as it heals by itself. Wet dressing may be recommended to reduce itching.

c) Urticaria

Itchy, sharply demarcated, erythematous, edematous, pale papules and plaques are often seen. Urticaria lesions last less than 24 hours, but as the previous lesion heals, new lesions may appear in other areas. Urticaria is a nonspecific cutaneous manifestation in COVID-19 patients. It can be seen in any part of the body, but is usually reported on the body. It can rarely be seen in the palmar area. While urticaria usually occurs at the same time as the symptoms of COVID-19, it can sometimes be seen in the late period and rarely in the early period. It is generally more common in middle age. The clinical picture regresses within an average of one week. Fever with urticaria is more specific for COVID-19 than urticaria alone.

Treatment: It is treated with antihistamines as classic urticaria.

d) Pernio-like lesions

Pernio-like lesions (pseudo-pernio) are lesions characterized by pernio-like erythematous, violous patches or plaques that usually occur on the feet and rarely on the hands. These may also occur as erythematous edematous or bullous types. These lesions are called *'COVID toes'*. The lesions are usually painful and/or itchy and heal within two weeks on average without leaving a scar. It can be asymptomatic sometimes. It mostly shows an asymmetrical distribution. It was generally reported in children and adolescents. This usually occurs in the later stages of COVID-19 disease.

Treatment: Avoiding cold exposure, wearing socks, smoking cessation is recommended. Topical corticosteroids, pentoxifylline, hydroxychloroquine and calcium channel blockers can be used in severe cases.

e) Livedoid/necrotic lesions

The vascular reaction that presents as a mesh-like (reticular) red, purple discoloration in the body or lower extremities is called livedo. When this manifestation is symmetrical and continuous, it is called livedo reticularis, and when it is asymmetrical and dashed, it is called livedo racemosa. These manifestations may be a complication of the primary lesion of COVID-19 or the hypercoagulapathy associated with COVID-19 and vascular occlusion resulting from vascular damage. Livedoid and necrotic lesions are among the least common findings and are generally reported in older patients with more severe disease. These lesions often start at the same time as other symptoms of COVID-19, but rarely after systemic symptoms or in the early period.

Livedoid skin changes can be unilateral. In severe patients, bulla and necrosis may develop on the lesion and these lesions heal with atrophic, white scar tissue within an average of 10 days.

If livedoid and necrotic lesions are observed in COVID-19 patients, early clinical recognition of these lesions is extremely important, as this is an important clue for systemic thrombotic vasculopathy.

Treatment: Follow-up may be considered in mild cases and anticoagulant therapy in severe cases.

f) Purpuric lesions

Purpuric lesions in COVID-19 can resemble other viral rashes such as dengue fever. Purpuric lesions can be seen localized, acrally or generalized distributed in intertriginous areas. These lesions were not observed on the face, palmoplantar area, fold areas of the skin and mucous membranes. Purpuric lesions may turn into hemorrhagic bulla in severe cases. It was reported that purpuric lesions are generally seen in elderly patients with severe COVID-19 and may indicate a poor prognosis. In dermoscopy of purpuric lesions, a yellow colored central globule with a violous edge has been reported.

Treatment: Topical corticosteroids can be used in mild cases and systemic corticosteroids in severe cases.

g) Other skin lesions

Other skin manifestation mostly reported as case reports: perifollicular papules, erythema induratum bazin, erythema multiforme like lesions, pityriasis rosea like lesions, dyshidrotic eczema like lesions, Grover's disease like lesions, SDRIFE (Symmetrical Drug Related Intertriginous and Flexural Exanthema) like lesions, miliaria like lesions, Sweet syndrome like lesions, erythema nodosum like lesions, perioral erythema, eyelid dermatitis, eosinophilic panniculitis, and androgenetic alopecia.

During the course of COVID-19 disease, the severity of pre-existing skin lesions such as acne, rosacea, seborrheic dermatitis, atopic dermatitis and neurodermatitis have been observed to increase.

Oral mucosal manifestation related to COVID-19 are co-infections such as nonspecific oral ulcers, desquamative gingivitis, petechiae, vesiculobullous lesions and candidiasis. The most commonly reported oral symptom in COVID-19 patients is taste disturbances.

In the early days of the COVID-19 pandemic, pediatric infections were rare, but over time, the frequency of COVID-19 in children has increased due to the transmission of the virus from the community and family. Cutaneous

symptoms such as erythematous rash, widespread urticaria, multiple erythematous-edematous macules and plaques resembling chilblain-like lesions on the dorsal faces of the fingers and varicella-like vesicles have been reported in COVID-19 positive pediatric patients.

Numerous erythematous-edematous macules and plaques resembling chilblain-like lesions on the dorsal faces of the fingers have also been described. Kawasaki-like hyperinflammatory syndrome and pernio-like bluish-red edematous lesions with borders on the dorsal surfaces of the toes have also been reported in children with possible COVID-19 infection.

Also, a syndrome with multiple organ involvement due to COVID-19 in children and adolescents has been defined and named as "Multisystem Inflammatory Syndrome". Polymorphic mucocutaneous manifestations such as erythema of the hands and feet, induration, oral mucositis, and bilateral nonpurulent conjunctivitis have been reported in this syndrome.

SKIN MANIFESTATION DUE TO THE USE OF PERSONAL PROTECTIVE EQUIPMENT

Long-term use of personal protective equipment such as an N95 or FFP2 mask, protective goggles, face shield, gloves, and hand hygiene cleaners can cause various skin lesions. It can also cause exacerbation of pre-existing skin diseases. Skin lesions due to personal protective equipment can also be seen in healthcare workers, especially those who follow personal hygiene rules excessively.

Undesirable skin reactions that may occur due to long-term use of masks and protective glasses are mainly dry skin, pressure damage, contact dermatitis, urticaria and pigmentation on the bridge of the nose. Besides, exacerbation of an existing skin disease such as acne vulgaris, facial dermatitis, seborrheic dermatitis and rosacea has been reported.

Using odorless, mild moisturizers after every hand wash during the day and using odorless moisturizer before bedtime and wearing cotton gloves under latex gloves also reduce sweating and skin irritation.

DERMATOLOGICAL MANIFESTATIONS DUE TO DRUGS USED FOR THE TREATMENT OF COVID-19

Maculopapular lesions, acute hemorrhagic edema, petechiae, vesicles, livedoid lesions, urticaria, papules and plaques can be observed during the course of COVID-19 disease. It is necessary to understand whether such lesions are associated with infection or the drugs used in the treatment of COVID-19. Taking a detailed anamnesis on this subject is very important for this differential diagnosis. Atypical lymphocytosis, neutrophilia, eosinophilia, high blood drug level, edema on skin biopsy and an eosinophilic inflammation in whole blood examination are findings that indicate cutaneous drug reaction.

Reported side effects of drugs used in the treatment of COVID-19 disease: morbiliform drug eruption, urticaria / angioedema, pruritus, xerosis, mucocutaneous dyspigmentation, skin atrophy, acneiform eruption, telangiectasia, petechiae, ecchymosis, striae, hirsutism, acute generalized exanthematous pustulosis, psoriasis exacerbation, Stevens Johnson syndrome, erythematous syndrome rash, erythema annulare centrifigum, photosensitivity, DRESS (Drug Rash with Eoshinophilia and Systemic Symptoms) syndrome, vasculitis, fixed drug eruption, anaphylaxis, various skin manifestations such as erythroderma, leukocytoclastic vasculitis, papulopustular eruption, psoriasiform dermatitis.

CONCLUSION

Information about the skin manifestations of COVID-19 infection during the pandemic process is important for early diagnosis of the disease, appropriate management and evaluation of patients. Pernio-like acral lesions are usually seen in young adults infected with COVID-19 with an asymptomatic or mild course. Livedoid/necrotic lesions are seen in elderly people and as a manifestation of more severe COVID-19 disease. In terms of its prognostic value, it is extremely important to recognize such skin lesions early.

Table 1: Classification of cutaneous findings associated with COVID-19

1.Mucocutaneous manifestations associated with COVID-19	2.Skin manifestation due to the use of personal protective equipment	3.Dermatological manifestations due to drugs used for the treatment of COVID-19
a) Maculopapular lesions	dry skin, pressure damage, contact dermatitis, urticaria,-pigmentation on the bridge of the nose	Morbiliform drug eruption, urticaria/angioedema, pruritus, xerosis, mucocutaneous dyspigmentation, skin atrophy, acneiform eruption, telangi ectasia, petechiae, ecchymosis, striae, hirsutism, acute generalized exanthematous pustulosis, psoriasis exacerbation, Stevens Johnson syndrome, erythematous syndrome rash, erythema annulare centrifigum, photosensitivity, DRESS (Drug Rash with Eoshinophilia and Systemic Symptoms) syndrome, vasculitis, fixeddrugeruption, anaphylaxis, erythroderma, leukocytoclastic vasculitis, papulopustular eruption, psoriasiform dermatitis
b) Vesicular lesions		
c) Urticaria		
d) Pernio-like lesions		
e) Livedoid/necrotic lesions		
f) Purpuric lesions		
g) Other skin lesions: perifollicular papules, erythema induratum bazin, erythema multiforme like lesions, pityriasis rosea like lesions, dyshidrotic eczema like lesions, Grover'sdisease like lesions, SDRIFE (Symmetrical Drug Related Intertriginous and Flexural Exanthema) likelesions, miliaria like lesions, Sweets yndrome like lesions, erythema nodosum like lesions, perioral erythema, eye lid dermatitis, eosinophilic panniculitis, androgenetic alopecia		

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CHAPTER 5

COVID -19 AND OCULAR FINDINGS

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INTRODUCTION

The coronavirus outbreak, which spread from the Chinese city of Wuhan to the whole world in early January 2020, has gained a new aspect when WHO declared the disease as a pandemic. Unlike previous pandemics, failure to detect the initial transmission route of the causative virüs and due to its rapid spread, the Covid-19 pandemics affected millions of people all over the world and caused many deaths at the end of a year. Covid-19, defined as a new RNA β corona virüs, is transmitted from person to person by coughing and sneezing from an infected patient, and direct contact and droplets. The primary target is lung epithelial cells in Covid-19 and this target is associated with angiotensin-converting enzyme (ACE-2) receptors. Patients may develop symptoms ranging from mild symptoms to death with severe respiratory failure, due to both upper and lower respiratory tract affection. Upon the demonstration of ACE receptors in the conjunctiva and retina of the eye, ocular involvement may be caused by the disease or a source of transmission. While no ocular

symptoms or signs were found in the SARS-CoV and MERS-CoV outbreaks in the past, Covid-19 has been demonstrated by PCR in the conjunctiva of patients. Therefore, Covid 19 may cause clinical findings with involvement in ocular structures and the ocular surface is also considered as an entrance to the body for SARS-Cov2. It should also be remembered that ocular contamination is potential occupational exposure for ophthalmologists. In this section; ocular findings of Covid-19, the treatments used, and side effects related to drugs will be discussed.

COVID -19 AND ANTERIOR SEGMENT FINDINGS

Transmission and treatment focused on respiratory disease in Covid 19. However, the ocular surface is presumed to be an entrance, potentially through exposure to aerosol droplets or hand-eye contact. Conjunctivitis is the most common ocular finding in the anterior segment in patients with Covid 19. Cases have been reported suggesting that conjunctivitis may be the first manifestation of the disease and then systemic symptoms begin after a variable time. The pathogenetic mechanisms of conjunctival infections are still unknown. Some studies have shown the presence of ACE-2 receptors in the cornea and conjunctival limbus. This condition may be a cause of conjunctivitis. Another mechanism thought to be responsible for conjunctivitis is an autoimmune-mediated macrophage activation syndrome. Although the exact incidence of Covid 19 conjunctivitis is not known, it is thought to range from 0.8% to 31.6%. Symptoms such as photophobia, stinging, burning, itching and blurred vision develop in patients with Covid 19 conjunctivitis, which are similar to other signs of viral conjunctivitis.

Chemosis, conjunctival hyperemia, follicular reaction of the tarsal conjunctiva, epiphora, watery discharge, mild eyelid edema, eyelid margin hyperemia, blepharitis, and enlarged submaxillary and preauricular lymph nodes were observed on examination. Although conjunctivitis is seen in patients with Covid 19, its incidence is observed to be extremely low compared to the general population. One cause for the less frequent occurrence of viral conjunctivitis may be the protective effect of antimicrobial agents such as lactoferrin and secretory Ig A on tears and continuous cleaning of the ocular surface with tear flow.

Covid 19 can be seen with symptoms similar to Kawasaki Disease (KD) in infants and children. Kawasaki disease is a sudden onset and often self-limiting vasculitis that mostly affects young children and is characterized by

oropharyngeal and limb changes, fever, polymorph rash, and cervical lymphadenopathy. It is of particular importance for ophthalmologists because ocular involvement can be seen in KD. The most common ocular findings in KD are iridocyclitis, subconjunctival hemorrhage, punctate epitheliopathy, papill-edema, vitreous opacities and conjunctival injection. It is estimated that the incidence of KD may increase with the spread of the outbreak, and ophthalmologists are recommended to act with awareness in terms of the signs and symptoms of the disease.

Although it is not directly related to the disease, care should be taken when using contact lenses in patients with Covid-19. Patients who wear contact lenses are recommended to suspend contact lenses as much as possible during this period, due to the possibility of more contact with their eyes and considering that one of the possible transmission routes of the disease is the conjunctiva. In case of mandatory use, it has been reported that the lens can be cleaned and used in its solution after providing hand hygiene.

Effects on the ocular surface have also been reported in Covid-19 disease other than conjunctivitis. However, this situation develops in intensive care units, depending on the environment itself or the treatment applied, rather than the direct effect of the disease. Ocular surface involvement can be seen in a broad spectrum, ranging from mild conjunctivitis to infectious keratitis. The absence of blinking and loosening of the orbicularis oculi muscle, which occurs due to the use of muscle relaxants and sedative agents in patients under mechanical ventilation, may lead to drying of the ocular surface and lagophthalmos. The usage of continuous positive airway pressure (CPAP) and oxygen masks in patients with Covid-19 may cause the ocular surface to dry and lead to infection development. Besides, symptoms such as conjunctival chemosis and subconjunctival hemorrhage were observed when the patients were placed in the prone position. Conjunctival chemosis may develop due to decreased venous pressure and increased hydrostatic pressure in the eye. Conjunctival hemorrhage may occur in case of increased central venous pressure. Both conditions have a good prognosis and do not require treatment as long as they do not develop an ocular surface problem. Although these conditions involving ocular surface problems are frequently observed in intensive care units, it has been shown that they can be prevented and their incidence can be reduced with appropriate protocols.

COVID -19 AND POSTERIOR SEGMENT FINDINGS

ACE receptors have been demonstrated in ocular tissues in the posterior segment such as the retina, retinal pigment epithelium, ciliary body and choroid. Since COVID-19 can target ACE-2 expressing vascular pericytes, viral infection can lead to complement-mediated, microvascular damage, endothelial cell dysfunction and thus ocular circulation involvement. Coagulopathy in Covid -19 may predispose to various thromboembolic events and this situation is mostly observed as pulmonary thromboembolism. Complement-mediated thrombotic microangiopathy is thought to be the leading factor in the pathogenesis of microcircular damage in patients with Covid-19. Adjunct system activation, which causes retinal artery and vein occlusions, was previously defined as directly responsible for vascular damage. It should also be noted that high serum C3 complement factor level is associated with an increased risk of developing microvascular complications in diabetic patients through endothelial dysfunction and thrombosis. Although there have been reports of retinal artery occlusion in patients with Covid-19, an increase in the incidence of retinal vein occlusion has not been noted. Similar to lung tissue, this situation may predispose to vascular events originating from an embolism in ocular tissues. There are few studies evaluating retinal findings in Covid-19 patients. In a study using optical coherence tomography (OCT) and color fundus photographs, hyperreflective foci were detected, especially in the papillomacular bundle, ganglion cell, and inner plexiform layers. However, OCT angiography findings and ganglion cell complexes of these patients were normal. Another finding was cotton wool spots and retinal microhemorrhages observed in the retinal passage, especially in red-free photographs, in the same study. However, no intraocular inflammation, decrease in visual acuity, and impairment in light reflexes were observed in the patients. Fundus photographs of 54 patients with Covid 19 were taken and the artery-vein diameters and possible retinal findings were evaluated in another study. It has been found that Covid 19 can affect the vascular structure of the retina, causing retinal findings such as retinal hemorrhages, cotton wool spots, and dilatation in the retinal veins. However, it has not been clarified whether this is a cause, or an immune response developed by the patient against the disease. Another patient group affected secondarily in the Covid -19 pandemic is vascular diseases of the retina such as age-related macular degeneration diabetic retinopathy and diabetic retinopathy. It is thought that the number of patients may increase in the future, especially in the diabetic retinopathy group, due to the restrictions in the pandemic, reduced physical

activity, additional problems brought by their diseases, and difficulties in accessing treatment.

COVID-19 AND NEUROOPHTHALMOLOGIC FINDINGS

Involvements of the cranial nerves have been reported in patients with Covid-19. This is due to direct invasion of the nerve or its inflammatory effects. Clinical findings such as diplopia and ophthalmoparesis may be seen in patients. Perineural changes could be demonstrated in some cases by magnetic resonance imaging. Although it has been experimentally demonstrated that Covid-19 can also affect the optic nerve, no cases of ischemic or inflammatory optic neuritis have been reported due to the pandemic.

POSSIBLE OCULAR COMPLICATIONS IN COVID-19 TREATMENT

The Covid-19 treatment has especially aimed at the treatment of lung findings and respiratory failure symptoms. With the increase in oxygen saturation in the blood with the prone position, treatment planning is made especially in this way. It is known that the prone position applied to the patient affects both the anterior surface and vascular structure of the eye. Ocular anterior surface problems of the intensive care patients were mentioned above. The effects of treatment on ocular perfusion will be discussed in this section. Ocular perfusion depends on intraocular pressure (IOP) and ocular blood flow. These are related to vascular resistance and arterial-venous pressure and vascular resistance. The prone position can significantly reduce ocular perfusion through on two mechanisms. While increasing venous pressure, it also increases IOP. Intraocular pressure is elevated in the prone position, besides, systemic conditions such as arterial hypertension, diabetes, and atherosclerosis can cause an increase in vascular resistance, further reducing ocular blood flow. Patients who are more likely to get Covid 19 and hospitalized in the intensive care unit due to their comorbidities also have a higher risk of developing ocular hypoperfusion. Publications are reporting that prone position ventilation applied in intensive care units before Covid-19 disease may uncommonly lead to acute ischemic optic neuropathy and develop permanent vision loss. Another rare complication of the prone position is angle-closure glaucoma. In the presence of underlying risk factors, besides prone position, acute angle-closure may also

develop due to anticholinergics, sympathomimetics, and other drugs (sulfonamide derivatives and topiramate). As a result, ocular complications can be observed rarely in intensive care units. However, vision-threatening complications can be recognized and prevented by expanding the awareness of intensive care staff.

OCULAR SIDE EFFECTS OF DRUGS USED IN THE TREATMENT OF COVID-19

There is no treatment with proven effectiveness in Covid-19 disease so far. However, antivirals, anti-malarial drugs, immune modulators, and steroids are used for the treatment of the symptoms and signs of the disease with partial efficiency. Antivirals are in the first place in the treatment planning of Covid -19. Antiviral drugs (lopinavir and ritonavir) commonly used in HIV treatment have been used in the early stages of the pandemic as a probable treatment in patients with Covid-19 infection. Signs of different types and degrees of toxicity in the retina due to these drugs have been described in the past.

The use of favipiravir, which was launched in Japan in 2014 and approved for the influenza pandemic, came up in the later stages of the Covid 19 pandemic. Favipiravir, which is strong in vitro efficiency against Covid 19 and has oral use, has been shown to have better disease cure rates than other antiviral drugs. Favipiravir has mostly gastrointestinal system side effects, and its ocular toxicity has not been reported yet.

Another group of drugs used in the treatment of Covid 19 is chloroquine and hydroxychloroquine which are known as anti-malarial drugs. In addition to their use in malaria, these drugs are also used in the treatment of many rheumatological diseases. Their efficacy in the treatment of Covid-19 has been determined in in-vitro and animal experiments and has been rapidly approved by the FDA for treatment. The mechanisms of action of these drugs are not fully known in the treatment of Covid-19 disease, but various hypotheses have been proposed. The first hypothesis is that they cause an increase in endosomal pH that inhibits viral fusion and replication. Another mechanism of action is that they affect terminal glycosylation of the ACE-2 receptor for cell entry targeted by the virus. It is also thought that these drugs provide immunomodulatory activity in patients with Covid-19. Studies have shown that chloroquine and hydroxychloroquine improve the clinical symptoms of the disease, reduce the exacerbation of pneumonia and encourage virus-negative seroconversion. Patients are treated for an average of 4-7 days with protocols

that vary according to clinics. The most common side effects related to treatment are hypoglycemia, cardiological problems due to prolongation of QT interval, anemia, extrapyramidal disorders, and ocular problems. Patients who used these drugs for rheumatological diseases were followed up in ophthalmology clinics for ocular side effects before the Covid-19 pandemic. Cumulative and dose-dependent side effects can be detected both in the anterior and posterior segments in the long term. Chloroquine and hydroxychloroquine may cause intraepithelial corneal lesions, posterior subcapsular cataracts, and ciliary body dysfunction at the anterior segment. They may accumulate in the retinal pigment epithelium and cause bilateral maculopathy, firstly parafoveal and then affecting the fovea at the posterior segment. The most serious risk factor for the development of chloroquine and hydroxychloroquine toxicity is excessive daily dosage. The American Academy of Ophthalmology recommends keeping the daily dosage of chloroquine less than 2.3 mg/kg and hydroxychloroquine 5.0 mg/kg to prevent the development of retinopathy. Duration of treatment is also an additional critical factor. The risk of ocular toxicity is below 2% after 10 years and increases to almost 20% after 20 years in long-term use of hydroxychloroquine at recommended doses. However, it has been reported that high doses of chloroquine and hydroxychloroquine can lead to retinopathy even in a shorter treatment period. The last two studies in patients receiving 800-1,000 mg of hydroxychloroquine per day over 1-2 years have shown an incidence of retinopathy from 25% to 40%. Retinal toxicity was not reported with 2 weeks of chloroquine or hydroxychloroquine administration. Therefore, it is thought that high doses of these drugs may increase retinal toxicity over weeks to years and drug-related effects can be detected after ophthalmological examinations to be performed in the post-covid period.

Interferons (IFN) have been proposed as a potential treatment for Covid-19 due to their antiviral, antiproliferative, and immunomodulatory activities. It has been observed that IFN-β, a subtype of IFNs, is particularly effective in the treatment of inflammatory symptoms of Covid-19. It is known that interferons affect especially the posterior segment of ocular tissues. They may cause changes in the optic nerve head and posterior pole, such as cotton wool spots and retinal hemorrhage. Findings can be seen at the late stages of treatment and improvement in symptoms is reported after discontinuation of treatment.

Interleukin-1 (IL-1) inhibitors (anakinra) and interleukin-6 inhibitors (sarilumab, siltuximab, and tocilizumab) are also immunomodulatory agents

used in the treatment of Covid-19. Increases in IL-1 and IL-6 levels have been observed in Covid 19 patients, but the effects of this situation on clinical outcomes have not been reported yet. A case thought to be associated with retinal toxicity of tocilizumab in the pre-Covid 19 pandemic has been shown in the literature. Multifocal cotton-wool spots and retinal bleeding and bilateral papilledema were described in thiscase. These ocular side effects, which are rarely seen during treatment, should be kept in mind.

Recently, steroids have been added to the treatment to suppress the inflammation that occurs in Covid 19. Systemic steroids are used in variable doses for a short time,depending on these verity of the disease. Although systemic steroids are frequently used in the treatment of ocular diseases (opticneuritis, uveitis, etc.), ocularsideeffects (glaucoma, cataract, etc.) may occur in patients receiving short-term and high-dose therapy. Besides, there may be an increase in the incidence of diabetic retinopathy due to high blood sugar levels during steroid use in patients with diabetes mellitus who also have increased risks against Covid 19.

CONCLUSION

As a result, apart from being a transmission route for the disease, ocular tissues may directly be affected and various clinical findings may be seen in Covid-19 disease. Also, various side effects may appear due to the drugs used during the treatment. Ophthalmologists should be aware of the clinical signs of the disease, the possibility of transmission during the examination, and the adverse situations that may occur during treatment. The long-term ocular effects of Covid 19 disease are still unclear. Future studies will be a guide to reveal the effects of the disease in both systemic and ocular tissues.

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CHAPTER 6

COPD AND COVID-19

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INTRODUCTION

As Coronavirus Disease 2019 (COVID-19) appeared in December 2019 in China, it began to spread rapidly throughout the world and as a result of this, it has been announced as a pandemic in March 2020 by World Health Organization (WHO). COVID-19 having a broad clinical spectrum can occur with clinical conditions ranging from asymptomatic cases to cases with severe respiratory failure requiring intensive care. As cases continued to increase, preliminary information relating with COVID-19 began to come from China, being the place of origin of disease. In a multi-center epidemiological study conducted with 1099 patients, the average age was reported to be 47 years, it was stated that it was seen more in men with ratio of 52.1%, and in 23.7% of patients at least one chronic disease such as Chronic Obstructive Pulmonary Disease (COPD), Hypertension (HT), Diabetes Mellitus (DM) accompanied it. In another study conducted with different case numbers, it was determined that COPD prevalence varied in the range of 1.1 and 2.9%.

Chronic diseases are defined as diseases that continue for three months ore more, having slow progress, being caused by more than one risk factor, being complicated and that generally impairing life quality of a person. As it

is the case with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) pandemics, in COVID-19 pandemic, in the increase of death incidents, these diseases constituting risk factor have been leading factors in causes of death in developed and developing countries throughout the world. COPD is a leading cause of death and disability worldwide, with persistent respiratory symptoms and characterized by airflow restriction due to airway inflammation and / or alveolar abnormalities. Attacks during the disease both increase the progression of the disease and cause an increase in mortality. As hospitalizations increase during an attack, there is also an increase in health expenditures. As it is known, the most important cause of COPD attacks is respiratory tract infections and it is seen that most of these infections are viral infections.

It is estimated that COPD patients will be more affected by this pandemic since the possibility of protection of these patients from COVID-19 infection may decrease due to the fact that COPD patients are older than the normal healthy population, they also have other comorbid diseases caused by age, and the cognitive functions related to the disease may decrease. At the same time, since the symptoms of COPD and viral infection are similar, patients may hesitate to apply to a healthcare institution. This situation may cause delays in diagnosis and treatment in both diseases.

RISK FACTORS, COPD AND COVID-19 PREVALENCE

COPD has been found to be associated with an increased risk of mortality and morbidity in community-acquired pneumonia. Altered local / systemic inflammatory response, impaired host immunity, microbiome imbalance, persistent mucus production, structural damage, and inhaled corticosteroid use have been suggested to contribute to such risks. Most of the risk factors mentioned are also considered as risk factors for COVID-19. With the spread of the pandemic around the world, it has been predicted that COVID-19 will be more common in patients with COPD and will be severely affected. However, according to currently available data, COPD does not appear to be a common comorbidity in COVID-19 patients. Different results were obtained from studies conducted in different countries. While the prevalence of COPD was reported to be 2-3% among patients with COVID-19 pneumonia in the first publications conducted in Wuhan, the first place of pandemic, in an article published in Italy in April 2020, COPD was among the comorbidities accompanying patients with COVID-19 with a rate of 18.3%. It has been shown to

be in 6th place. Later, in a study conducted in Europe, it is seen that the rate of COPD, which is one of the comorbidities accompanying COVID-19 cases, has changed. In a review by Lippi et al., It was reported that COPD carries a 5-fold higher risk for severe COVID-19 infection. Again, in this review, it is especially emphasized that patients with a history of COPD should pay attention to restrictive measures in order to minimize the possible exposure to COVID-19 and show necessary care to avoid contact with COVID-19 cases. Close and careful monitoring of all COPD patients with suspected COVID-19 is recommended for clinicians. In another publication where 1590 cases from different regions were examined, all diseases accompanying COVID-19 were investigated and accordingly it was determined that the most obvious differences of COPD cases compared to non-COPD cases at the time of application were older age, higher fever, less dry cough, but more sputum, shortness of breath, and loss of consciousness. Again, considering the course of the disease in this study, it was reported that the rate of development of respiratory failure, intensive care requirement, intubation and ultimately mortality rates were higher in COPD patients. Although more than 97 genetic factors have been identified in the pathophysiology of COPD, smoking is the most important environmental risk factor for COPD. While 15% to 50% of smokers develop COPD, 80% to 90% of COPD patients are smokers or ex-smokers. Although there is no definitive evidence that smokers are at increased risk of COVID-19 in studies conducted to date, WHO argues that smokers are at risk for COVID-19 infection. In a study conducted on 1099 COVID-19 patients supporting WHO, it was stated that while 4.7% of non-smokers died, 12.7% of smokers have died or were subject to a serious clinical situation and 16.9% of severe cases were smoking while 11.8% of milder cases were smoking. On the other hand, in a meta-analysis conducted in China, it has been shown that active smoking is not significantly associated with COVID-19 severity. In another review that included 2002 patients in which eleven case series were examined, it was reported that the risk of serious disease was quadrupled in COVID-19 patients accompanied by COPD, and this risk was approximately 2 times in active smokers. In the same study, it was calculated that mechanical ventilation and intensive care need and mortality were statistically significantly higher in patients with COPD. Apart from smoking, other risk factors that play a role in the development of COPD are also predicted to affect the incidence and prognosis of COVID-19. Biomass resulting from biomass combustion is considered to be the main risk factor especially in non-smoking COPD patients. Biomass has been shown to alter the pulmonary defense like tobacco smoke,

and this effect has been emphasized to increase and accelerate the progression of COPD. The effect of biomass on the lungs is supported by several epidemiological studies that report an increased risk of acute respiratory infections in people exposed to this environmental pollutant. While there are no studies on COVID-19 infection with biomass exposure yet, a report by Harvard University researchers reported an increased mortality rate with COVID-19 associated with long-term exposure to fine particulate matter (PM 2.5), one of the main components of biomass. The reason for the relatively low prevalence of COPD in COVID-19 patients compared to other comorbidities is thought to be due to the difference in data from different countries, as well as the length of time since the beginning of the pandemic. Another reason for low prevalence can be attributed to the avoidance of close contact by COPD patients, strict observance of quarantine and general hygiene rules and therefore not being infected.

THE RELATIONSHIP BETWEEN COVID-19 PATHOGENESIS AND COPD

In the pathogenesis of COVID-19, lung epithelial cells are the main target for the virus. Coronaviruses attach to host cells through the spike (S) protein on their outer surface and enter the cell. The life cycle of the virus in humans begins with the binding of the S protein to angiotensin-converting enzyme 2 (ACE2) receptors on the host cell surface. Therefore, increased ACE2 receptor level in a host affects the prognosis and mortality of COVID-19. In the studies conducted, increased ACE2 expression was found in the lower respiratory tract bronchial epithelial cells of patients with COPD and smokers. This explains the possibility of having COVID-19 severe in the population with COPD.

CLINICAL COURSE OF COVID-19 IN COPD

COVID-19 pneumonia and COPD attack symptoms are similar in clinical practice. At this point, the question that comes to mind is whether we will accept COVID-19 as a cause of COPD attack. Although corona viruses are accepted as the cause of COPD attack, imaging and postmortem studies in COVID-19 show that the pathophysiology is different from COPD exacerbation pathology. In this case, the need for a rapid differential diagnosis by the clinician arises. Some tips for the differentiation of this situation may provide

convenience to physicians. One of them is fever which is a common finding in COVID-19 cases, but which is not a common finding in COPD exacerbations. Similarly, while cough is dry in COVID-19, it is more productive in COPD. Cough with sputum is also in the foreground in patients with COVID-19 and COPD. Studies have shown that exposure to viral infection may increase bacterial colonization in the lower respiratory tract and even increase the risk of bacterial infection in the period after COPD. Therefore, it can be predicted that the clinical course of the infection with COPD and COVID-19 may be poor. The most important auxiliary tests in differential diagnosis are of course the patient's laboratory data and radiological images. The most commonly used method for COVID-19 pneumonia in radiological imaging is lung computer tomography (CT). Radiological findings were classified for COVID-19 pneumonia as the CT images accumulated with the increase of cases. Typical CT findings are specified. (Table I) Emphysema, bronchiectasis, peribronchial thickening and possible cardiac pulmonary edema findings can be seen on CT during COPD attack. Although these images contribute to us in the differential diagnosis, the possible cause of the COPD attack may be COVID-19 pneumonia, and signs of viral pneumonia can also be added to these images. Comparison with the previous radiological images of the patient, if any, may be helpful in differential diagnosis. Definitive diagnosis can be reached by Polymerase chain reaction (PCR) and other blood parameters.

Table 1. Radiological Findings That May Be Seen in COVID-19 Pneumonia

Typical findings	Atypical findings
• Frosted glass opacity • Consolidation • Paving stone • Air bronchogram • Airway changes, air cyst • Reticular appearance • Nodules (with halo and inverted halo sign)	• Pleural fluid • Lymphadenopathy • Pericardial fluid • Cavitation

PARTICULARS TO PAY ATTENTION TO DURING TREATMENT AND FOLLOW-UP OF COPD DURING PANDEMIC PERIOD

A stable course of the disease is important in the follow-up of the patient with COPD. The continuity of the treatment they receive during the follow-up of these patients has been the main strategy of COPD patient management during the pandemic. An interim report was published separately by the Gobal

Initiative for Chronic Obstructive Lung Disease (GOLD), which is the COPD Global Initiative, and the National Institute for Health and Care Excellence (NICE), mentioning the management of COPD and emphasizing the importance of continuity of treatment. General preventive measures in stable COPD management can be listed as keeping the general body resistance high, paying attention to nutrition and sleep patterns, wearing masks in case of contact with the external environment and paying attention to general hygiene recommendations, not to ignore the possibility that the disinfectants used may cause bronchospasm and have a worse course of COVID-19 pneumonia as it increases the risk of COPD attacks. It is considered to quit smoking because it increases the risk. If we need to emphasize the nutrition of COPD patients again, especially poor nutritional status causes the risk of skeletal muscle loss or sarcopenia in these patients. Physical therapy and adequate nutritional supplementation are extremely important in helping COPD patients during recovery from severe illnesses, as neuro-muscular blockade will be required in both those with COVID-19-induced Acute Respiratory Distress Syndrome (ARDS) and the group that needs mechanical ventilation due to acute exacerbation of COPD. It is also stated in these reports that these patients should not come to the hospital for routine control, face-to-face contact should be minimized as much as possible. In this context, it is recommended to communicate with patients by phone, online interview or e-mail. Another important point that should not be forgotten is that while trying to physically protect patients with COPD, we should not ignore their emotional states. Even under normal conditions, approximately 40% of patients with COPD exhibit clinically depressive symptoms such as extreme fatigue, loss of interest in activities enjoyed, and 36% show anxiety symptoms such as nervousness, fear, and panic. It is thought that these symptoms will increase even more due to the pandemic. For this reason, COPD patients should be evaluated as multidisciplinary in face-to-face doctor interviews or online interviews, and necessary support should be given in terms of mental health.

It was also emphasized in the report that the stable COPD patients should continue their treatment regularly. In the same report, the view that inhaled corticosteroids (ICS) or oral corticosteroids used in COPD maintenance treatment are inappropriate during the COVID-19 pandemic does not constitute scientific evidence. In recent studies, it has been reported that dexamethasone will likely become the standard care treatment for COVID-19 patients, including patients with COPD. Although there are studies showing that the use of ICS increases the risk of pneumonia, published reports emphasize that patients using ICS should continue to use their medications and the current state of

the disease should not deteriorate during the pandemic period. Again in the GOLD report, it is said that even if the discontinuation of ICS was planned before, it should be postponed. The same is true for patients on long-term oral corticosteroids. These patients should continue to take their medication at the same dose. Prophylactic antibiotic use recommended for selected patients should continue as it was before the pandemic; however, prophylactic antibiotics should not be used to reduce the risk of COVID-19 pneumonia. Pulmonary rehabilitation programs recommended for COPD patients in groups B, C and D in a routine way should be continued using online resources. Patients who receive long-term oxygen therapy should continue their treatment without any change. Another important point is that COPD patients who smoke should be encouraged to quit smoking both to protect the bad prognosis of COVID-19 and to reduce the risks of acute exacerbation.

CONSIDERATIONS ON THE USE OF INHALERS AND DEVICES USED IN TREATMENT

The equipment used by patients in treatment is also of great importance in the pandemic process. Face masks and spacers used should be cleaned regularly in accordance with the cleaning instructions, inhaler devices should not be used with others. Some patients receive their inhaler therapy with a nebulizer. In another report published by NICE, it is stated that the use of nebulizers by patients will not pose an additional risk in terms of contamination, since the aerosol comes from the liquid in the nebulizer compartment and does not carry virus particles from the patient. However, if the patient has COVID-19 infection, the possibility of infecting others may increase. For this reason, patients should not be prescribed a nebulizer unless necessary, and if they do, it should be stated that they should be used in a well ventilated separate room. Likewise, patients using non-invasive mechanical ventilation (NIMV) at home should be instructed to use the device alone, if possible, in a well-ventilated room by taking appropriate precautions. Whether nebulizer or NIMV interconnections, both equipment should be disinfected frequently and regularly.

MANAGEMENT OF COPD PATIENTS DURING PANDEMIC PERIOD

As the epidemic spread, its effect was felt particularly in COPD patients. Pulmonary rehabilitation and face-to-face doctor meetings had to be post-

poned in most patients. This situation has created anxiety and worry in most COPD patients. Therefore, a written action plan should be prepared for all COPD patients. With this plan, it is planned to reduce the anxiety and worry of the patients and to provide information about the situation in which they should apply to the hospital. Pandemic prevention methods do not differ in COPD patients.

Hand hygiene and other preventive cleaning recommendations for these patients are no different from the normal population. Patients should be warned to use only substances that are used for disinfection and that they may cause bronchospasm. Regular nutrition, adequate hydration, regular sleep are recommended and exercise at home is also recommended for preventing COPD patients from COVID-19 and other infections.

Since coexistence of chronic diseases such as cardiovascular disease, hypertension and diabetes mellitus is common in patients with COPD, as the presence of these diseases may increase the possibility of having COVID-19 and the possibility of having a more mortal course if COVID-19 pneumonia develops, treatment of accompanying diseases should be followed regularly.

COPD patients should pay attention to daily changes in themselves, if there are symptoms such as high fever, cough, increase in sputum or shortness of breath, weakness, muscle pain, if the present symptoms do not disappear after symptomatic treatment at home, especially in the presence of high fever, shortness of breath and cough that does not decrease despite symptomatic treatment. They should apply to the nearest health institution. In order to reduce the risk of COVID-19 transmission while going to the healthcare institution, if possible he should go alone and if it is not possible, he should be accompanied by a maximum of one person. In addition to the precautions to be followed in the pandemic in polyclinics, routine respiratory function tests should not be requested from these patients.

Whether the cause of COPD attacks is COVID-19 or other reasons, different methods are not recommended for exacerbation treatment. If these patients are clinically indicated, oral steroids and / or antibiotics should be given. If the patient needs to be hospitalized due to an attack, the use of an inhaler intermediate device (such as spacer, aerochamber) should be prioritized, as far as possible, in terms of contamination risk. Continuation of routine oxygen therapy is recommended in COPD patients during an attack. Again, in the recommendations, it is stated that oxygen support should be given with oxygen mask in possible or definite COVID-19 patients, and high flow nasal oxygen should be avoided as much as possible in COPD patients

with COVID-19. Again, procedures such as sputum induction and nasotracheal aspiration, which are applied from time to time in hospitalized or advanced COPD patients, which may produce high amounts of infectious aerosols and pose a high risk for COVID-19 transmission, should be avoided, and if it is required, the necessary precautions should be taken.

CONCLUSION

COPD is one of the risk factors that increase mortality for COVID-19, both because of the elderly patients' age and its prevalence with other comorbid diseases. This risk is further increased as most COPD patients are smokers and / or ex-smokers. For this reason, COPD patients should have a written action plan that informs the methods of protection from COVID-19, the status of the treatments they are using, and how they will behave if they become infected with COVID-19. In order to avoid contact with patients with COPD, online and telephone calls should be organized even if there is no face-to-face meeting, and patients should be interviewed in a way that supports both medical support and mental health. Patients should continue their current treatment without any change. Even if hospitalization is required, they should receive their treatments in line with the recommendations without risking both themselves and healthcare professionals in terms of contamination. Again, pulmonary rehabilitation becomes important in these patients as it helps both functional and psycho-social recovery. In addition to COPD, patients should be encouraged to quit smoking as smoking affects the course of the disease negatively.

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CHAPTER 7

EMERGENCY SURGICAL APPROACHES TO COVID-19 PATIENTS

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INTRODUCTION

By the end of December 2020, the corona virus outbreak that began in China in December 2019 had infected more than 66 million people and caused the death of more than 1,5 million. It has affected and continues to affect the whole world. Although individuals of all ages are at risk, the risk for severe disease is greater in people aged 60 and over, who have chronic medical conditions and live in nursing homes. Regardless of chronic conditions, the mortality rate is highest for those over the age of 70. Community-based inequalities, such as access to healthcare and personal protective equipment, contribute to higher rates of serious illness. However, if we want to be successful in the fight against a global outbreak, all communities or all local areas within the community should be reached and provided with equal health services, as far as possible. The disease can be asymptomatic or progress to pneumonia with severe respiratory distress that can cause death. The most usual symptoms are fever, cough and shortness of breath, while headache and muscle aches are also relatively common. According to recent publications, an impaired sense of smell and taste are also among the common symptoms. Although imaging most commonly reveals bilateral diffuse opacities on chest radiographs and bilateral

peripheral ground-glass opacities on thoracic computed tomography scans, imaging may be completely normal. Leukopenia and lymphopenia are the most common laboratory findings. Elevated liver function tests, D-dimer and C-reactive protein levels may be detected. The potential long-term Covid-19 complications are not clearly known yet. Remdesivir is the only drug approved by the FDA (Food and Drug Administration) for use in Covid-19. It is routinely recommended for patients who are hospitalized and receiving oxygen support. It is however not routinely recommended for patients on mechanical ventilation. Severe Covid-19 patients have a severe inflammatory response that leads to multiorgan failure. A severe cytokine storm causes this inflammation. Corticosteroids may be added to the Remdesivir therapy because of their anti-inflammatory effects to counteract cytokine storms.

Even though everyone around the world is exhausted by the battle against the Covid-19 pandemic, the fight continues and we do not know how long it will persist. The data are updated every day and all the algorithms can be changed, depending on new findings. We have examined the emergency surgical approach to Covid-19 patients using the available Covid-19 guidelines and data from other colleagues. One of our primary goals is to provide healthcare professionals and hospital facilities that will provide treatment for patients who do not have Covid-19 but who need emergency surgical treatment in hospitals. Consequently, in the management of the Covid-19 outbreak, it is very important to determine which patients admitted to hospitals and requiring surgery will undergo emergency operations and which operations can be postponed.

Due to the intensive workload, rates of depression and anxiety among healthcare personnel are increasing. Emergency surgical intervention is a field that requires serious attention but may also result in irreversible outcomes in the event of any trouble. Therefore, assessing and managing the physical and mental state of healthcare professionals, as well as the management of patients, is very important for success. In this respect, the distribution of hospital duties must involve a responsible person who observes healthcare personnel and when required, vulnerable staff should be relocated or provided with psychiatric support.

There are several guidelines on the management of emergency operations during an outbreak; however, these are mainly related to the most familiar situations. There will be diseases about which physicians have to decide in accordance with medical ethics and in different surgical situations, based on their medical knowledge and experience and by evaluating approaches to similar situations. Furthermore, when following the existing guidelines, to

make the correct decision the surgeon must be fully acquainted with the hospital facilities. Reliable information can then be given to the patient and the risks explained accordingly. Local organization and communication within the hospital is very important in this context.

EMERGENCY SURGICAL APPROACHES DURING THE COVID-19 OUTBREAK

Approaches to Patients in Emergency Departments during the Outbreak

In an environment of high hospital occupancy, non-emergency procedures should be postponed as they require personal protective equipment, increase the workload and decrease the efficiency of healthcare personnel, and increase the unnecessary risk of infection. There will, likewise, be a greater need for ventilator support, due to the increase in pandemic cases. To meet this need, a better approach would be to only perform emergency operations. About half of Covid-19 patients develop postoperative pulmonary complications and are associated with high mortality rates. This association is greater especially in male patients over 70 years of age. In this respect, operations on patients with confirmed or strongly suspected Covid-19 should be delayed as much as possible. The literature involves studies indicating that emergency surgery should be delayed when indicated or can be performed safely in pandemic hospitals. Since the emergence of Covid-19, each country will evaluate its own experiences and find better solutions to the problems that arise. Thus, although the guidelines to be followed have been published, the information is likely to change in the future.

Trauma is a condition for which emergency surgical treatment does not vary a great deal during an epidemic. However, during the pandemic many countries have observed a reduction in the overall number of patients presenting to the emergency department and the number of trauma patients. This is believed to result from the non-referral of people to hospitals due to the fear of infection, despite pandemic-related restrictions and the emergency situations. Although there is generally no difference in mortality rates by the number of inpatients, the low number of referrals to hospitals and mortality rates can be compared unambiguously only by investigating the long-term effects.

Acute hemorrhoidal disease is usually resolved with local anesthesia without surgery on an outpatient basis, while cases with massive bleeding, necrosis and non-responsive to treatment require emergency surgery.

Perianal or perirectal abscess can be treated by drainage under local anesthesia. If the operating room is not available, percutaneous drainage can be performed as an alternative and temporarily. However, care should be taken at this point since inadequate drainage will prolong the hospital stay.

Soft tissue abscesses can be treated on an outpatient basis with drainage under local anesthesia. However, the inadequate drainage of abscesses that are large or extending into muscles may prolong the hospital stay. Thus, treatment should be performed under operating room conditions. Necrotizing infections are conditions that require debridement with an emergency intervention.

If necrotizing acute pancreatitis is infected, appropriate antibiotherapy should be initiated immediately. In cases requiring drainage, percutaneous or endoscopic drainage should be performed first in eligible patients, and laparoscopic or open surgical drainage in failed or non-eligible patients.

Acute appendicitis is the most common condition requiring emergency surgery. Despite the presence of non-surgical follow-up in the literature, the gold standard treatment for these patients is laparoscopic appendectomy. During an outbreak, non-operative antibiotherapy is recommended for eligible patients in line with hospital resources. Due to the increased perioperative pulmonary complications and mortality rates,antibiotherapy is recommended primarily and especially if appropriate in patients with confirmed or strongly suspected Covid-19. If patients are to be surgically treated, then open appendectomy is recommended due to the risk of aerosol transmission. Previous studies have suggested that a very small proportion of patients treated without surgery require surgery, and that non-surgical acute appendicitis treatment can be used more widely in the future without any association with an outbreak. However, prospective analyses with far more data may be more useful. Delays in referral to hospital increase the number of complications that require long-term treatment, such as perforation and periappendicular abscess, in patients with acute appendicitis. Complicated acute appendicitis patients with localized perforation and abscess can be followed up with percutaneous drainage if there are no signs of diffuse peritoneal irritation. During the Covid-19 outbreak, the situation that is and will continue to be a big problem for people is the fear of being infected with Covid-19. Despite having serious symptoms, many people delay their referral or do not refer to emergency clinics. There are publications supporting a similar delay in acute appendicitis.

Conditions with signs of diffuse peritoneal irritation, for reasons such as perforation, bowel obstruction, closed loop obstruction, and intestinal isch-

emia, require emergency surgery. If intestinal obstructions are due to adhesions and there are no examination findings of acute abdomen, patients should be followed up with nasogastric drainage and supportive treatment.

Acute cholecystitis is one of the common conditions seen in the emergency department. Laparoscopic cholecystectomy should be performed on patients with acute cholecystitis who are not at high surgical risk, if deemed appropriate having evaluated the hospital resources. If the operating room and hospital resources are not available, or the patient is at high risk for surgery, intravenous antibiotherapy should be administered. When patients with cholelithiasis or chronic cholecystitis present with pain, symptomatic treatment should be provided, and the operation should be postponed if possible. If there are repeated referrals to hospital and there are available hospital resources, the operation may be recommended. Percutaneous cholecystostomy should be performed on complicated patients who do not respond to antibiotherapy, who are at high risk and who have a delayed referral.

For patients with choledocholithiasis, if the stone is large and there are signs of cholangitis, ERCP (Endoscopic Retrograde Cholangiopancreatography) should be performed, and if necessary, elective cholecystectomy should be performed in the late period. Patients with small stones without symptoms and cholangitis can be followed up for a while. Broad-spectrum antibiotherapy should be attempted first in patients with cholangitis. ERCP and sphincterotomy should be performed on non-responsive patients. Due to the high risk for aerosol transmission in ERCP, it should be performed by taking necessary precautions and in line with hospital resources.

Patient selection is very important in diverticulitis patients. Hinchey class 1 and 2 patients should be treated with intravenous or outpatient antibiotherapy and percutaneous drainage should be performed on patients when necessary. If treatment fails, surgery is performed immediately. Purulent or fecal peritonitis patients with diffuse intra-abdominal free air should be operated on immediately.

Colorectal cancer patients may present to the emergency department for reasons such as obstruction, perforation, and bleeding. Cancer patients are more vulnerable to infections due to chemotherapy, radiotherapy and surgery, as well as due to the disease itself. In addition, complication rates have increased in cancer patients with Covid-19 and the need for intensive care units has also increased. In conclusion, cancer patients have a poorer prognosis when infected with Covid-19 compared to those without cancer. Therefore, elective surgeries of stable cancer patients should be postponed, and if these patients

are to undergo surgery, they should be followed-up more closely and carefully. If there are available hospital resources and the ventilator availability in the intensive care unit is high, then obstructive colorectal tumors, colorectal tumors requiring frequent and massive blood transfusions and cancers causing perforation and sepsis are cases that should be operated on immediately, depending on the prevalence of Covid-19 cases. Rectal cancers that do not respond to neoadjuvant radiochemotherapy and early rectal cancers should also be operated on electively and without delay. If there are too many Covid-19 patients in the hospital and there is a reduced number of unused ventilators in the intensive care unit, stenting should initially be attempted in eligible patients, among those with obstructive gastroesophageal junction and colon tumors without signs of peritoneal irritation, and patients for which this failed should undergo surgery. In addition, hospitalized patients with bleeding, as well as cancer patients with perforation and sepsis, should be operated on immediately. Other patients can be transferred to alternative hospitals with a low occupancy rate. When hospitals are wholly reserved for Covid-19 patients and the intensive care units and ventilators are fully occupied, emergency operations are performed on patients who may die within hours if the operation is postponed. These are obstructive patients with perforation and sepsis or patients with massive bleeding. Other patients should be transferred to other available hospitals. A temporary stoma can be administered to eligible patients.

Emergency drainage is required for patients with breast abscess and hematoma presenting to the emergency department. If ischemia develops in mastectomy flaps, the revision should be performed immediately. However, if the hospital has reserved all its facilities for Covid-19, reconstruction operations should be postponed.

Patients with confirmed or strongly suspected Covid-19 should be followed-up by avoiding surgery as much as possible, considering the issues we have mentioned. Patients who are designated for surgery should be operated on as soon as possible and should remain in hospital for the shortest possible time. For patients who are followed-up without surgery, an operation should be reconsidered if there is no success and the hospital stay will be prolonged.

Endoscopic GIS (Gastrointestinal System) Interventions

Emergency GIS endoscopy is needed especially in patients with upper and lower GIS bleeding. Covid-19 is highly contagious via droplets and aerosol,

and although it is found in high concentration in the nasopharyngeal mucosa, the presence of the virus has also been demonstrated in the lower GI tract. Even though it is necessary to determine which patients will undergo emergency endoscopy, the main point to consider is the provision and use of personal protective equipment. Personal protective equipment is very important as the virus is transmitted via droplets and aerosols and can be contracted by contacting with surfaces. Fecal-oral transmission has not yet been proven; however, the upper GIS is as dangerous as the respiratory system in terms of infectivity. Viral RNA can be detected for approximately 16 days in respiratory tract analyses and for approximately 27 days in stool analyses. There is information in the literature that it may be a marker in determining asymptomatic patients, regardless of the disease severity and because it remains positive in stool for a longer time. Although patients are screened with the Covid-19 test, the biggest problem is the group with negative test results but who carry the disease. In the future, the determination of IgG and IgM may be the solution to this problem.

In Covid-19 positive or suspected-unknown patients, the endoscopist should ensure hand disinfection, use surgical gloves, goggles and bonnets, wear a liquid-tight gown and an FFP2/3 mask prior to the procedure, just like in operating room conditions. Then the endoscopist should wear a face shield and a second layer of gloves. After this preparation, the endoscopist should enter the room in which the procedure will be performed, and personal protective equipment must be changed for each procedure. Malignant polyps, prophylactic interventions for hereditary reasons, large benign asymptomatic polyps, and asymptomatic carcinoids of the colon and rectum are conditions that can be postponed for three months, regardless of a previous resection.

Operating Environment and Conditions

There is no need to take precautions for surgical patients who have tested negative for Covid-19, without any symptom and suspicion. For patients who have tested positive and have a suspected disease that cannot be ruled out by test, the operation should be planned to include taking precautions for Covid-19. The entrance door to the operating room, in which suspected or positive Covid-19 patients will undergo surgery, should be different from other rooms. As far as possible, throughout the outbreak, stable materials in the room (such as ventilators, tables...) should not be moved. Also, as far as possible, as one of the most important issues in the prevention of infection, there should be

minimum staff in the room, and all unnecessary personnel should be prevented from entering this room.

Emergency Surgical Procedures for Suspected or Positive Covid-19 Patients

General surgical operations, procedures that are usually carried out as preoperative, perioperative and postoperative teams, require continuous information exchange among the team, and may be prolonged due to complications. When we consider the long working hours of our teams, it is not hard to realize that the people with whom we are most in contact are our team members. Therefore, in the management of the Covid-19 outbreak, the number of people in the surgical team is crucial. Minimum contact is ensured if emergency outpatient clinic services can be carried out by dividing the surgical team into several groups. Furthermore, when a positive case occurs in the surgical team, the team with the positive member should be isolated, while other teams maintain the emergency outpatient clinic services without disruption. To minimize contact even within the same team, patient visits should be made by a single physician, and information should be shared and evaluated in a digital environment. The approach to patients who will undergo surgery can be classified as before, during and after the operation.

Preoperative assessment is the surgeon's evaluation of the patient in terms of preoperative indication for the operation. In order to prevent excessive contact with personnel, it is important that the person who will examine the patient is also the person who will decide on the operation. The surgeon should examine the patient's file beforehand, to avoid excessive and unnecessary contact with the patient. The surgeon should record patient information electronically. If suspected or positive for Covid-19, the patient must be informed that surgery could cause respiratory complications and mortality. Even in the event of not having Covid-19, the patient should be informed about any positive inpatients and the perioperative and postoperative risk for infection. The information provided to the patient must be documented, and the patient's signed informed consent must be obtained. If possible, information should be shared digitally with other physicians who will assess the patient preoperatively.

During the operation, the surgeon should wear personal protective equipment. Personal protective equipment includes mask (FFP2/3 or N95), goggles or transparent face shield, liquid-tight gown, long surgical gloves, disposable bonnet (personnel should cover all their hair with the bonnet), and sterile

rubber boots or liquid-tight shoes covering up to the ankles. Beards that prevent the mask from fitting properly should be shaved. After putting on the personal protective equipment, the surgeon should wear a sterile gown and a second glove should be worn after disinfecting the first one. The operating room should be a negative air pressure room. Furthermore, the anteroom must also be equipped with negative pressure. The ventilator in the room must remain constant; however, an additional filter is attached to the expiratory extension. This filter should be changed after each patient. If possible, the patient should be intubated with a video laryngoscope to avoid time-wasting. Anesthetic medications are kept in the induction room and all necessary medications are taken inside on a tray before each operation. In the event of an intraoperative requirement for an additional medication, the medication should be removed from the medication trolley only by paying attention to hand sterility and without touching anywhere. Airway equipment should be disposable, as far as possible. For out-of-room transport procedures, such as sending arterial blood gas samples, a person who is outside the room and has full personal protective equipment is kept on standby. It is still unclear whether the operation should be conventional or laparoscopic. While the surgeon's exposure to body fluids and cautery smoke is higher in conventional operations, due to the gas in laparoscopic surgery there may be a risk for aerosol transmission. Smoke generated during laparoscopic surgery may have a viral load. Using central aspirators or CO_2 filters may be a solution. Whether to undertake laparoscopic or open surgery should be determined by considering the surgeon's experience and the method that will enable the patient to have the shortest hospital stay.

In the event that there will be no postoperative stay in the intensive care unit, the patient should be fully awakened in the operating room and then sent directly to the bed. For patients where it is known that they will require postoperative intensive care in the preoperative assessment, the ventilator scheduled for use in the intensive care unit can be used perioperatively and the patient is taken to the bed using the same ventilator. The routes and elevators used by the patient while going from the operating room to the bed must be cleaned by hospital security. The same cleaning procedure is carried out by hospital security while the patient is taken to the operating room from the ward or examination room, and the accompanying nurse should wear personal protective equipment such as N95 mask, face shield or goggles, gloves, and liquid-tight apron. If the ventilator is to be changed for patients coming from or going to the intensive care unit, the endotracheal tube should be

completely closed with forceps. Any unused materials in the perioperative room are also considered to be contaminated. Everything, from the computer cables to the unused keyboard, should be considered soiled and cleaned. The required disinfection of the operating room should be ensured by taking a minimum of a one-hour break between two operations. The cleaning of the operating room should not be limited by a specific time; another patient should be taken after cleaning is completed. Thus, the waiting period between two patients may take up to two hours. After a patient with confirmed Covid-19, the operating room should be disinfected with hydrogen peroxide vapor. Patients should be followed-up in postoperative isolated rooms and if necessary be initiated on Covid-19 treatment. Empirical antibiotherapy is routinely administered in some clinics to patients postoperatively admitted to the intensive care unit, while other clinics use it as needed. It should be kept in mind that severe patients are at greater risk for venous thromboembolism. For these reasons, the postoperative follow-up of the patient should be carried out by several clinics and in cooperation.

CONCLUSION

In future, epidemics have the potential to be the greatest disaster for the entire planet. While we could not imagine our current state prior to experiencing the pandemic, at this article is being written, live without isolation and Covid-19 has almost been forgotten. Whatever the cause of the pandemic, our world needs to have a defense plan against this immense danger. A joint declaration should be published on how each surgeon and healthcare professional will act in the event of an outbreak, by adding any future ones to the knowledge and experiences we now know and share, and this should be taught as a topic in medical school.

In society there is a widespread fear of infection. Patients who are at risk of severe disease are more frightened of infection, but delays in the referral of this vulnerable group can result in situations that are even more complicated. Since patients are not wrong about the fear of infection, seeking solutions in a pandemic is essential for all algorithms. As a solution, digital environments should be established to assess patients and the infrastructure should be strengthened and made available to every patient. Thus, each patient can be assessed by a healthcare professional, preventing unnecessary hospital referrals and referring patients with severe symptoms to hospital, which avoids, for the most part, delayed referrals and increased complications.

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CHAPTER 8

THE POINTS TO BE CONSIDERED IN AIRWAY MANAGEMENT IN ANESTHESIA APPLICATIONS OF PATIENTS WITH COVID-19

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a contagious disease that started in Wuhan in late December 2019 and spread all over the world, and resulting in a pandemic being declared by the World Health Organization. COVİD-19 also named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can materialize with symptoms as mild as the common cold or as severe as causing acute respiratory distress syndrome.

Although some information regarding COVID-19 is still unclear, what is certain is that the virus spreads very quickly among individuals. Its transmission occurs by respiratory droplets and contact routes. When a patient who has COVID-19 coughs, sneezes, or talks, the virus is passed on to healthy people via respiratory droplets. Similarly, COVID-19 can also occur when a person touches their eyes, nose, or mouth after touching an infected surface. Therefore, healthcare workers are at great risk against a virus that can spread

so quickly and easily, and those dealing with aerosol-generating procedures should be more careful in this regard.

Aerosol-generating procedures include airway management (e.g., endotracheal intubation, bronchoscopy, or tracheostomy), cardiopulmonary resuscitation, invasive and noninvasive mechanical ventilation applications, endoscopy, and colonoscopy. It is hypothesized that airway management may be one of the most important issues for both patients and healthcare professionals. As such, in this review, airway management in anesthesia applications of patients with COVID-19 will be discussed.

PREOPERATIVE ASSESSMENT

Preoperative assessment, which employs a face-to-face interview to assess a patient's history, symptoms, and laboratory and radiologic parameters, plays an important role in anesthesia applications. However, these interviews are being re-evaluated by practitioners due to the COVID-19 outbreak, and alternatives have been developed. The common idea from the literature is to consider every patient who arrives at a hospital as potentially infected with COVID-19, and therefore attention should be paid to preventive equipment. Furthermore, preoperative assessment of COVID-19 positive or suspicious patients should be done by primary anesthesiologists and the patients' cardiac and pulmonary functions should be evaluated as a priority.

The South African Society of Anesthesiologists recommend behaving in accordance with a set of guidelines (e.g., wearing a surgical mask, maintaining a distance of > 1 m, hand hygiene) and utilizing a short checklist during the interview. Chinese anesthesiologists recommend measuring the body temperature of patients before preoperative assessment; patients with higher body temperatures (>37.3 °C) should then be consulted by the relevant clinics. Furthermore, Chinese anesthesiologists emphasized the importance of detailed chest examinations. The Indian Society of Anesthesiologists underlined the importance of taking anamnesis in terms of combating COVID-19. Alternatively, Mihalj et al. highlighted the benefits of telemedicine, a technological approach for preoperative evaluations.

In preoperative assessment, one of the most important examinations an anesthesiologist carries out is an airway evaluation to determine possible difficulties for intubation. However, airway evaluation in patients with suspected or confirmed COVID-19 may be risky for the person who undertakes it. During the interview, if the patient has a difficult intubation history or there

is no obvious feature, an evaluation without removing the patient's surgical mask will be sufficient. On the contrary, if there is a possibility of difficult intubation, a detailed examination is required and all team members should be informed before the operation, and preparations for difficult intubation should be made in the operating room. On assessment of a patient with a difficult airway, the MACOCHA score is clearly useful as the only validated tool. The MACOCHA score consists of seven items over three categories: factors related to the patient (Mallampati class III or IV, obstructive sleep apnea syndrome, reduced mobility of cervical spine, limited mouth opening <3 cm), factors related to pathology (coma and severe hypoxemia), and factors related to the operator (non-anesthetist). MACOCHA scores range from 0 (easy) to 12 (very difficult), and a MACOCHA score above 3 predicts difficult intubation.

PREOPERATIVE PREPARATION

COVID-19 is a highly contagious disease. Hence, airborne precautions and personal protective equipment (PPE) training are two issues that must be considered before operating on patients with COVID-19.

To prevent the spread of infection, it is recommended that airway management and any subsequent operation or interventions should preferably be applied in negative pressure rooms or positive pressure in operating rooms must be turned off. In addition, the doors of the operation room must remain closed.

Furthermore, the number of personnel in the operating room should be kept to a minimum, and all personnel should be wearing appropriate PPE before the patient arrives. PPE includes fit-tested N95 masks or higher level aspirators, disposable head covers, goggles or face shields, waterproof gowns, two pairs of gloves, and shoe covers. In addition, disposable PPE should be changed for every patient, and reusable PPE should be cleaned after each patient. Donning and doffing PPE should be done according to the rules to avoid accidental self-contamination.

Another consideration in preoperative preparation is the anesthesia machines and the drugs and devices used. To prevent contamination of the operating room atmosphere, heat and moisture exchange (HME) filters can be used. A HME filter can eliminate approximately 99% of airborne particles larger than 0.3 microns. However, care should be taken since the properties of HME filters can vary depending on the manufacturer. HME filters can be

installed between tracheal tubes or face masks and breathing circuits, as well as between expiratory limbs and anesthesia machines.

Only essential devices and medications for anesthesia application should be kept in an operating room to prevent contamination. The emergency tracheal intubation kit includes an oropharyngeal airway, a stylet, a bougie, a tracheal tube with subglottic suction, a second generation supraglottic airway (SAG) device, a yankauer suction, tube fixations, lubrication, a syringe, a mapleson C circuit, a videolaryngoscope, and a tube clamp. In addition, the emergency front-of-neck kit (FONA) should be readily available for use and kept in another room to be used in possibly difficult intubation scenarios; if necessary, it can be delivered to the operating room by the personnel present outside. To reduce medication contamination and wastage, the required medications should be prepared by drawing them into syringes and labeling them, and the vaporizer should be filled with the specific volatile agent. Finally, the anesthesia machine and aspirator should be checked to ensure they are functioning.

FACEMASK VENTILATION

The prime purpose of airway management of patients with COVID-19 is to apply aerosol-generating procedures (AGP) safely and without increasing the viral load in the operating room. Facemask ventilation is one of the AGPs; however, in the COVID-19 setting, the application of facemask ventilation may be avoided to decrease the viral load in the environment. If facemask ventilation is applied, the following points should be considered.

During facemask ventilation, aerosol generation is associated with peak airway pressure, duration of facemask ventilation, and removal of the mask from the face during the procedure. Additionally, it is inevitable that there will be leakage with masks that do not fit well on the face during the procedure. If a facemask is to be used, it should be done so with the aim of minimizing the spread of aerosol. Therefore, recommendations are as follows: optimal airway position, airway maneuvers, sufficient anesthesia depth, and early use of an oropharyngeal airway. If there is an air leak despite these recommendations, the following points should be considered: repositioning, two-handed two-person bag-mask technique with the VE hand position, neuromuscular blockers, and the use of a SAG device.

ENDOTRACHEAL INTUBATION

Briefly, principles of COVID-19 airway management are expressed as safe, accurate, and swift. In patients with COVID-19, general anesthesia is suggested to decrease both airborne and droplet transmission. It is known that in terms of practitioners' exposure, endotracheal intubation is a high-risk procedure that can cause the patients to spray secretions or blood, or produce aerosols. Therefore, this procedure should be managed quickly, accurately, and safely by experienced practitioners.

Patient positioning

In general, the head up (including 45^0) or ramped position is recommended for all patients, including COVID-19 patients. This is especially important for high-risk patient groups, such as hypoxemic, obese, and pregnant, since they are prone to rapid and profound desaturation during anesthesia induction. These positions seek improved preoxygenation and ventilation; prolonged safe apnea time; and facilitated face mask ventilation, direct laryngoscopy, and tracheal intubation. Sometimes, these positions may not be practical for those performing intubations, and alternative methods such as using elevation pillows or a footstool to provide the optimal height may be considered.

Preoxygenation

In patients with COVID-19, preoxygenation is a recommended practice whereby 100% oxygen is utilized via a tight-fitting mask for five minutes through a closed circuit (an anesthesia breathing circuit or a Mapleson C). The bag-valve-mask method is not recommended because it expels exhaled breath contaminated with virus. During the procedure, a minimum gas flow (≤ 6 L/minutes) should be used to decrease aerosol contamination.

For preoxygenation, there are no clear recommendations for the use of low-flow nasal oxygen, high-flow nasal oxygen, and non-invasive ventilation modes. However, the general opinion of the authors is to avoid these applications in terms of aerosol dispersion.

The intubation procedure

Rapid sequence induction is recommended for patients with COVID-19. Induction drugs are determined according to the hemodynamic findings of

patients. Ketamine, etomidate, and propofol can be used for induction of anesthesia. For neuromuscular blockage, rocuronium (1.2 mg/kg) is recommended, however succinylcholine (1.5 mg/kg) can also be considered. It is important to note that rocuronium is a long-acting neuromuscular blockage agent relative to succinylcholine, and furthermore it reduces aerosol generation in contrast with the possibility of early cough response with succinylcholine. Neuromuscular blockage can be evaluated via neuromuscular monitoring or by waiting one minute after drug administration. If there is no leakage with a tight-fitting mask, gentle continuous positive airway pressure may be applied after loss of consciousness.

The use of cricoid pressure, which has a place in rapid sequence induction, blocks the esophagus and prevents aspiration of gastric contents. However, its use in patients with COVID-19 is controversial due to the potential for unfavorable effects, such as airway obstruction, impeding SGA insertion, and inferior laryngoscopic views. In such cases, the risks and benefits of applying cricoid pressure should be cautiously evaluated.

For adequate endotracheal intubation, the choice of laryngoscopy is determined by the anesthetist's experience and training. Videolaryngoscopy or conventional direct laryngoscopy can be used for endotracheal intubation in patients with COVID-19; however, videolaryngoscopes offer a better view than conventional direct laryngoscopes and while also increasing the distance between the airway practitioner and the patient during airway management. Therefore, videolaryngoscopy is recommended as the first preference for the airway practitioner.

In patients with COVID-19, it is recommended that endotracheal intubation is applied at the first attempt by an experienced airway manager to reduce aerosol contamination and protect healthcare workers. Immediately after the endotracheal tube (ETT) is placed in the trachea, its cuff should be inflated with air so that there is no leakage and the cuff pressure should be measured. The patient should not be ventilated before this procedure is performed due to aerosol generation. If a stylet or bougie is used, attention should be paid to their removal and subsequent disposal due to droplet spread. Similarly, the laryngoscope blade should be sheathed immediately after endotracheal intubation. Successful ETT placement is confirmed with end-tidal carbon dioxide. Another option to confirm ETT placement may be auscultation of the chest; however, auscultation is not recommended due to the difficulty in applying pressure in the presence of PPE, and stethoscope and practitioner can become contaminated. To confirm ETT placement, other suggestions are as follows:

observing for bilateral chest wall expansion during ventilation, lung ultrasound, and chest x-ray, if necessary. If ETT suction is required, a closed airway suction system should be applied. If the closed airway suction system is not available, the minimum number of aspirations required are applied using the non-closed suction system by disconnecting the circuit. To prevent aerosol generation during circuit disconnection, the following points must be considered: the adjustable pressure limiting valve should be opened fully, fresh gas flow should be turned-off and positive pressure ventilation should be stopped, and the ventilator bellows should be at end-expiration. Moreover, it should not be forgotten that the ETT is clamped when the circuit is interrupted.

The use of airway tents, aerosol boxes, or airway shields during the intubation procedure

Previously, plastic sheets and rigid plastic barriers with arm holes were described in the SARS outbreak. The goal was to decrease droplet and aerosol transmission to healthcare workers during the intubation procedure. However, using barriers during the COVID-19 outbreak is a controversial issue. There are concerns that the complexity of these materials and the risk of contamination during their use may increase. A recent study shows that barriers can increase intubation times and may increase the risk of contamination due to damage to PPE. If a barrier is to be used, it is recommended to choose a simple system that allows good visibility, sufficient seal, free arm movements, and does not cause any contamination.

THE USE OF SUPRAGLOTTIC DEVICES

After an unsuccessful primary endotracheal intubation attempt, it is recommended to use a second generation SGA device (e.g., i-gel, LMA® Protector™) since repeated endotracheal intubation attempts may increase aerosol generation. Successful SGA ventilation causes reduced leakage compared to face mask ventilation.

After successful SGA placement and ventilation, four different options subsequently present themselves during airway management. First, airway management may be continued via SGA devices. However, this option is not recommended due to airway leaks and the fact that endotracheal intubation has already failed. Second, SGA devices allow for endotracheal intubation with flexible bronchoscopy and the patient can be intubated. However, it should be

noted that efforts should be made to not increase contamination while performing these practices. Third, the patient can be woken up. Fourth, FONA can be applied in the presence of SGA devices if there is an indication to do so.

AWAKE INTUBATION

Awake intubation should be avoided as it carries a high risk of droplet spread and aerosol generation. There are very limited indications for this procedure (e.g., neck abscess compromising the airway). If there is an indication, the procedure should only be performed by an experienced airway manager. Antisialagogue and sedative agents may be used to reduced droplet spread and the patient's anxiety. In addition, mucosal atomizers, local anesthetic- impregnated swabs and cotton pledges, and nerve blocks may be used. Provided that decontamination is observed, ultrasound-guided techniques may be helpful for the procedure. The use of single-use flexible bronchoscopy and videolaryngoscopy may be considered. If awake intubation fails, an awake tracheostomy performed under local anesthesia is another option to consider. While performing these procedures, the goal should be to minimize aerosol generation and droplet spread.

FRONT-OF-NECK ACCESS

In the event of a "cannot intubate, cannot oxygenate" scenario, the options are as follows: a surgical (scalpel, bougie, and tube) or a cannula cricothyroidotomy. A cricothyroidotomy poses a high risk in terms of aerosol generation. The Difficult Airway Society guidelines recommend administration of supplemental oxygen during FONA. However, as mentioned above, the goal should always be to reduce aerosol generation and droplet spread in the airway management of patients with COVID-19. Aerosol generation may be relatively higher when performing the cannula technique due to aerosolization during oxygen insufflation or jet ventilation. During the procedure, sufficient neuromuscular blockage should be provided. Finally, the use of suctioning should be limited during cricothyroidotomy.

EXTUBATION

When a patient has all criteria for extubation after surgery, he/she should be extubated in the operating room. Otherwise, the patient should be transferred to an intensive care unit as intubated. Extubation is a risky stage of airway management in terms of aerosolization as well as intubation. Furthermore, when patients wake up agitated, the process can get more complicated.

To prevent the spread of patient secretions, two layers of wet gauze should be available. The materials (e.g., suction system, face mask, oxygen mask, and nasal cannula) to be used should be checked. Vomiting can cause droplet spread and should be prevented via antiemetic drugs. There is no clear recommendation about the routine use of drugs such as dexmedetomidine, lidocaine, or opioids, to reduce coughing at emergence.

The patient may be placed in a head-up position. Deep extubation may be considered to reduce the patient's airway response. SGA device exchange is not recommended as a bridge to extubation to minimize coughing. The extubation procedure may be performed under a clear plastic sheet to reduce aerosol generation and droplet spread.

At the end of the extubation process, if the patient has adequate effort capacity, he/she can be transitioned to a standard facemask or nasal cannula for oxygen supplementation. Facemasks with in-built viral filters are ideal for these patients. If there is a surgical mask in the operating room, it can be placed over the supplemental oxygen delivery device contributing to reduced aerosol generation.

CONCLUSION

It is a fact that we will continue to fight the COVID-19 outbreak in the coming years until an effective treatment is found. During this time, protection from the virus is the main goal. Airway management in patients with COVID-19 presents considerable risk in terms of aerosol generation and droplet spread, and practitioners who perform these procedures must first be protected. The second consideration is that these cases should be taken for surgery in appropriate operating rooms (e.g., negative pressure rooms) in the company of healthcare workers wearing appropriate PPE. Third, it is recommended to have only the necessary materials, such as drugs and the emergency tracheal intubation kit, in the operating room to prevent contamination. Fourth, while intubation and extubation procedures are performed by the airway manager,

aerosol generation and droplet spread should be kept to a minimum. As a result, it can be said that the use of any unknown technique or drug can make this process difficult.

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CHAPTER 9

NON-INVASIVE MECHANICAL VENTILATION TREATMENT IN THE PATIENTS WITH COVID-19

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INTRODUCTION

Coronavirus disease 2019 (COVID19) is a new coronavirus infection that spread from Wuhan, China to the whole world since December 2019, forming a pandemic. It is also named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its potential to cause serious acute respiratory illness and similarity to SARS-CoV-1.

COVID19 primarily causes damage to the capillary endothelium and thus it leads to ventilation-perfusion mismatch. The patients with COVID19 require admission to intensive care units (ICUs) are usually male gender, over the age of 60 and have comorbidities such as hypertension, diabetes, chronic respiratory disease, heart disease, malignancy, immunodefiniency and obesity. Recent consensus statements have focused some topics including infection control, laboratory tests, hemodynamic and ventilator support for treatment management of COVID19 in the ICUs. Part of discussion in the treatment modalities of the COVID19 has focused on invasive and noninvasive ventilation strategies of severely ill patients. In critically ill COVID19 patients, hypoxia plays a

decisive role for predicting prognosis, so correction of hypoxia is the main goal of the treatment.

Among the patients with COVID19 admitted to the ICUs, although different rates of intubation are specified in published reports, the true incidence of intubation is not clear. When hypoxemic respiratory failure develops, many methods can be applied according to the patient's clinic, from low flow oxygen support with nasal cannula to invasive mechanical ventilation. According to our current knowledge, there is insufficient evidence about the superiority of invasive and noninvasive mechanical ventilation in the patients with COVID19 pneumonia.

Gattinoni et al described COVID19 patients as two phenotypes, H and L. The treatment modalyties recommended for Type L (low elastance) and Type H (high elastance) patients are different. In the patients with Type L, respiratory system compliance upper than 50 mL/cmH2O and the patients have low elastance, low ventilation perfusion ratio, low lung weight, low lung recruitment. The first option to reverse hypoxemia is to increase inspired oxygen fraction (FiO2) in this phenotype. Conversely, H phenotype is similar to ARDS, the patients have high elastance, high right to left shunt, high lung weight, high requirability in addition to low respiratory system compliance (<50 mL/cmH2O). In the H phenotype, treatment may need to be more invasive, for example intubation, recruitment maneuver, prone position, positive end expiratory pressure (PEEP), sedation with paralysis or inotropic support. During the illness, transition from phenotype L to phenotype H may be observed.

Many center avoid the use of non-invasive modalities in the patients with COVID19, but with non-invasive mechanical ventilation (NIV) strategies, the risks of ventilator-induced lung injury (VILI) can be prevented. If the patient has dyspnea, non-invasive strategies can be applied via continuous positive airway pressure (CPAP or BPAP) or high-flow nasal cannula (HFNC). More satisfactory results can be obtained with non-invasive strategies, especially in Type L patients. However, one of the most important concerns regarding the use of non-invasive ventilation techniques is the increased airborne transmission. In the recent guideline of Surviving Sepsis Campaign, supplemental oxygen therapy is recommended as the first choice for adult COVID19 patients with acute hypoxemic respiratory failure. If conventional oxygen therapy fails to correct hypoxia (persistent SpO2<90%), using HFNC instead of non-invasive positive pressure ventilation (NIPPV) is suggested. In this guideline, NIPPV is only suggested if HFNC is absent and the patient does not require urgent endotracheal intubation.

If possible, inspiratory esophageal pressure measurement with esophageal manometry is recommended before non-invasive administrations. Increase in esophageal pressure between 5 and 10 cmH2O is generally well tolerated. However, the risk of lung injury increases as esophageal pressure rises above 15 cmH2O, in this situation endotracheal intubation should be considered. In the absence of the esophageal manometry, central venous pressure swings or clinical observation of excessive inspiratory effort should be used. Observation and palpation of increased contractions accessory respiratory muscles (such as sternocleidomastoid muscle) may be a more convenient, simple and easier method for clinicans.

The failure indicators of non-invasive strategies include increased tachypne and tachycardia, impaired oxygenation despite a high flow rate or FiO2, development of dyssynchronous or abdominal breathing, alteration in mental status, hemodynamic instability, increase in PaCO2.

HIGH FLOW NASAL CANNULA OXYGEN THERAPY (HFNC)

High flow nasal cannula oxygen therapy (HFNC) refers to the delivery of high flow oxygen through nasal cannula, which is heated (37° C) and humidified (100% relative huminity) at maximum flows ranging from 40 to 80 liters per minute with 21% to 100% fraction. Flow rate and FiO2 can be titrated according to the patients' requirements, comfort and clinical condition.

Although HFNC has not been used as long as other NIV methods, it has become more preferred in recent years. HFNC treatment is simple, safe and easily tolerated in suitable patients. It is more comfortable than standart oxygen therapy with non-breating mask and NIPPV. The nasal cannula has a soft and loose structure, thus it does not prevent the patients from talking and eating during HFNC therapy. A dry and cold gas at such high flow rates causes rapid drying of the nasal mucosa and an uncomfortable burning sensation. Heating and huminition contributes to the elimination of these side effects. Another benefits of heat and humidification are the hydration of secretions and protection of the mucosilier activity.

The working principle of HFNC is to aid oxygenation by washing the nasopharynx during exhalation. The washing the nasopharynx also clears anatomical dead space, increases ventilation efficiency, decreases airway inflamation and reduces the work of breathing. External PEEP of approximately 4-6 cmH2O is provided during HFNC. Other advantages of HFNC include avoiding unnecessary intubation and protect much-needed ICU ventilators

for the patients really needs it in resource-limited settings. However, NIPPV provides better oxygenation than HFNC due to its ability to provide higher positive pressure. There are numerous studies in the literature comparing standard oxygen therapy, NIV and HFNC, and 90-day mortality were significantly less in the ICUs patients undergoing HFNC therapy. However, we do not have sufficient evidence to show the effectiveness of HFNC compared to standard oxygen therapy and CPAP in the patients with COVID19.

Due to its many advantages, HFNC should be considered the first-line strategy in the patients with mild to moderate hypoxemic COVID19 pneumonia. However, it should be kept in mind that HFNC is an aerosol-generating procedure and the risk of COVID19 transmission is increased. Therefore the use of negative pressure rooms, high energy particulate collector (HEPA) filters and personal protective equipment are extremely important. In addition, the use of surgical masks over the nasal cannula during HFNC therapy may greatly reduce aerosol distribution.

When using HFNC, especially unstable or severely hypoxemic COVID19 patients should be closely monitored due to possible respiratory arrest. Otherwise, the deepening of hypoxia and the urgent intubation may result in catastrophic consequences. In recent years, ROX index [(SaO2/FIO2)/respiratory rate] is suggested for estimate the failure of HFNC and thus low or high risk for intubation. The ROX score> 4.88 at 12 h predicts HFNC success but ≤ 3.85 indicates HFNC failure. A reasonable target peripheral oxygen saturation (SpO2) range is between 92% and 96% for COVID19 patients receiving oxygen therapy. It is not recommended to maintain SpO2 higher than 96%.

NON-INVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)

Non-invasive positive pressure ventilation (NIPPV) has been used successfully in the treatment of chronic obstructive pulmonary disease (COPD) exacerbation, hypercapnic respiratory failure and acute cardiogenic pulmonary edema. The use of non-invasive positive pressure ventilation may also beneficial in the early post-operative period. It is less invasive than endotracheal intubation and does not include risks associated with intubation. Randomized controlled trials and meta-analyses showed that non-invasive positive pressure ventilation decreased intubation rate and mortality in these patient groups. Non-invasive positive pressure ventilation with helmet, oronasal or full face mask is suitable for the patients with mild to moderate respiratory failure. Generally,

the initial FiO2 is set to 100% and is titrated to SpO2 between 92 to 96. However, it has low success rate in the patients with acute hypoxemic respiratory failure without cardiogenic pulmonary edema.

Although there are various studies on the successful use of NPPV in previous pandemics (Middle East Respiratory Syndrome; MERS, H1N1, SARS, etc), data on use of NIPPV in the COVID19 pandemic is still not clear.

Non-invasive positive pressure ventilation types

Non-invasive positive pressure ventilation can be applied in two ways; continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BIPAP). While CPAP is preferred in acute hypoxemic respiratory failure (AHRF), BIPAP is generally useful in hypercapnic respiratory failure. Since the patients with COVID19 pneumonia have severe hypoxemia, CPAP may be more beneficial than BIPAP. However, BIPAP may be considered in obese patients (or other obstructive airway disease) with COVID19 pneumonia because of hypercapnia.

Using non-invasive positive pressure ventilation in COVID19 patients

Although some association do not recommend and there is insufficient data on this issue, NIPPV is still widely used in many centers in COVID19 patients, especially with L phenotype. In a small number of observational studies, the use of NIPPV have been shown to reduce the need for intubation in COVID19 patients. Non-invasive positive pressure ventiIation can be also used after unsuccessful HFNC therapy or in addition to HFNC due to providing more positive inspiratory pressure.

Like many health organizations, World Health Organization (WHO) guideline also recommended the use of NIPPV in the selected patients with COVID19. However, American Thoracic Society does not include NIPPV in the treatment of COVID19 patients and NIPPV has not any role in their COVID19 guideline. They recommend prone ventilation as first opinion for progressive COVID pneumonia, if it fails they suggest that extracorporeal membrane oxygenation (ECMO). Similarly, Infection Diseases Society has not comments any breathing strategies including NIPPV in their COVID19 guidelines. In Australian and New Zealand Intensive Care Society Guideline routine use of NIPPV is not recommended.

The effects of non-invasive positive pressure ventilation on lung mechanics

NIPPV can be administered with most intensive care ventilators. It is often used with spontaneous modes to increase patients' synchronization and comfort. Therefore, deep sedation is not preferred during NIPPV. The use of NIPPV is limited to mild to moderate hypoxaemic patients only, because it is pressure-supported ventilation rather than volume-targeted. The purpose of using NIPPV is to contribute to the improvement of oxygenation by providing external pressure support. NIPPV increases tidal volume, improves alveolar ventilation, lowers PaCO2, increases end-expiratory volume, opens atelectatic and collapsed lung areas and alveoli, provides higher mean airway pressures, reduces work of breathing and thus improves PaO2 levels and oxygenation. However, it provides high tidal volumes and thus may increase the risk of ventilator-induced lung injury. In addition, it does not provide mucociliary clearance as much as HFNC. Moreover, NIPPV is not suitable for the patients with hemodynamic instability, multiorgan disfunction and abnormal mental status. From this point of view, it can be said that NIPPV is less comfortable than HFNC. Some meta analysis and randomized controlled trials are demonstrated that mortality rate and ICU length of stay are higher with NIPPV than conventional oxygen therapy and HFNC. However, the results of the same studies comparing the intubation rates of NIPPV and HFNC are contradictory. Frat et al showed that 50% of patients with hypoxic respiratory failure who received NIPPV required intubation. In the patients with MERS, NIPPV therapy had a failure rate as high as 92.4%. The use of NIPPV for other pandemic respiratory infection is also controversial, for example most guidelines do not recommended using NIPPV as first-line therapy in the patients with H1N1. Therefore, data on the effect of NIPPV strategies on intubation rate, mortality and morbidity in the patients with COVID19 is still insufficient.

The combination of HFNC and NIPPV in post-extubation patients may reduce the re-intubation rate comparing HFNC alone. Especially if weakness is significant, alternating NIPPV and HFNC may be a good option, so that while NIPPV provides more ventilation assistance, HFNC also provides better tolerance and humidification.

Risks of non-invasive positive pressure ventilation and preventions

Although non-invasive positive pressure ventilation treatment may contribute clinical improvement with its many positive effects especially in selected

patients, it also causes some negative situations. One of the main determinants of treatment success is patient-ventilator compliance. For example, the patients with claustrophobia may poorly tolerated NIPPV administration. If the mask does not fit the patients' face tightly, both the effectiveness of the treatment decreases and the viral spread increases. It is also important that understanding the technical features of the non-invasive ventilator and masks by the user to increase the success of NIPPV. Care should be taken due to the risk of aspiration, aerosol transmission and self-induced lung injury.

One of the underlying concerns the controversy about non-invasive treatment is that NIPPV may worsen lung injury due to increased transpulmonary pressure and high tidal volumes. As a result, the risk of pulmonary edema is further increased, especially in lung already damaged by COVID19. The lung damage leads to increased work of breathing and a vicious circle. Therefore, it should be kept in mild that lung damage may worsen with the effect of excessive negative pressure during NIPPV administration.

Aerosol generated by the use of NIPPV increases the risk of infection for healthcare professionals compared with HFNC, standard oxygen and even invasive mechanical ventilation (excluding intubation period). The most important barrier to prevent transmission of COVID19 during NIPPV is the wearing of personal protective equipment (PPE). Personal protective equipment includes respirator masks (N95 respirators, FFP2 or functionally equivalent), eye protection (goggles or full face shield), gown and glows. The use of negative pressure rooms, HEPA filters and full PPE for healthcare providers are recommended. Therefore, negative pressure rooms are one of the most effective protective methods especially in pandemic control. It is recommended for use when performing aerosol-generating procedures such as tracheal intubation, bronchoscopies, NIPPV or HFNC to prevent cross-contamination and reduce the risk of infection for health worker and other patients. The main purpose of using negative air pressure is to keep the pathogen in the room and prevent its spread from room to room. If there is no negative pressure rooms, according to WHO guidance on COVID19, the rooms should be naturally ventilated at least 160 L/second/patient. HEPA filters should be used and change every 24 hours. The risk of viral spread via aerosol with NIPPV can be significantly decreased with the using HEPA filter on the expiratory circuit and prevention of interface leak. Another option is to use portable HEPA filter device in the patints' room, if possible. In addition, the presence of unnecessary medical personnel in the room should be avoided. To reduce aerosol formation, the mask should place before turning NIV on and remove after turning NIPPV off.

Cooperation between experienced healthcare professionals (intensivists, infectious diseases and respiratory therapists) and availability of adequate equipment increase the success of treatment. The use of old ventilators or anesthesia machine and the use of a single device for more than one patient are among the problems during NPPV therapy. The most common reason for these problems is equipment limitations caused by the pandemic.

Non-invasive positive pressure ventilation with Helmet

Helmet masks are generally preferred in the patients with pressure ulcers on the face area or leakage with the other masks. Non-invasive ventilation with Helmet masks have several advantages including better tolerability and less leakage.

The least aerosol-generating mask (helmet, full face mask, oronasal mask, nasal mask, respectively) for NIPPV during pandemics should be considered and so, using the helmet mask is suggested due to safety of health-care personnel. Therefore, NIPPV with a helmet mask would be a correct approach in the patients with COVID19 pneumonia.

Helmet mask allows positive pressure ventilation without pressure on the face and thus without pain and device-related pressure necrosis. Another advantage of the Helmet mask is to increase patients comfort, the patients can read and talk during NIPPV with Helmet. However, the use of helmet masks is limited because they are more expensive than the other masks and they are not avaible in every center. Moreover, claustrophobic patients may have difficulty in adaptation to the Helmet mask.

Sedation for non-invasive positive pressure ventilation therapy

After evaluating all factors may cause NIPPV intolerance, sedation and analgesia may be applied to increase the success rate. Conscious sedation by titrating analgesic and sedative agents improves patient tolerance without significant effect on respiratory pattern, respiratory drive and hemodynamics. Short-acting agents such as dexmedetomidine, propofol or midazolam can be used successfully in case of patient-ventilator asynchronie.

Considerations during non-invasive positive pressure ventilation therapy

Insistence on NIPPV in COVID19 pandemic may result in increased the need for intubation, morbidity and mortality rates. If NIPPV fails, 'delayed intuba-

tion' may be associated with an increase in complications due to urgent procedure (unstable intubation, increase the risk of aerosol transmission to the healthcare workers, etc). Therefore, selection of the appropriate patient is very important. Bellani et al demostrated that using of NIPPV was associated with higher mortality in the patients with a PaO2/FiO2 ratio (Harovitz index) of less than 150 mmHg.

Patients receiving NIPPV should be monitered closely, especially the first 1-2 hours are important. Increased respiratory rate and work of breathing, the use of accessory respiratory muscles should suggest the possibility of intubation. Therefore, specialized healthcare professionals are more needed than standard oxygen therapy and HFNC.

CONCLUSION

In selected patients with COVID19, the use of non-invasive ventilation modalities may be considered after the balance between benefit and harm is carefully calculated. Especially when resources are limited for practicing invasive mechanical ventilation, non-invasive ventilation strategies are crucial. However, high failure rate, the possibility of delayed intubation and the increased risk of aerosolization due to poor mask fit should be kept in mind. And rutin use of NIPPV should be avoided in the patients with COVID19. The patients should be closely monitoring during non-invasive ventilation therapy for worsening of respiratory condition and clinical deterioration. Intubation should be considered if inability to maintain PaO2/FiO2 rate > 150 mmHg, no reduction in respiratory rate (≥ 30 breath/minute), FiO2> 80% after 1 hour of CPAP therapy.

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CHAPTER 10

THE USE OF PERSONAL PROTECTIVE EQUIPMENT IN ANESTHESIA OF PATIENTS WITH COVID-19

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INTRODUCTION

While healthcare workers are providing healthcare services for diagnosis and treatment purposes, they expose to many risks such as infections, radiation, physical, chemical, etc. in their areas of work. Therefore, healthcare workers are required to wear protective clothing and equipment to reduce aforementioned risks. Protective clothing and equipment should comply with the standards and be used properly. The new Coronavirus disease (Covid-19), which emerged in China in December 2019, was classified and announced as a pandemic by the World Health Organization in January 2020. Covid-19 virus is transmitted between people through close contact and droplets. The patient's respiratory activity and medical interventions can generate aerosols. These aerosols contain particles that can stay longer in the air. The risk of contact

with these aerosols is higher during airway maneuvers, especially during tracheal intubation. It has been shown that those who perform tracheal intubation during the severe acute respiratory failure syndrome (SARS) epidemic have a higher risk of infection. Anesthesiologists are in one of the most risky groups among healthcare professionals, as they are in the group performing high-risk aerosol-forming medical interventions in intensive care and operating rooms. Personal protective equipment is an important factor in minimizing the risk of infection to healthcare workers. The World Health Organization (WHO) and other international public health authorities recommend applying safety protocols for healthcare workers. The use of appropriate personal protective equipment takes a special place among the precautions to be applied by healthcare professionals who care for Covid-19 patients. Personal protective equipment includes gloves, medical masks, goggles or a face shield and gowns, as well as respirator masks (N95, FFP3 or FFP2) and hospital gowns during specialized procedures.

Anesthesiologists may encounter potential Covid or Covid-positive patients in both intensive care and emergency or elective surgeries. Full personal protection including a liquid-proof long sleeve gown, pair of gloves, eye protection, full face protection, headgear, suitability tested respirator mask or air-purifying respirators is recommended for anesthesiologists in case of confirmed or possible Covid-19 patients.

Procedures such as balloon mask ventilation, tracheal intubation, and tracheostomy are considered as high-risk aerosol-forming medical interventions.

The proper use of personal protective equipment is important in terms of both protecting the healthcare workers and preventing the spread of the disease.

Table 1. Recommended Infection Prevention Precautions

Suggested Practice	**Comments**
Respirator mask during anesthetic care	Such as N-95 or FFP-2. Assumes abundant supply ofmasks. Conservation efforts should be implemented if in short supply.
Ordinary surgical masks in public areas of the health care	ecommended by CDC. Assumes abundant supply ofmasks. Reusable cloth masks could be used if surgical masks are not available in sufficient quantities.
Hand gel close to provider or personal, wearable gel dispenser	Frequent hand hygiene is essential for personal protectionand protects patients from hospital-acquired infection.

Eye protection at all times during anesthesia care	Required by US Department of Labor, Occupational Safetyand Health Administration Standard 1910.1030.
HEPA filter (or similar) on exhalation side of anesthesia circuit(at least) and/or between the airway and the Y of the circuit (to filter gas in both directions)	HEPA filter (or similar) effectively filters small particlesincluding viruses.
Reusable standard and videolaryngoscopes should undergohigh-level decontamination or sterilization	Recommended by CDC. Consider single-use standard andvideolaryngoscopes if available and cost-effective. Be aware that some videolaryngoscopes cannot undergo high-level decontamination or sterilization (Supplemental Digital Content, Table 1, http://links.lww.com/AA/D186).
Avoid entering anesthesia cart without performing handhygiene first	Contents of anesthesia cart are easily contaminateddu-ring use.
Single-use plastic covers for parts or all of anesthesia machine and anesthesia computers, keyboards, and touchscreens	Covers can reduce bioburden on contaminated, difficult toclean surfaces.
Wipe anesthesia machine high touch areas with hospital antiseptic wipes (if not covered with plastic covers)	High touch areas of anesthesia machine have been shownto be frequently contaminated.
Double glove for airway management	Discard the outer glove immediately following airwaymanagement to limit surface contamination.
Enclose cell phones and other personal communications devicesin plastic bags or wipe with antiseptic wipes compatible with electronic devices	Cell phones have been shown to be contaminatedwith antibiotic-resistant pathogens during use in the hospital.
Manage endotracheal tubes to minimize aerosolization followingplacement	HEPA filter (or similar) on open lumen of double-lu-men tube during single lung ventilation.
Consider gowns for airway management	Gowns could be used during airway management to protectproviders' skin and clothing from contamina-tion. Be aware of variable permeability of gowns depending on rating.
Consider airway management adjuncts such as coversand boxes	Effectiveness has not been well studied and may interferewith airway management.
Consider surgical smoke evacuation	Risk of infection of providers by surgical smoke is unknown,but surgical smoke evacuation was a recommended practice before the SARS-CoV-2 pandemic.
Consider how to protect the surgical team	The surgical team should consider whether to utilize N-95masks and whether to vacate the operating room during airway management.
Consider discussing infection prevention measures duringthe "time out" (safety checklist)	Be aware that not all providers can be fit for N-95 masks.

Key recommendations are in boldface.

Abbreviations: CDC, Centers for Disease Control and Prevention; HEPA, high-efficiency particulate air; SARS-CoV-2, severe acute respiratory syndrome coronavirus

RESPIRATORY MASKS

Respiratory masks such as the N-95 mask (**Figure 1**) (or equivalent FFP-2) appear to provide reasonable protection against the spread of viruses both by droplets and the air. Respiratory masks differ from ordinary surgical masks since they fit tightly to the area of the face while filtering very small particles, limiting the penetration of airborne particles. The definition of N-95 means that at least 95% of 0.3 μm particles are filtered by the mask. The N-95 mask is approximately 10 times more effective in filtering small particles than surgical masks. Although it is still unclear whether this means better infection prevention is feasible through the N-95 masks. As a result of a meta-analysis, it has been put forward that N-95 masks have a greater effect than surgical masks in preventing transmission of the SARS-CoV-2 virus.

It can be suggested that the N-95 mask probably provides more protection than an ordinary surgical mask. Routine use of an N-95 mask or similar respiratory masks in the operating room during the SARS-CoV-2 pandemic has been recommended by the American Society of Anesthesiologists (ASA).

Figure 1: Different types of N 95 Masks

Although the use of N-95 and similar respirators is recommended for the protection from the respiratory viruses, these masks have serious limitations. A 'fit-test' should be performed to users to ensure that there is sufficient fit between mask and face. Facial hair typically causes air to leak from the sides of the mask. For this reason, users must wear a specific brand and model of masks. If a specific mask is not available, a fit test for a different mask should be performed. N-95 masks are only for single use, but reuse could be considered in such cases where respiratory masks are insufficient.

Wearing a standard face mask over the N-95 mask allows reuse of the N-95 by preventing further contamination, but this may increase the work of breathing. Many users report that the N-95 mask causes breathing difficulties because of its greater airflow resistance compared to surgical masks. Some users report nasal congestion and skin deterioration due to prolonged use of N-95 masks.

Elastomeric respirators are reusable masks with a replaceable filter, made of rubber or synthetic material, and fit tightly. As with the N-95 mask, fit testing is required.

RESPIRATORY MASKS FOR THE SURGICAL TEAM

Anesthesia-related airway management is one of the procedures with the highest risk of aerosolization and transmission from patients with suspected SARS-CoV-2 infection, with the exception of surgical cases involving the direct airway. Therefore, N-95 masks or similar masks should be used by the entire operating room team; however, if the number of N-95 masks is insufficient, the surgical team, including nurses and surgeons, may evacuate the operating room during airway management, including anesthesia induction and extubation. Operating rooms normally have a slightly positive pressure and higher air exchange. The time required to remove foreign particles from the air from an operating room can be estimated if the number of hourly air changes is known; generally, approximately 7 air changes in total are required to reduce foreign particles by 99%. An operating room with 15 air changes per hour requires approximately 30 minutes to reduce foreign particles by 99.9% . It may not be practical to adhere to such waiting times, but even shorter waiting times can reduce the risk. Cautery or laser used during surgery may cause aerosolized particles, but if not performed in the respiratory tract, dispersal of infective SARS-CoV-2 viral particles may not be possible. However

the use of N-95 masks by surgeons and surgical smoke evacuation systems are recommended.

EYE PROTECTION

The conjunctiva is a possible site of infection by respiratory viruses. Therefore, eye protection is generally recommended during exposure to droplets or aerosols containing respiratory pathogens. For this purpose, it is thought that glasses with side shields can provide more effective protection.

PROTECTIVE CLOTHES

In the care of patients with known or suspected SARS-CoV-2 infection, gowns that cover a part of the body or medical overalls covering the whole body are widely used.

Gowns are graded on the basis of their permeability; 4 levels have been defined for gown standards, ranging from minimum (level 1) to high risk (level 4). Repeated washing of reusable gowns can make gowns more permeable. There is no specific recommendation regarding the types of gowns to be used for protection from respiratory tract viruses. It is assumed that the infection does not occur directly through contact between the virus and the skin. However, virus particles on the skin or clothing can pass into the respiratory tract with fingers. Therefore, it appears to be a reasonable precaution to routinely wear a gown during airway management or other aerosol procedure. **(Figure 2)**

Figure 2: Protective clothing

ROUTINE USE OF SURGICAL MASKS IN THE HOSPITAL AND OPERATING ROOM

During the SARS-CoV-2 pandemic, healthcare professionals, patients, and visitors were recommended to wear surgical masks when they are inside the healthcare facility. Standard surgical masks should be worn within the operating room complex, including waiting rooms, corridors, patient retention and recovery areas, break rooms and other areas where staff can meet. Anesthesiology staff should be aware that they or their colleagues may have an undiagnosed SARS-CoV-2 infection.

HAND HYGIENE AND SURFACE CLEANING

Cleaning the anesthesia area of work is very crucial, as the SARS-CoV-2 virus can be transmitted through contact with contaminated surfaces (from surfaces to fingers and respiratory tract). SARS-CoV-2 is easily inactivated with sodium hypochlorite, alcohol or hydrogen peroxide, and some other hospital-approved disinfectants. Hand hygiene is critical in protecting hospital staff and patients; hand disinfectants should be placed near to the anesthesia and surgical team. People with dermatitis due to frequent hand hygiene may consider applying disinfectant to examination gloves.

Cleaning the anesthesia machine and supply cart is difficult, especially in a busy operating room, due to the limited time between cases. Plastic cloths covering all or a part of the anesthesia machine have been suggested in operating rooms exposed to SARS-CoV-2. It should be taken care to cover the computer keyboard, mouse and computer touch screens with disposable plastic covers. Another alternative consists of an anesthesia machine sleeve built for the purpose including a special storage pocket for airway aspiration (**Figures 3-4**). Contaminated covers should be discarded carefully to avoid cross contamination.

A partial view of the anesthesia machine cover with a pocket for Yankauer aspiration is shown. (Photo courtesy of Murlikrishna Kannan, MD, FRCA.) (Integrated Anesthesia Medical Group, Los Angeles, CA and AnesthesiaHygiene.com.)

In such situations where the anesthesia machine is not covered with a plastic cover, hospital antiseptics can be used to clean contact areas. Personal items such as mobile phones can be wiped with 100 antiseptic wipes or covered with plastic bags.

Figure 3: A partial view of the anesthesia machine cover with a pocket for Yankauer aspiration is shown. (Photo published with consent of Murlikrishna Kannan, MD, FRCA.) (Integrated Anesthesia Medical Group, Los Angeles, CA and AnesthesiaHygiene.com.)

Figure 4: Another view of the anesthesia machine cover is shown. (AnesthesiaHygiene.com, Los Angeles, CA).

Ultraviolet light is used in the decontamination of operating rooms. Ultraviolet light can also be used to neutralize airborne pathogens. Some ultraviolet light wavelengths can be harmful to human skin and eyes; however, this problem can be managed by controlling the wavelength of light and the intensity of exposure. A recent study has shown that ultraviolet light at 222 nm wavelength inactivates airborne coronaviruses.

AIRWAY MANAGEMENT

During airway management, respiratory viruses can become aerosol and cause the spread of infection in the anesthesia team. Airway management can also spread pathogens to the surfaces of the anesthesia area of work and airway equipment. It is said that wearing double gloves for airway management and immediately discarding the outer glove can reduce surface contamination of the anesthesia area of work. Laryngoscopes are classified as "semi-critical" (in contact with mucous membranes) devices that require a high level of decontamination or sterilization. However, some video laryngoscope handles cannot be subjected to high levels of decontamination or sterilization, for this reason, conventional and disposable laryngoscopes or videoyngoscopes may offer a more cost-effective alternative.

It is recommended to place a HEPA filter or similar filter on the exhalation side of the breathing circuit, or to place a filter in the «Y» part (protecting both the breathing and exhalation sides of the circuit) to protect the anesthesia machine from contamination with aerosolized airway secretions.

In addition, opening the lumen of any endotracheal tube or supraglottic airway device to the operating room atmosphere should be minimized as much as possible. It makes sense to place an anesthetic circuit filter in the lumen of the endotracheal tube for this.

Several methods such as covering the patient's head with plastic covers or plastic boxes have been proposed, in order to prevent the spread of aerosolized airway secretions during airway management. However, the effectiveness and impact of such practices on airway management are unknown. Plastic materials that got contaminated during airway management should be disposed of or the decontamination of reusable materials should be done carefully. The results of a simulation study performed on plastic intubation boxes has revealed that this way intubation takes longer, first attempts are less successful, and when the boxes are used, the gowns of the anesthetist are frequently opened, which raises safety problems.

Various recommendations including the use of rapid sequential induction, avoidance of balloon and mask ventilation, and the use of videolaryngoscopy over standard laryngoscopy have been made for airway management in patients with known or suspected SARS-CoV-2 infection . While these recommendations are reasonable, there is little evidence for the reduction of infection transmission.

TEST AND STANDARD MEASURES APPROACH

A range of respiratory precautions has been recommended for all patients. As mentioned earlier, this is similar to "standard" measures for bloodborne pathogens (such as HIV or hepatitis C viruses), which assume all patients are potentially infected. PCR testing is recommended to identify infected patients. However, this test has some handicaps. Firstly, PCR testing for SARS-CoV-2 may give a false negative result. Secondly, testing takes time. Tests are usually done about 2 or 3 days in advance. Hypothetically, patients may be infected after testing and before anesthesia. Third, this approach is not suitable for emergency procedures because the test takes time to perform. For this reason, it is recommended to apply respiratory precautions to all patients. More detailed measures could be required in patients with known or suspected SARS-CoV-2 infection.

CONCLUSIONS

Fundamentally, it is recommended that anesthesiologists wear a surgical mask at all times in the hospital and routinely wear breathing masks when providing anesthetic care. Eye protection should also be worn and hand hygiene should be done frequently. The surfaces of the anesthesia workplace should be kept as clean as possible. Healthcare facilities and government agencies should prioritize the production and distribution of needed personal protective equipment, especially high-quality respiratory masks. It is essential to continue research to better understand the SARS-CoV-2 virus and that will help us improve our approach to protect ourselves and our patients. The SARS-CoV-2 pandemic is not the first respiratory virus pandemic of the 21st century, and will probably not be the last one. Anesthetic care for patients diagnosed with definite or suspected SARS-CoV-2 infection requires more detailed measures.

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CHAPTER 11

ANESTHESIA MANAGEMENT IN OBSTETRIC PATIENTS WITH COVID-19

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INTRODUCTION

Through the ends of year 2019 the world has met a new infection first reported from Wuhan, China which was caused by a new type of Corona Virus named as "severe acute respiratory syndrome corona virus 2 or SARS-CoV-2", which would be named as COVID-19 by world health organization on 11 February 2020. Within a month, on 11 March 2020, WHO declared the new infection outbreak as a pandemic. We all had some knowledge about SARS outbreak happened at 2003 but the new pandemic caused by SARS CoV-2 spreads faster and affects many people worldwide with an unpredictable course.

SARS-CoV and Middle East Respiratory Syndrome (MERS-CoV) were both reported to have more severe course when the patient was pregnant however it is not the case with COVID-19 infected parturients according to the literature that we obtained up to date regarding the clinical outcomes of

COVID-19 infected pregnant women. According to present data on COVID-19 infected patients, men has higher fatality rate than women although there is no clinical explanation for this documentation. The reason may be related to gender, underlying comorbidities or other reasons.

In the context of COVID-19 global pandemic, management of pregnant patients have become more challenging. The parturients are anxious about their health status, their babies' health status, and the risks related to bonding and ability of breast feeding in case of separation of their baby is indicated or recommended by the care givers.

The most common symptoms of COVID-19 are fever (>37 degrees Celsius), cough (generally dry but may be productive), flue-like symptoms, diarrhea, vomiting, myalgia, tachypnea, shortness of breath, and loss of taste sensation. These symptoms however can be seen during the routine course of pregnancy and therefore can confuse the diagnosis. With the increasing rate of reverse transcriptase polymerase chain reaction (PCR) test accessibility, universal testing of pregnant women admitted to hospital is advised. Pregnant women with one or more of these symptoms should be accepted as patients under investigation for COVID-19 infection on admission to hospital and should be hospitalized at a designated service of the hospital for COVID-19 patients under investigation (PUI). Universal testing of pregnant women is essential thus most of the COVID-19 positive patients are asymptomatic on admission to hospital.

Management of pregnant patients in the context of COVID-19 global pandemic has emerged several challenges for the care givers. Early and strict communication of the obstetrician with the anesthesiologist, labor and delivery nurses, midwifes, neonatologist, intensive care specialist, infectious disease and infection control experts, employee health services is essential in the context of COVID-19.

LABOR ROOM AND OPERATION ROOM PREPARATION

Every hospital must generate their own protocols to provide optimal healthcare for the pregnant mother who is a confirmed case for COVID-19 or suspected to be COVID-19 and under investigation, meanwhile strategies for the prevention of the dissemination of the disease, as well as protecting the health care workers by providing personal protective equipment (PPE) is crucial.

A designated labor and delivery room should be addressed preferably apart from the main labour service to prevent the transmission of the disease

to the pregnant women tested negative for COVID-19. Patients that are confirmed cases or under investigation for COVID-19 should wear a surgical mask on admission to hospital. PPE should be present in the designated labour unit, an area to don and doff the PPE should be assigned for the health care workers, and the health care workers should be trained for the proper donning and doffing of PPE. There must be proper signages on the doors of the labor and delivery rooms regarding the presence of an infected case. Minimum number of personnel should be present in the labor room while maintaining the optimal care for the laboring patient to decrease the risk of infecting the health care workers.

The designated labor and delivery unit should preferably be isolated for single patient and should have negative pressure that has at least ten fresh air changes per hour. If negative pressure system is not the choice, air conditioning must be turned off and a natural aeration must be used.

The standard equipment used during the labor and delivery process must be kept in closed sterile trays aiming to prevent contamination. An invigilator personnel should be readily present close to the dedicated labor and delivery room, but outside the room, to provide any extraordinary medical equipment if needed during the labor and delivery. Since communication under PPE is often difficult and may lead to misunderstandings under PPE, all stuff taking part in the labor process should be trained for different possible scenarios. The role of all medical stuff must be well defined, their names should be clearly written on the coveralls.

TESTING ON ADMISSION

COVID-19 is a highly contagious infection that can be transmitted via droplets, aerosols, and with close contact with confirmed cases. Current data suggests that even an asymptomatic patient can transmit the disease to their close proximity before any symptoms of the disease is present. Although most of the early common symptoms of COVID-19 (fever, myalgia, shortness of breath, fever, headache) overlap with the symptoms of pregnancy, during the COVID-19 pandemic health care personnel should be awake and should keep in mind the possibility of taking care for an infected case. Apart from the previous severe acute respiratory syndrome (SARS) outbreak in 2002, the clinical course of COVID-19 in pregnant patients is mild and most of the pregnant patients admitting to hospital for delivery are asymptomatic. Therefore; patients with the symptoms of fever (>37C), caough (dry or pro-

ductive), shortness of breath, diarrhea, or pregnant patients that had a close contact with a confirmed COVID-19 patient should be tested for COVID-19.

The specifity of reverse transcriptase polymerase chain reaction testing for viral ribonucleic acid is unclear and may report false negative results if the viral load is small and/or if the specimen was not sampled in an appropriate manner. But especially in high prevalence communities it is advocated to perform PCR testing to the pregnant women on admission to hospital for labor and delivery thus most of the pregnant patients are asymptomatically infected or may be asymptomatic at the time of admission. The importance of testing the parturient on admission to the hospital has two arms. One is that if the parturient is tested positive, she will be isolated in a dedicated labor and delivery unit and the second arm is the transfer of the patient will be through the predetermined route to the dedicated labor and delivery room that will assure to limit the contamination of the hospital, and transmission of the disease to the health care providers.

PREANESTHETIC CONSULTATION

To assure the optimal anesthetic care for a confirmed COVID-19 or highly suspicious pregnant women admitted to hospital for delivery, a team of anesthesiologists, obstetricians, neonatologists, midwives, critical care experts, infectious disease and infection control experts must be in close communication.

Pregnant patients must be evaluated for vital signs and physical examination excluding lung auscultation with a sthetescope to prevent transmission. Ultrasonographic evaluation of pulmonary system is recommended to assess the presence of consolidation or atelectasis of the lungs. Laboratory test should include complete blood count. Although thrombocytopenia is a common occasion during pregnancy, a platelet count of less than 100000 x 10^6/L is rare. In the very early phase of the pandemic, a clinical report from China reported that pregnant patients with COVID-19 disease had lower platelet counts but the recent studies could not confirm this finding.

An arterial gas sampling is indicated for patients whose SpO2 level is below 93% at room air, tachypneic and or needing oxygen support. Hypoxia (SpO2<93% at room air), severe dyspnea, tachypnea (>30 breaths/min), respiratory distress are the signs for the severity of the disease indicating the progression of the respiratory function deterioration.

LABOR ANALGESIA

There is no clinical evidence for avoiding neuraxial labor analgesia for pregnant women that is a confirmed COVID-19 case or suspected to be positive and under investigation. The obstetricians must inform the obstetric anesthesiologists early on admission of the parturient to the hospital and keep close communication to inform the clinical progression of labor. Furthermore an early implemented epidural catheter is essential in the context of COVID-19 to avoid deterioration of respiratory status of the patient due to labor pain and to reduce the possibility of the need for general anesthesia induction if intrapartum cesarean section is needed.

Epidural analgesia is not accepted as an aerosol generating procedure therefore an impervious gown, a surgical mask, eye protection and sterile surgical glows are the adequate PPE that must be donned by the anesthesiologist during the epidural analgesia placement process. The PPE should be donned outside the labor and delivery room preferably at a predefined and dedicated area for donning and doffing of the PPE in the labor and delivery unit. The patient must wear a surgical mask at all times starting from the admission to the hospital for delivery to minimize contamination with droplets. To minimize the risk of transmission and to keep the minimum number of healthcare providers within the room of a COVID-19 infected patient, a midwife dealing with the pregnant patient may assist the anesthesiologist while placing the epidural catheter. All routine medical equipment necessary for the placement of an epidural catheter must be in dedicated trays and preferably disposable materials must be used whenever possible to prevent the contamination with droplets.

The laboratory tests of a pregnant women receiving epidural analgesia who is a confirmed COVID-19 positive case or symptomatic and under investigation for COVID-19 must include a complete blood count before epidural analgesia placement. A platelet count of > 70000 x 10^6/L or above is accepted to be safe to provide a neuraxial analgesia in pregnant patients to avoid general anesthesia and its probable inadvertent side effects as respiratory compromise and aerosol generating procedures during intubation and extubation that will increase the risk of transmission of the disease to the medical stuff taking care of the patient within the labor and delivery unit. Clinical reports from China in the very beginning of the pandemic reported a platelet count of less than 150000 x 10^6/L in 36.2% of the pregnant patients with COVID-19 infection and this was supported by another meta-analysis reporting that the severity of thrombocytopenia increases with the increasing severity of COVID-19

infection. Although epidural hematoma is a big threat with platelet counts less than 70000 x 10^6/L, up to date there is no reported case of epidural hematoma formation following epidural catheter placement for labor analgesia in a COVID-19 infected pregnant women.

To avoid any possible complications as inadvertent dural puncture, to increase the success rate of epidural analgesia, and to decrease the time spent within the same room while placing an epidural catheter to a parturient tested positive for COVID-19, preferably the most experienced anesthesiologist must carry out the epidural procedure. Minimum number of personnel must be present in the labor and delivery room during epidural placement while assuring the optimal assistance to the stuff anesthesiologist.

Epidural analgesia results in an increase in body temperature and this may worsen the clinical course of a parturient tested positive or symptomatic and under investigation for COVID-19 infection. A common feature of COVID-19 tautologous is pyrexia and the increased maternal body temperature may also lead to fetal compromise. Recommending fetal monitoring during the placement of an epidural catheter for labor analgesia is therefore logically a necessity.

Treatment of inadvertent dural puncture with epidural blood patch is another challenging concern in parturients tested positive or symptomatic and suspected for COVID-19 infection. When conservative follow up, hydration and paracetamol are ineffective for the management of post-dural puncture headache, epidural blood patch is used to stop the leakage of cerebrospinal fluid from the punctured dura however in COVID-19 parturients injecting the viremic blood may result into meningitis or encephalitis. We recommend staying on the safe side of the treatment of post-dural puncture headache and postponing epidural blood patch although there is no reported encephalitis or meningitis case following epidural blood patch during the COVID-19 tautologous.

There is no clinical data about the aerosolization of nitrous oxide used for labor analgesia but it is recommended to suspend the use of nitrous oxide for labor analgesia in the context of COVID-19.

Using remifentanil patient controlled analgesia also is not recommended for a pregnant patient tested positive or symptomatic and under investigation for COVID-19. The threat in the use of remifentanil for labor analgesia is the risk of respiratory depression which may be life threatening for a pregnant patient with COVID-19 infection that has a respiratory compromise.

ANESTHESIA FOR CESAREAN SECTION:

As formerly mentioned, the route of the pregnant patient who tested positive or symptomatic and under investigation for COVID-19 infection must be well defined and protocolized starting from the hospital admission to the labor and delivery unit. Moreover, the transport of the parturient to the operation room, to the postoperative service or intensive care unit must be well documented to minimize the risk of hospital contamination and transmission. The patient must be the last in the order of operation list to minimize the risk of transmission and contamination of the operating theatre.

Neuraxial anesthesia is recommended for parturients with confirmed or suspected cases of COVID-19 to avoid the transmission with aerosol generating procedures as intubation and extubation during general anesthesia. The usual contraindications as coagulation disorders, thrombocytopenia, and fever also apply to the COVID-19 infected parturients. The neuraxial anesthesia may be provided by either extending the epidural analgesia or de novo spinal or combined spinal epidural anesthesia.

The cesarean rates increased during the COVID-19 tautologous either due to medical reasons (fetal compromise due to maternal fever) or due to the willing of the parturients to undergo cesarean section rather than vaginal delivery since they are anxious about vertical transmission to their babies. For scheduled cesarean sections, epidural, spinal or combined spinal epidural anesthesia can be the choice of neuraxial anesthesia. Neuraxial anesthesia is accepted as non aerosol generating procedure therefore the PPE needed for anesthesiologists includes a waterproof apron, sterile gloves, eye protection, and water resistant surgical mask. The patient must wear a surgical mask at all times. The risk of conversion to general anesthesia from neuraxial anesthesia for a scheduled cesarean section is less and generally be anticipated. Neuraxial anesthesia must be performed by the most experienced anesthesiologist available to increase the success rate of neuraxial anesthesia, and to reduce the risk of complications as failed block or inadvertent dural puncture.

Emergent intrapartum cesarean section may be needed during the course of parturition therefore close communication between the anesthesiologist, midwife and the obstetrician is crucial for assuring the best anesthetic care for the parturient. The midwife can inform the anesthesiologist about the performance of an epidural catheter inserted for labor analgesia. For the successful extension of epidural analgesia to neuraxial anesthesia for cesarean section, the obstetrician must inform the anesthesiologist about the timing of cesarean

section to provide the necessary time for local anesthetic spread. If the epidural catheter inserted for labor analgesia is not functioning well, the anesthesiologist should consider de novo spinal or combined spinal anesthesia induction which is not more time consuming than induction of general anesthesia when applied by the most experienced anesthesiologist available.

The conversion risk to general anesthesia from neuraxial anesthesia in emergency cesarean section cases is higher than scheduled cases and the emergency cesarean section cases often do not have a PCR test for COVID-19 within the last 48 hours, therefore the anesthesiologist must don a FFP3 or N95 mask, eye protection, long sleeved waterproof gown, and gloves. All medical stuff must don their appropriate PPE outside the operation theatre before the patient has arrived. Minimal number of care givers must be present in the operation room during the neuraxial procedure. Conventionally necessary equipment and medications for neuraxial anesthesia must be readily available in sterile trays to prevent contamination. A runner outside the operation room must be standing to assure any extra need during the process of neuraxial anesthesia and cesarean section. A dedicated operation room must be used for all confirmed or suspected cases for COVID-19.

A research article reported that the incidence of hypotension following neuraxial anesthesia was increased in pregnant patients with COVID-19, however this study had limitations. The information about the use of a vasopressor agent or intravenous crystalloid infusion following induction of neuraxial anesthesia and the blood pressure trends were lacking and the sample size was only 19 patients. According to our clinical experiences with neuraxial anesthesia in COVID-19 positive parturients, neuraxial anesthesia is well tolerated if management of hypotension is managed properly with intravenous crystalloid infusion and vasopressor administration.

Another common complication of neuraxial anesthesia is nausea and vomiting that should be properly managed. The use of dexamethasone for the management of nausea and vomiting for a confirmed or suspected COVID-19 infected parturient is not recommended since high dose steroid may worsen the clinical course of the disease. Alternative antiemetic medications should be mentioned.

Uterotonic medication should be used with caution. Avoid using carboprost tromethamine as the first line uterotonic medication since it may cause bronchoconstriction and pulmonary vasoconstriction that will increase the aerosol production. Oxytocin and methylergonovine should be considered as alternative uterotonic medications.

GENERAL ANESTHESIA

General anesthesia is an aerosol generating procedure during intubation and extubation of the patient. The threat of general anesthesia induction for cesarean section in a confirmed or suspected COVID-19 infected pregnant patient is the respiratory compromise due to endotracheal intubation. The threat on the medical care givers side is transmission of the disease via aerosols during the intubation and extubation processes.

Preoxygenation is mandatory as is usual for induction of general anesthesia in obstetric population without COVID-19 infection. However, high-flow nasal oxygenation or face mask oxygenation should be avoided since they are accepted as aerosol generating procedures. Patient must be preoxygenated with a tight fitting mask applied by two hand technique with usual oxygen flow rates to minimize the risk of aerosolization. Rapid sequence induction and intubation is recommended for parturients that are confirmed cases or suspected to be COVID-19 infected.

All medical stuff should don proper PPE for aerosol generating procedures before the patient is transferred to operating theatre. The anesthesiologist should don a FFP3 or N95 mask, long-sleeved waterproof gown, eye protection, and at least two pairs of gloves. Difficult airway is an anticipated condition in obstetric population and the additional respiratory compromise with COVID-19 infection increases the difficulty of airway management of parturients that are tested positive for or suspected to be COVID-19. The most skilful and experienced anesthesiologist must handle the intubation process to increase the first pass success rate. Fiberoptic laryngoscopes should be used whenever possible to decrease the risk of cross-contamination. A cross clamp on the intubation tube is recommended until the cuff is inflated and the patient is connected to the anesthesia circuit to minimize the risk of contamination with aerosols and transmission of the disease to the medical stuff in the operation room. Before starting induction of anesthesia, care givers other than the anesthesiologists must leave the operation room whenever possible to decrease the transmission risk. Intraoperative anesthesia management is carried out as usual. Small tidal volumes (8-10ml/kg) with a frequency of not more than ten are recommended. Positive end expiratory pressure may be used to maintain the desired oxygen saturation levels in arterial blood gas analysis samples.

The extubation is an aerosol generating procedure which poses the risk of high aerosol production during the cough on extubation. Several measures have been tested for to prevent or at least reduce the cough produced following

extubation. Dexmedetomidine, lidocaine, remifentanil, and fentanyl were used for this purpose and dexmedetomidine was found to be most effective amongst these drugs in decreasing the frequency of post extubation cough. Anesthesiologist must always keep in mind that dexmedetomidine and opioids may result in respiratory depression in a pregnant patient whose lung capacity is decreased and respiratory system is compromised with COVID-19 infection.

POSTPARTUM ANALGESIA

For the asymptomatic and mild symptomatic patients usual postoperative analgesia modalities can be used. The epidural catheter can be used to initiate an epidural patient controlled analgesia (PCA). The PCA provides the opportunity of efficacious control of pain but the anesthesiologists should be alert for the possibility of respiratory depression due to the opioids. In the early periods of the pandemic, avoiding non steroidal anti-inflammatory drugs were recommended without any clinical robust data. The logic was the non steroidal anti-inflammatory drugs increase the ACE-II receptor which was defined as a binding site for COVID-19.

An alternative postoperative pain control modality is adding a transversus abdominis plane block or a low thoracic/high lumbar erector spinae plane block as the part of a multimodal analgesia.

CONCLUSION

COVID-19 is a global emergency health threat challenging all health care management strategies. Management of confirmed or suspected COVID-19 parturients in the labor and delivery units increased the importance of communication and team work to assure the best care for the pregnant woman while protecting the health care providers from transmission of COVID-19.

Based on the data on the management of COVID-19 infected parturients up to date, most of the pregnant patients are asymptomatic on admission therefore care givers must don the appropriate PPE while providing best health care to the parturient unless the patient tested negative for COVID-19.

Providing early neuraxial labor analgesia is very important in the context of COVID-19 that can be extended to surgical anesthesia if intrapartum cesarean section is needed. De novo spinal or combined spinal epidural anesthesia

should be applied in case of a failed labor epidural analgesia. If general anesthesia is unavoidable, the patient must be consultated with the intensive care unit expert and the health care providers should don the appropriate PPE for aerosol generating procedures.

All effort must be on the prevention of transmission to the health care workers while assuring the optimal care for the parturient who tested positive for or suspected to be COVID-19 positive.

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CHAPTER 12

THE CONTAMINATION RISKS AND PREVENTIVE PROTOCOLS DURING THE COVID-19 PANDEMIC IN DENTISTRY

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INTRODUCTION

At the late 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), known as COVID-19 (novel coronavirus), which outbreak in Wuhan, China and formed severe pneumonia in patients, was declared as a "Public Health Emergency of International Concern" on January 31, 2020, and identified as pandemic on March 11, 2020 by World Health Organization (WHO. As of February 20, 2021 according to data from the worldometer 111,319,738 million people affected by COVID-19 in 221 countries, and 2,465,384 fatalities have been reported worldwide, with daily increasing case. Since the first reported case in Wuhan, despite all efforts by the various governments to stop

the novel coronavirus, the pandemic has not been prevented, and moreover the third wave continues to occur in many countries. Due to the increasing number of confirmed cases each day, the COVID-19 global pandemic continues to have impact on economic ressesion, social effects and even which greatly affects the of healthcare services.

TRANSMISSION ROUTE

Researchs conducted that the COVID-19 pandemic probably outbreak through animal-to-human transmission, followed by human-to-human diffusion. The novel coronavirus attachs to angiotensin-converting enzyme 2 (ACE-2) receptor through the receptor-binding domain (RBD) of the S1 and S2 domains of the spike protein, which is similar to the route of SARS-CoV that mainly spreads cause to the respiratory tract disease. According to our knowledge, the novel coronavirus is transmitted through aerosol and/ or droplets difussion, which is the infection can be mainly occurs through coughing, sneezing, and saliva. When droplets and/ or aerosols of the different diameter are generated (>5 μm large diameter, and ≤5 μm small diameter) usually unlike small particles larger droplets due to their weight fall to the ground quickly through gravity. However, small droplets may remain suspended in the air for the longer duration, and travel through air diffusion further which can enter the respiratory system or contact the different areas. Even without the clinical signs of COVID-19, infected droplets can be difussion throught air towards to the mouth, nose, and eyes by asymptomatic patients. Researchers conducted that SARS-CoV-2 pandemic infection can be accompany such as non-compliance with social distance for more than 15 minutes or after contact with contaminated surfaces or hands that come into contact with airborne particles.

COVID-19 TRANSMISSION RISKS IN DENTAL PRACTICE

According to our knowledge about transmission route for different contagious diseases such as SARS-CoV or Middle Eastern respiratory syndrome coronavirus (MERS-CoV), after pandemic outbreak many authorities suggested various warning about regarding possible hazardous activities or workplaces. Aerosol known as one of the transmission route is difffused through to respiratory tracts different ways of contamination especially in closed environment,

and constitute to high risk for the individuals. In dentistry during routine dental procedures, SARS-CoV-2 infection poses potential hazards to dentists, dental care personnel and patients due to exposure of saliva, blood, aerosol and/ or droplets or contaminated instruments and exposed surfaces. In particular, the use of high-speed drills during in general dental procedure may form aerosol that increase the possibilty of infection and transmission risk of COVID-19. Oral cavity mucosa has a high expression of ACE-2 receptor which is responsible for the entry of the coronavirus into the cell and its infection. For all these reasons, dental services have been closed in various countries around the world since March, 2020 therefore, dentists, dental professionals or therapists and dental nurses all assigned to support healthcare delivery system during in this COVID-19 crisis.

COVID-19 pandemic is became a tremendous challenge for occupational health for especially healtcare employee. Considering the exposure jeopardy for different occupational categories, dental professionals are facing the greatest risk for COVID-19 infection. The very nature of the dentistry profession, it is impossible to maintain social distances from the patient, which makes the dentist potentially exposed to the risks of contagious disease. According to the ADA report recently published, it has been reported that the rate of COVID-19 transmission among dentists approximately 1% and the risk of dying from COVID-19 infection is 0.008%.

In the literature, though no reported cases coronavirus contamination and spread during the dentist examination, considering the high contagiousness of the disease, dentists should provide a wholesome surroundings for both patients and themselves, and some special measures should be taken in addition to basic precautions in this particular period.

PREVENTIVE PROTOCOLS TO LIMIT CONTAGION

Although dental practices are starting to re-open slowly and in a controlled manner, the recommendations published by WHO for dental profession have been interpreted differently by countries around the world, therefore considerable variation in the guidance on the safety procedures. Due to well known that widespread immunization with vaccination takes a long time, it is very important to implement preventive protocols during routine dental practices during the COVID-19 pandemic process. Dentists are often very familiar with universal Personal Protective Equipment (PPE), other cross-infection control measures, and risk assessment.

Reducing the Number of Patient

Reducing the patient number before their routine clinical visit can be help the avoid cross-infections among the patients and dental practitioners.

Phone Triage

Before admitting any patient to the practice, triage is highly recommended to investigate risk factors posed by the current health status and/ or the COVID-19 symptom. Patients should be asked if there has been any recent contact with a coronavirus-positive people or they have traveled to outbreak areas. If the patient has positive contact history and / or symptoms, it is recommended to postpone dental treatments for 14 days at least. In addition, the patient must be notified to health authorities for rapidly home or hospital quarantine depending on the severity of the COVID-19 infection. In the absence of contact and / or symptoms, a dental examination can be applied, provided that preventive measures are applied. Before each examination, body temperature should be recorded with a contact-free forehead thermometer and the presence of coughing or breathing difficulties symptoms should be supervised. These security preventions should be applied to attendant of the patient.

Waiting Area

By reducing the number of patients in the waiting room at the same time, the interdistance people can be maintained at approximately least 1 m. This may provide enough time for the disinfection of the examination area for both dentist and patient. In particular, for the patients with that has severe chronical disease (i.e. immunosuppressed, or influenced with severe systemic diseases and comorbidities) can be on-site waiting time reduce. According to the American Society for Testing and Materials (ASTM) classification, basic recommendation for the prevent pandemic is use of the disinfection of the hands and surgical mask that meets at least protection level 1, as it can reduce the aerosols up to 97%.

Hand Sanitation

Hand hygiene is crucial importance to decreasing SARS-CoV-2 contagious disease. As suggested by WHO (2009), in case of contact with patients and non-disinfected surroundings or instruments, it is advised to prevent touching eyes, mouth and nose in absences of any cleaning or aseptic treatment.

Furthermore, WHO (2020c) reported that hand hygiene is equally effective to clean with either an alcohol-based hand rubs or soap and water.

Personal Protective Equipment (PPE)

Due to the fact that SARSCoV-2 transmission occurs through airborne droplets, particles mostly spread towards the dentist's facial area, such as the inner part of the eyes or surronding of nose, during dental practices. For these purpose, the use of PPE can be necessity in healthcare employee. To maintain the eyes from aerosols generated treatment during the dental procedure, goggles and a face shield must be worn and disinfected between every patients. In addition to this, waterproof disposable gowns that covering the entire body, respirator/masks, gloves (two pair of disposable gloves), and headgear caps are extremely recommended. When aerosols occured with using the high-speed handpiece, air-water syringe, and ultrasonic scaler during the dental treatment , professionist must use minimum as protective as a National Institute for Occupational Safety and Health (NIOSH)-certified N95, European Standard Filtering Face Piece 2 (EU FFP2), or coequal.

Preprocedural Mouth Rinse

As we know, mouth washes such as chlorhexidine (CHX), essential oils, and cetylpyridinium chloride (CPC) can be effective on herpes simple virus (HSV), human immunodeficiency virus (HIV), and hepatitis B virus (HBV). Although there is no evidence that mouthwashes could remarkably decreased the COVID-19 virus, their administering may be reduce the aerosol transmisson in oral tissue.

Use of Rubber Dam

During aerosol-generating dental procedures, the rubber dam can remove pathogens from respiratory tract. It has been observed that dam reduces the spread of microorganisms up to 90% during the preparation of the cavity. Although the rubber dam is required to be accommodatedin the whole aerosol generating treatments, it cannot be used in subgingival operations, such as subgingival restoration, subgingival dental calculus removing and subgingival crown margin preparation.

Removal/Filter of Contaminated Air

Since it is known that SARS-CoV-2 can stay in the air for up to 3 hours, if high-speed hand-piece devices are used during the procedures, a complete air exchange in the clinical area is mandatory after every treatment to reduce the hazard of airborne contamination. With stationary devices with air suction, filtration and plasma cluster ion technology, UV lights, inexpensive high-volume evacuation device (HVE) and expensive high-efficiency particulate arrestor (HEPA) filters or special negative pressure chambers, a continuous air exchange can be achieved to remove / filter contamination in clinics. These devices as known reduce aerosol generation must be used in dental practices particularly those involving the use of an ultrasonic scaler. HEPA filter which is 0.3 μm in diameter can remove 99.97% of the particles, although microorganisms held in the filter can be dispersed back into the cleaned air if device care is not maintain regularly. Although the effects of air conditioner devices on the spread of COVID-19 particules in the air are still uncertain, in clinics where centralized air conditioning systems are used, devices should be maintained to prevent virus contamination. As a result, air exchange is recommended after each patient in clinics.

Limitation of Aerosol-Producing Procedures

According to the study, it has been reported that the use of hand tools and ultrasonic devices poses a risk in dental procedures. Dentists, dental personnels and dental assistans must use protective glasses before in contact with the patient. Before the procedures, rubber dam is apply for every patient to reduce aerosols and droplets generation.

Cleaning of Potentially Contaminated Surfaces

After the dental procedure, the patient's disposable gown and other PPEs should be cautiously removed and disposed of it. After removing the first pair of gloves from the two used gloves, the dental personnel should gather entire contaminated instruments and place them in the disinfection and sterilization environment. Since the COVID-19 virus cannot survive for more than 30 minutes at temperatures above 56 °C, common autoclaves may be effective in preventing cross-infection in clinics. Complete sterilization must be perform on whole surroundings of the dental unit, particularly in the spittoon circumference. It is recommended to leave in a 1% hypochlorite or 70% alcohol solution for at least 1 minute and after then clean it carefully. In addition, the dental unit should be cleaned with 0.5% hypochlorite solution before each use.

In order to prevent SARS-CoV-2 cross infection, it is imperative that the areas touched by patients, dentists and personnels (door and/ or window handles, waiting room seats, PC keyboards, mouse etc.) are regularly disinfected.

RECOMMENDATIONS FOR FUTURE GENERAL TREATMENTS

Endodontics

According to the ADA COVID-19 Dental Emergency document, if endodontic treatment is necessery, manuel instrumentation must be preferred to rotary systems. Rubber dam should be used every procedure. If it is possible, pulpotomy and pulpectomy or vital pulp therapy should be preferred to root canal treatment for patient with irreversible pulpitis.

Restorative Dentistry and Pediatric Dentistry

Hand instruments should be preferred instead of rotating systems during cavity preparation. Chemochemical caries removal methods or atraumatic restorative techniques should be applied during the caries removal process instead of high-speed handpiece.

Periodontics

During periodontal treatment, manual scaling and polishing are recommended instead of ultrasonic scalers for removing calculus and plaque.

Prosthodontics

In prosthodontic treatments, disinfection of materials and impressions is important in prostodontic laboratories to minimize the risk of cross contamination. In patients with gag reflex, oral mucosa can be anesthetized with local anesthetic before impression. At the same time, saliva suction should be used and the trays should be selected in the right size to take measurements. To reduce aerosol formation, rubber dam application is recommended during the preparing of a fixed partial denture or single crown. After applying a soft lining to the removable prosthesis causing discomfort, it can be temporarily restored. After the patient has tried the removable partial denture or complete denture on the oral mucosa, the patient should avoid touching any environment due to saliva contact.

Oral and Maxillofacial Radiology

In the radiographs to be taken from the patient for diagnostic purposes, it is recommended to use extraoral radiographs such as Dental Panoramic Radiographs (DPR) or ConeBeam Computed Tomography (CBCT) instead of intraoral radiographs.

Oral and Maxillofacial Surgery

High volume saliva ejectors should be used during tooth extraction. Patient must lie in the supine position, and if suture is necessary, absorbable suture fiber should be preferred. When the patient is admitted to the clinic with excessive toothache, retraction of teeth may be considered instead of a conservative treatment to reduced the treatment period and the risk of infection. Antibiotic therapy is recommended in case of third molar abscess or pericoronitis.

ENVIRONMENTAL SANITATION

Aerosols, droplets containing infective pathogens, generated during dental procedures can accumulate on environmental surfaces. Due to the ability of SARS-CoV-2 to survive on surfaces some time, proper sanitation is required in the potentially contaminated environment. Infection due to contamination can be neutralized by disinfecting surfaces within a minute. Several surface disinfectants which usually use in dental profession are effective on virus (such as sodium hypochlorite 0.5%–5%, or Povidone-Iodine 10%). According to the European Center for Disease Prevention and Control (ECDC) recommendation, if these surface sanitation are not efficient, it can be use neutral soap or 70% alcohol solution.

CONCLUSION

Dentists, dental personnels, dental nurses and dental hygienists are at hazard of exposure to contagious diseases due to nature of the profession. Given the unstable propagation of the COVID-19 pandemic, which is not expected to dissipate in the near future, the risk of infection has increased even more, particularly for dentists. Dental procedures can be enforced within the framework of the above-mentioned rules without ruled out the cross contamination

risk. It should be avoided unnecessary aerosol-generation procedure. With the availability and widespread use of the vaccine in the future, protocols to prevent the spread of COVID-19 will definitely change. However, for now, we must conduct with our knowledge, and protect both dentists and patients against COVID-19 infection.

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CHAPTER 13

INFECTION CONTROL PREVENTIONS IN DENTISTRY DURING THE COVID-19 PANDEMIC PROCESS

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INTRODUCTION

In December 2019, it was announced to the world that the cause of pneumonia cases of unknown etiology in Wuhan city of People's Republic of China, is coronavirus (SARS-CoV-2) that has not been detected in humans before. World Health Organization (WHO) has identified the disease caused by this virus as coronavirus disease (COVID-19) and declared as pandemic disease. The social and economic devastating effects of this virus, which has spread to many countries in a short time, continue.

SARS-CoV-2 is mainly transmitted by the inhalation of droplets scattered by sick individuals into the environment through speech, coughing, sneezing, or by hand contact with contaminated surfaces and the transmission of the agent to the oral, nasal and eye mucosa. Studies have revealed that COVID-19

positive patients have a large amount of viable virus particles in the oral mucosa, epithelial surfaces, and dorsum of the tongue. It is also stated that although the incubation period of SARS-CoV-2 is between 5-14 days on average.

Due to the aerosols formed during dental treatments and long-term face-to-face work with the patient, dentistry is among the risky occupational groups with a high probability virus transmission. The preliminary problem regarding COVID-19 in dentistry is related to the swift spread of viral agents during dental procedures to the air. Therefore, as the main source of transmission of COVID-19, aerosol forms the first step of the risk exposure scale of dentists and assistant health personnel.

The second problem concerns the permanence of bio-aerosols in dental treatment rooms. Aerosols produced by high-round rotary instruments and ultra-sonic devices can stay in air and on surfaces for many hours. Although dentists and assistant staff take protective measures during dental treatments, contaminated air may pose a risk to the dentist and assistant staff after removal of personal protective equipment (PPE) and subsequent patients.

Due to direct exposure to pathogens of patients and indirect contact with microorganisms present on both surfaces and air of the dental office after aerosol generation procedures (AGP's), dental offices can be a dangerous source of SARS-CoV-2 transmission if appropriate infection control measures are not applied. Therefore, it is required to use strict and assertive treatment protocols that can classify dental treatments according to risks. In this study, the protocols recommended in the literature to protect dentists, auxiliary staff and patients from the risk of SARS-CoV-2 transmission throughout the dental treatments that were examined.

COVID-19 TRANSMISSION SOURCES

The most common transmission of respiratory system diseases occurs through inhalation of droplets (>5 to 10 μm) and aerosols (≤5 μm) resulting from coughs and sneezes of patients who are infected or direct contact of these droplets with the mucous membranes of the mouth, nose and eyes. The air-borne spread of aerosols generated by people during inhalation and speech plays a major role in the spread of COVID-19. The major forms of SARS-CoV-2 spread are by droplet transmission and fomites (objects or materials likely to carry infection). Santarpia et al. detected viral contamination in all samples in their study in which they gathered air and surface samples to study

viral contamination from isolated people. It has also been stated that there is a prevalent environmental contamination of SARS-CoV-2 surround the COVID-19 patients and there may be a potential risk of airborne contamination.

The large number of cells expressing angiotensin-converting enzyme 2 (ACE2) receptor in SARS-CoV-2 transmission is considered to be potential high risk. It has been shown that epithelial cells in the oral cavity (tongue, buccal mucosa, gingiva and salivary gland ducts) also express high levels of ACE2. It has been stated that SARS-CoV-2 is present in the saliva of infected patients. Given the main transmission mode of COVID-19 disease, airborne release of saliva particles during dental treatments will increase the likelihood of contamination. Therefore, it should be taken into account that the patient's saliva may be a strong focus of infection in dental procedures that generate aerosol.

In humans, the incubation time of SARS-CoV-2 has been reported to range from approximately 2 to 14 days (possible extreme values: 0–27 days). Virus transmission starts 2-3 days prior to the onset of symptoms, therefore asymptomatic individuals have an important role in the transmission of SARS-CoV-2. Considering that most of the dental instruments are made of metals and polymers, the virus spreading from asymptomatic individuals can be permanent on these surfaces for a long time. Therefore, if these instruments used in patient treatments are not sufficiently decontaminated, they may pose a risk of virus transmission.

It is important to know that dental procedures produce aerosols that can carry the virus to help identify the level of risk posed by these procedures. The risk level has a significant effect on the suitability of the PPE to be selected.

Measures of COVID-19 in dentistry

It is very important to develop effective prevention strategies in destistry, especially for dentists, to prevent COVID-19 and alleviate the transmission risk. The main challenge in dental care during the pandemic period is the need for both a suitable diagnostic model (test swabs) and the presence of asymptomatic patients, patients whose infections cannot be identified exactly. Therefore, in order to avoid the risk of contamination, all of the patients must be treated as if they were infected. To date, it has not been proven that a patient with COVID-19 history has acquired an absolute and persistent immunity for the disease. However, reactivation of the disease and even reinfection has been reported.

Triage and categorizing patients

Dentists carry high risk of infection of coronavirus, due to face-to-face interaction with patients and exposure to aerosol containing saliva and blood during dental treatment. Therefore, in both safety and dental treatment procedures that should be followed during the COVID-19 pandemic period, the use of tele-consultations is emphasized first. This method helps patients to reduce their screening and clinic visits. Secondly, it encourages the triage development to investigate the present health status of patients and the risk factor presence for COVID-19 before performing a dental examination.

The triage review is recommended to be based on a standardized survey to be able to identify patients who may have had any kind of contact with COVID-19 or have a history of travel to an area effected by COVID-19. In the triage process, patients with flu-like symptoms, taste and smell loss should be identified. In addition, patients' fever should be measured. It is suggested that as a preventive measure of COVID-19, there should be no companions (except minors and disabled patients) at dental clinics to comply with social distancing norms. It is also recommended that reception areas have a mandatory seating plan with patients separated by 2 meters. For the disinfection of hands in waiting areas, a solution containing at least 60% ethanol should always be available.

Patient categories in triage applications

- COVID-19 symptomatic patient
- Asymptomatic COVID-19 positive patient
- Formerly symptomatic and recovered patient
- Formerly asymptomatic recovered patient
- Negative patient

It is stated that, as a result of triage, dental facilities can provide dental treatment for COVID-19 negative patients. However, for the category of COVID-19 positive patients or patients showing symptoms, the treatment plan of the patients must be made through medical consultation, taking into account the patient's physical condition and findings. It is also recommended to postpone even emergency procedures and use pharmacological agents for symptomatic relief in case of unstable respiratory symptoms. Dental treatment can be performed after it is confirmed by PCR test that the patient, who has been diagnosed with COVID-19 and recovered symptomatically or asymptomatically, is negative.

Preparation of the patient registration, waiting and treatment rooms

It is recommended to leave at least 1 meter of a safe distance from the patient in the registration of patients scheduled for a dental treatment appointment and, whenever possible, to use isolation type of transparent Plexiglas from the patient. All unnecessary objects (magazines, mouse pads, children's play corners, etc.) should be removed from the dentist office and registration table, including the tools that are not utilized during the dental procedure.

During dental treatments, a large amount of droplets and aerosols containing blood, saliva and microorganisms quickly travel a short range and reach all surfaces in the treatment room. Therefore, all non-disposable surfaces and tools utilized during treatment should be sanitized and disinfected after each patient. Any part that may be more difficult to sanitize should be wrapped with cling film and changed after each patient. Kampf et al. found that coronaviruses were effectively inactivated with 0.5% hydrogen peroxide, 62-71% ethanol, or 0.1% sodium hypochlorite, but they stated that biocidal agents such as 0.05-0.2% benzalkonium chloride or 0.02% chlorhexidine gluconate were less effective.

Disinfection procedures for objects and flat surfaces should be carried out in an order as follows: first, cleaning with disinfectant moistened disposable wipes as not to raise the spray, and secondly, spray the surface and wipe once again. Solution containing 0.5% hydrogen peroxide, 62-71% ethanol or 0.1% sodium hypochlorite should be applied for at least 1 minute to eliminate the virus.

In addition to chemical disinfection of treatment rooms, an ultraviolet irradiation lamp (UV-C) can also be used. The effectiveness of UV-C disinfectant lamps depends on the radiation intensity, air movement, the amount of aerosol passes from the device per unit time, the duration of action, the particle size and the moisture of the penetration barrier.

Treatment rooms should be ventilated for a minimum of 20-30 minutes between patients. In addition, high volume filters (HVE) and high efficiency particulate air (HEPA) filters are widely used to remove/filter contaminated air.

To prevent the formation of pathogenic biofilms, dental unit water lines should be cleaned with a specific disinfectant agent for 2 minutes at the start and end of each day and 20-30 seconds between patients. All contaminated surfaces such as pipes of high-volume aspirators and saliva ejectors, etc. should

be disinfected with 70% alcohol and 0.1% sodium hypochlorite after each patient.

Adequate sterilization of instruments is essential to prevent cross infection. Rotary instruments (aerotor, contra-angle, etc.) must be sterilized after each patient in the DAC device (Dentsply sirona, Germany) or in the autoclave (Statim5000, SciCan).

Dental treatment rooms working with aerosol should be separate and their doors should be closed during the procedure. Only the materials to be used in the treatment of the patient should be included in this room. If the dental treatment room is used for all dental procedures, the room should be adequately ventilated (minimum 20-30 minutes) after the procedures containing aerosol. In these treatments, disposable materials should be preferred whenever possible.

The risk of cross-infection from dental treatments in an open-plan clinic seems small with a distance of ≥5 meter between compartments. Most settled aerosol is detected within 10 min indicating environmental cleaning may be appropriate after this. Also, even low volume suction (40 L/min air, with a wide bore suction nozzle) provides a significant benefit.

Personal Protective Equipment (PPE)

The choice of effective PPE should be determined by the risk assessment and the dental treatment to be performed. Hand hygiene has a critical importance to reduce SARS-CoV-2 transmission. It is stated that the first step of PPE should be hand washing for hand hygiene before and after dental procedures, and then 60% hydroalcoholic solution should be used before and after treatment.

Most useful PPE in dentistry:

1. A filter mask should be used to prevent airborne contamination of particles. Wearing a face mask reduces the risk of airborne infections in healthy individuals, therefore, WHO recommends the use of masks. Particle masks used in various countries (by percentage of filtration) include: (a) European Union: CE certified Filtration Facepiece class1 (FFP1) (80%), class 2 (FFP2) (95%) or class 3 (FFP3) (99.7%); (b) United States: National Institute for Occupational Safety and Health (NIOSH) certified N95 (95%), N99 (99%), N100 (99.7%).
2. The powered air-purifying respirator can be considered a standard component of PPE in certain situations, including aerosol generation

procedures in high-risk environments.
3. Goggles and face shields should be used.
4. Disposable protective gowns and coveralls are not considered PPE over dental uniforms.
5. Disposable gloves should be used for each patient. Gloves protect the dental operator from direct contact with mucous membranes and saliva. Prolonged use of gloves, washing with soap, chlorhexidine, or alcohol can cause micro-holes to form, with increased biological risk. The simultaneous use of double gloves significantly reduces the passage of pathogens through these micro perforations.
6. Head and hair should be protected with a disposable or sterilizable (autoclave) bonnet.
7. Disposable protection should be worn on shoes.

Measures for infection control should be chosen based on direct contact with the patient's body fluids and risk assessment (Table 1).

Determination of dental treatment risk level

The high risk of transmission of COVID-19 and its rapid spread all over the world have brought with it an innovative risk scoring system that shows the risk during dental treatments. Based on the known transmission risks of SARS-CoV-2, it is stated that the risk score parameters for dental treatments for dentists, assistant staff and patients are as follows:

- Direct saliva contact (1 point),
- Direct blood contact (2 points),
- Low spray generation levels/aerosol via air-water syringes (3 points),
- High level of spray/aerosol production using rotary instruments and piezo-electric instruments (4 points),
- The procedure duration (0.25 points, 30 minutes; 0.50 points,30-60 minutes;0,75 points, min 60 minutes).

After this analysis of dental treatments, they are classified as: low risk (1-3 points), moderate risk (4-5 points) and high risk (≥ 6 points). One procedure can accumulate multiple points. The duration of the dental treatments also plays an important role in defining the severity of the risk. Personal protective equipment (PPE) for each procedure is recommended based on the final risk score.

Table 1 Recommendation for PPE according to the level of risk scored for typical dental procedures

Risk Level	Protective Measure
Low risk	Disposable or sterilizable bonnets Surgical mask Goggles or face shield Disposable or sterilizable gowns Disposable gloves
Medium risk	Disposable bonnet Goggles or face shield Protective respiratory mask (FFP2) Disposable suit (Gown or coverall) Disposable gloves
High Risk	Disposable bonnet Goggles or face shield FFP3 or Powered air-purifying respirator (PAPR) Disposable protective clothing (Coverall) Disposable gloves Shoe protector

ADDITIONAL PROTECTIVE RECOMMENDATIONS IN DENTAL TREATMENTS

- The waiting room and treatment room should be designed to be easily disinfected.
- All clinical entrance gates should have motion sensors to reduce contamination.
- All patients in the waiting room should be separated by a distance of not less than 2 meters.
- A disinfectant should be put in waiting rooms for hand hygiene.
- Before the dental session, all patients should gargle 0.2% povidone iodine or 1% hydrogen peroxide and continue rinsing with 0.12% chlorhexidine after treatment. Yoon et al. stated that after using 15 ml of 0.12% CHX, SARS-CoV-2 was suppressed for two hours and this suppression would be beneficial for the control of COVID-19.
- Intraoral x-ray examination will induce salivation and cough, and therefore extraoral radiographs such as panoramic radiography and cone-beam CT may be alternative.
- The use of the air/water syringe, rotary/ultrasound/piezo instruments should be minimized by air polishing.
- A rubber-dam should be used in dental procedures where aerosol will occur.

- During dental treatments, disposable or autoclavable saliva absorbers with high absorption capacity should be used.
- Touching patient documents/digital registries and pens with used gloves should be avoided.
- Self-resorbable sutures are preferred in surgical procedures.
- The use of bulk-fill composite resins and self-etch adhesive systems in restorative dentistry can shorten treatment times.
- Traveling by public transport should be avoided while going for dental treatment.

CONCLUSION

In dentistry, instruments such as air-water syringes, rotary instruments, ultrasonic and piezo produce a large amount of droplets and aerosols containing blood, saliva and microorganisms. This splash quickly travels a short distance to the ground (near sterilized surfaces), the dental health staff or the patient. It has long been recognized that saliva may contain potential pathogens in amounts sufficient to infect individuals.

The presence of SARS-CoV-2 in saliva may cause direct transfer of infectious agents from infected individuals to healthy individuals. In addition, it has been confirmed that a person who is positive for SARS-CoV-2 can transmit the disease to other individuals in the same room. It can therefore be argued that most dental procedures that generate droplets and potentially highly contaminated microbial aerosols are extremely dangerous for anyone in the treatment room.

In dental treatments, the application of triage by phone, patient treatments by appointment, shortened treatment sessions, sterilization and ventilation of the treatment room come to the fore. In addition, the risk of SARS-CoV-2 transmission should be minimized by taking the necessary PPE measures according to the innovative COVID-19 risk classification in dental practices. However, it is considered that using all measures together instead of a single measure will be more effective in preventing SARS-CoV-2 contamination.

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CHAPTER 14

ADVANCES IN DENTAL EDUCATION DURING AND AFTER THE COVID-19 PANDEMIC

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19), which first appeared in Wuhan, China in December 2019 and spread all over the world and was declared as a pandemic by the World Health Organization (WHO) in March 2020, still continues to affect the world. The virus causing this disease transmitted from person to person by droplet, aerosol or fecal-oral route and manifests itself with viral pneumonia is called severe acute respiratory coronavirus 2 (SARS-CoV-2; formerly 2019-nCoV). Although the effects and course of the disease differ from person to person, common symptoms are fever, dry cough, myalgia, shortness of breath, weakness, confusion, loss of taste and smell, headache, sore throat, vomiting and diarrhea. In reference to the latest figures (17 March 2021), a total of 120.38 mil. people were caught the disease and 2.66 mil. people died. Countries have resorted to prohibitions such as various restrictions and quarantine methods as a result of this disease, which has caused many deaths and health problems around the world since its onset. Daily living standards and routines have changed, and such standards have been replaced by new lifestyles including social distance rules. In many countries

around the world, these restrictions and rules are preserving their continuity.

As a result of this disease, dental practices and dental education have been affected as well as other fields. The situations such as droplet diffusion, inhalation and contact of oral, nasal and eye mucous membranes of respiratory secretions and oral fluids during dental practice; direct contact with blood, oral fluids, and other patient materials insufficient social distance; the aerosol spreading into the air posing a risk for cross infection may be a problem in terms of the spread of SARS-CoV-2 infection. Therefore, with the emergence of the pandemic, as in most countries, as a result of many legal and scientific regulations in accordance with the recommendations of Consultative Board of Coronavirus of Ministry of Health; a circular was issued by the Ministry of Health of the Republic of Turkey on 17.03.2020 in order to only perform urgent and compulsory dental treatments and postpone non-urgent procedures. As a result of this circular, while the emergency procedures related to dental health continued to be carried out, routine and elective procedures were suspended. Like dental practices, dental education has also been interrupted in terms of both theoretical and practical applications during this period. The aim of this study is to address the COVID-19 pandemic and its subsequent changes and developments in dental education.

COVID-19 AND DENTAL EDUCATION

Dental education generally consists of three stages all over the world. The first of these stages is the theoretical courses applied to ensure the theoretical knowledge of the students and to create a problem-based learning model for them; the second is preclinical applications, where preliminary experience is gained by working in models and simulation laboratories before proceeding to clinical practice and patient treatment, and the last one is the clinical applications involving the diagnosis and treatment performed by the student on the patient. During the Covid-19 period, difficulties were occurred in all three stages of dental education.

Theoretical Education

The theoretical part of dental education has also been affected by the COVID-19 pandemic, as all educational units around the world have been affected. Face-to-face education was suspended in order to reduce the spreading rate

of the pandemic, to overcome the anxiety of the students and the uncertainties about the pandemic. For this reason, postponements were made in the current academic calendars and extra intersessions were put forward. With the onset of the pandemic, distance education has replaced face-to-face education all over the world. Although the distance education model was not a method adopted for dental education before COVID-19, its popularity increased with the pandemic. During this period, dentistry faculties around the world have developed various methods in order not to affect the dental education that provides the academic competence of undergraduate students. It has been reported that with the pandemic, many dentistry faculties in Europe planned or implemented an online education model to replace educational materials in the period when access to academic buildings was restricted. Firstly, online courses, case studies, and problem-based learning techniques have been applied in order not to gather individuals together as much as possible, especially during pandemic periods, and to reduce the risk of infection associated with this.

Distance education enables the student, who is not physically present in the classroom, to learn about the subject. With the purpose of distance education applications, institutions have obtained digital programs in agreement with some digital program providers. Thanks to these programs, the lecturers had the opportunity to teach their lessons to the students both live (synchronous) and asynchronously, which allows the course recordings to be accessed later. Apart from these programs, applications such as lectures, case discussions, discussion of scientific articles and reviews were performed interactively using video conferencing programs (Zoom, Google Meet, Skype, etc.). With the pandemic, the use of these applications and the number of their users have increased rapidly. For example, the number of users of the Zoom application has increased by about 30 times from December 2019 to April 2020. While conducting the lessons live has advantages such as direct interaction with the students, participation in the lesson and instant feedback; the other method (course recordings) offers the student the right to benefit by repeating it as many times as he/she wants. Studies have reported that synchronized or asynchronous courses give contradictory results in terms of preferences and there is no consensus on which one is more effective. However, it has also been stated that synchronously interactive distance dental education can be as effective as traditional face-to-face education. In addition to the courses, the midterm and final exams of the related courses have also started to be held online. During the exam, browser options have been developed that prevent

the student from searching for the answer to the question in the new tab and cheating. Technology-mediated approaches to this education provided an active learning environment for dentistry students and yielded positive results in terms of education and training. In the literature, it has been reported that online education is as effective as traditional face-to-face education and gives positive results. Using online distance education in environments where traditional face-to-face education cannot be provided can be advantageous at such times and offers an interactive sharing opportunity among the participants. The desire of dental professions and their students to take live online courses and classes shows that this mode of education has great potential for learning in the future.

Although online distance education has a very important place in theoretical dental education, it also has some handicaps. Distance online education is different from traditional face-to-face education and therefore some requirements are needed for this mode of education to be successful. The lecturer and the student should have knowledge about hardware technology, internet connection, and the use of media tools. In one study, it was reported that the distance education process was affected by students' basic computer skills and internet access. In addition to the necessity of having the same conditions, part of the responsibility normally undertaken by the lecturer passes to the student in distance education and the student may have motivation problems in distance education. Therefore, distance online education may not be suitable for all students. Since interaction plays an important role in distance education, arrangements should be made considering the needs of the student and it should not be forgotten that the number of participants is important in terms of interaction. As institutional support is necessary for the success of distance education; the institutional strategy should be designed to facilitate the adoption of basic skills and methodologies by faculty members.

In the COVID-19 process, the use of education blended with online distance education or hybrid education model has also gained importance. This education model means supporting face-to-face education in traditional and indispensable classrooms and laboratories, as a complement and reinforcement, from online platforms (lecture or lab videos, use of social media platforms, etc.). In a study, dentistry students wanted online education to be used together in a supportive way instead of replacing traditional education. Nevertheless, in order to prevent the spread of infection, this form of education is generally used in preclinical and clinical education rather than theoretical education. In addition, some dentistry faculties make the exams of the

relevant courses face-to-face in small-group classes, considering the social distance rules.

As a result, in the period of COVID-19 and the process we are in, which is called the "new normal" and in the near future, theoretical dental education is generally being carried out and is planned to be continued in the form of online distance education in the world and in our country.

Preclinical Practical Education

Preclinical education, which is taken together with theoretical education in dental education, is one of the most important parts. In general, the first three years of dental education are intensive in terms of the practical lessons taken in preclinical laboratories. Before clinical education, preclinical education is used to improve students' psychomotor skills, to increase the skills and competence of students on these models and to minimize the harm that can be given to the patient in the clinic. The lecturer aims to improve the professional skills of the students with training slides, videos and anatomical models, artificial jaws and phantom head and jaw models, demonstrations on extracted teeth prepared for this course. After the lecturer's necessary knowledge and demonstration processes, the student imitates the lecturer by using this knowledge and practical knowledge on models and improves her/his skills.

Although the theoretical dental education can be taught online with distance education, it is very difficult to receive preclinical education by distance education. In order to prevent crowds due to the emergence of the pandemic and violation of social distance rules, the face-to-face provision of preclinical education with the restriction of access to academic buildings in the early days has also been disrupted worldwide. The disruption of preclinical education, which has an important place in dental education, caused concern and the ways of students to receive this education appropriately were tried to be found out.

One of the methods applied for preclinical education is to transmit the demonstration video of the application to be performed in a synchronized form and online recorded form to the students in order to provide the opportunity to watch again later. Some of the dental schools provided portable handpiece units and typodonts for students to continue to improve their hand skills. Preclinical education can be given as distance education in the form of online simulation on dental training manikins, but this application is very difficult. Although various simulators have been developed for preclinical education; the operations performed on these simulators do not include all

branches of dentistry and are not available in all institutions. Video simulations and virtual reality (VR) applications can be used in conducting preclinical courses during the pandemic period. Galibourg et al. reported a model in which clinical skills can be gained using virtual reality and haptic. Advances in virtual reality systems increase the opportunity to use simulation technology in dental education. The use of such systems in dental education provides a continuous and integrated feedback between the lecturer and the student. VR technology is a system that has tactile feedback capability by allowing students to virtually touch and feel dental tissues. Studies have reported that the use of VR technology in operative courses increases hand skills in dental practices. Although VR simulation technologies are a useful tool for students' education, their use is limited due to their high cost and lack of availability in most institutions. Nonetheless, among the methods that can be used for preclinical education during the pandemic process, it is one of the safest methods that can be preferred to prevent the spread of infection.

Although most educational institutions suspend preclinical education with the onset of the pandemic; preclinical education continued in countries where the pandemic was brought under control with the strict measures taken at the beginning. In addition, preclinical education in small groups have begun in countries where the rate of spread of infection and the number of cases has decreased over time. In preclinical education, the preference of students is generally to take the education face-to-face in the laboratory, and it has been stated that online education cannot replace face-to-face education. In addition, blended learning or hybrid learning models are also used in preclinical education. Face-to-face practical applications, which were diluted and decreased lesson time due to the pandemic, were supported with online training materials to increase efficiency. Although the face-to-face preclinical practices were initially used in small groups in some regions with the introduction of the so-called "new normal" period, the effect of the pandemic still continues. While some of the dentistry faculties in Turkey continue their preclinical education remotely, some of them have switched to the hybrid education model. As in some countries, students go through triage at the entrance to faculty buildings and students with symptoms and risk of contamination are not admitted to the building. In regions where the number of cases has decreased, the preclinical education part of dentistry has started to be carried out in small groups diluted face to face and within intensive programs.

Preclinical practical education's being the last step before clinical education and application on the patient makes this education important. Therefore,

although technological applications provide advantages for the student in this period, making the preclinical education face-to-face is important for the manual dexterity of the student in dental practices. Regardless, attention should be paid to the development of virtual reality, video simulation and haptic technologies that play a role in the distance education of students against the continuity of the pandemic uncertainty and the possibility of a rigging in the course of the pandemic.

Clinical Practical Education

Clinical practical training, the third and last part of dental education, is the most important part of the education life in which clinical skills that prepare students for the dentistry profession are acquired. Clinical training includes the diagnosis and treatment of dental and oral diseases on the patient in the presence of a specialist. At this stage, intern dentists are now under close interaction with patients, as much as lecturers are. During the pandemic period, the most affected portion of dental education was the clinical education. In addition, in vivo studies that require human contact with both undergraduate and postgraduate education have been highly affected by this situation. With the onset of the pandemic, access to academic buildings and clinics has been restricted in many parts of the world, thus, it has become impossible to conduct clinical practice and research. This situation caused the internship training to be delayed and the trainee physicians to experience less patient practice and less case variety than normal.

The emergence of the pandemic and the uncertainties tailed the pandemic in many countries of the world have limited dental practices, and cases except emergency and cases that could not be delayed have been postponed. Clinical work in dental hospitals in Europe was mainly carried out with the participation of senior staff (96%) and postgraduate students (30%). Undergraduate students (11%) only helped non-clinical activities. For dental practices, academics have taken into account the literature on infectious diseases as well as the protocols defined in relation to COVID-19, and have applied the directives and guides described on a country basis.

The methods applied at the beginning of the pandemic for the clinical education of students bear a resemblance to preclinical education. Simulation technologies, which are a safe form of training that will prevent students from being exposed to infection and patient contact in a clinical environment, have been gravitated. Case-based discussions are an important learning method applied in dentistry education and this method can be used in this pandemic

period. Virtual patient (VP) based learning improves the diagnosis and diagnostic skills of students by simulating clinical cases. Case-based, live-participation discussions conducted online via video simulations can be beneficial by attracting the attention of students and motivating them in their remote education period. Teledentistry can be applied by imitating patient care in the clinical education of students. Although all these virtual reality, video simulation and case-based discussions can be used as remote education materials in the clinical education of students, studies have shown that these materials cannot replace the practical application on the patient and that clinical practice and patient-trainee physician interaction are more effective in terms of education of the students.

The fact that clinical education cannot be carried out without patient care and practice on the patient and that students cannot be graduated without training on patients has paved the way for taking necessary precautions in most of the countries, even during the COVID-19 period. Since most of the dental applications involve aerosol formation, clinical training has begun to be taken carried out all around the world, taking into account the necessary regulations deemed in clinics and the safety of patients, physicians, students and clinical staff by the reason of the COVID-19 pandemic. Patients were subjected to triage practices when they reached dentistry faculties for examination and treatment; their body temperatures were measured, short and scrutinizing questionnaires were conducted regarding the COVID-19 transmission and symptoms, and diagnosis and treatment procedures were initiated. Instructions on hygiene, wearing masks, distance and breathing related to the pandemic were posted in commonplaces in the hospital, hand sanitizers were provided in appropriate corners of the building, companion entrance was blocked unless deemed necessary in the presence of the patient, and the number of patients were restricted by arranging the sitting areas in the waiting rooms as per the social distance rules. Regulations were made in dental clinics due to the COVID-19 pandemic, and in order to prevent cross infection, applications such as control of aerosol formation and distribution and air flow, high-efficiency particulate arresting (HEPA) air purifiers, cabin systems and screen assembly were performed. Before starting the education, the students were taken to the campus after various screening and they were warned in terms of social distance.

The following regulations were recommended for the students to practice on the patient in clinical education during the COVID-19 process. Students should be trained by infection committees established in schools before clini-

cal practice. Before starting patient treatment, all materials to be used should be adjusted in order to prevent contamination of the environment and other staff. Before starting the treatment of the patient, both the intern physician and the staff responsible for the patient should wear enough disposable or disinfected personal protective equipment (PPE) (N95 mask, surgical mask, hair restraint, protective visor and goggles, boxing apron or overalls). The student should use a rubber-dam to avoid contamination with saliva during treatment, and if it is not possible, prescribing mouth rinses before treatment is recommended. Rinses should contain 1% hydrogen peroxide, or 0.2% to 1% povidone, or 0.05% to 0.1% cetylpyridinium chloride agents. Attention should be paid to the disinfection and sterilization of the instruments used. It is very important to use "runner" students who are responsible for four-hand work and bringing necessary materials to the application site in order to shorten the time of interaction with the patient and prevent contamination during the study. Considering the treatment procedure, the time spent with the patient should not be prolonged. PPE should not be removed before leaving the treatment area, and hygiene rules should be applied while removing PPE. Students, lecturers, and auxiliary staff should be evaluated for COVID-19 at regular intervals, and people with symptoms or those who are at risk of transmission should be isolated by abiding the quarantine parameters.

Developments are taking place in the clinical practice of the dentistry education all over the world, and the situation in Turkey is as mentioned. Fourth and fifth grade students, who are given clinical practical training, have started or are planned to start their education in most faculties. Upon the notification of the faculty management to the Ministry of Health of the Republic of Turkey, the students in this group were included in the priority groups in terms of vaccination administration and COVID-19 vaccines were administered at the request of the student. By making the clinical and student-based arrangements described above, the students were enabled to start clinical practical education with the hybrid education model, which was diluted and concentrated in small groups. Students generally preferred patient practice in the clinic. In addition, the delays caused by the pandemic also worried the students regarding the inefficacy of the education they receive.

Considering the effects of the COVID 19 process on clinical education, it is obvious that it will affect clinical education in the medium and long term. Historically, most of the dental education has been in the form of practical application. In order to continue clinical education during the COVID-19 pandemic, the safety of patients, employees and students should be kept in the

foreground, and the regulations related to the clinical and personnel should be taken into consideration and students should be given the necessary support.

CONCLUSION

All phases of dental education have been significantly affected by the COVID-19 pandemic. In the present situation, it remains uncertain how long the pandemic will continue, whether it will end, and when will we adapt the "new normal" or traditional education model in dental education. It is important to benefit from all the fields of technology at the maximum level in order to continue both the theoretical and practical part of dentistry education in the future. Regardless, deemed regulations should be made accordingly, taking into account the anxiety and concerns of the students regarding the education. Studies on this issue should be supported and popularized by institutions. It should not be forgotten that each crisis causes a new opportunity and each will contribute to the management of such problematic processes that will be encountered in the future.

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CHAPTER 15

THE IMAGING AND RADIOLOGICAL DIAGNOSIS METHOD IN PATIENT WITH COVID-19

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INTRODUCTION

Infection originated by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), since December 2019, give rise to a global pandemic in the first few months of 2020 that currently affects almost every country in the world. Coronavirus disease 2019 (COVID-19) infection and the clinical spectrum of the disease vary, ranging from asymptomatic infection or mild upper respiratory disease to respiratory failure and, in some cases, severe viral pneumonia with death. Major clinical signs include fever, cough, shortness of breath, fatigue, and shortness of breath. In the study, first published in January 2020, chest imaging results of COVID-19 reported involvement in the form of ground glass opacities (GGO) in the bilateral lungs of most hospitalized patients. However, these results are not specific, as they

may occur with other diseases such as viral pneumonia, atypical bacterial pneumonia, drug toxicity, eosinophilic pneumonia, or cryptogenic organizing pneumonia. It has been reported that 20% of COVID-19 pneumonia cases and 41% of hospitalized patients are complicated as acute respiratory distress syndrome (ARDS).

Covid-19 is a new infectious disease that spreads very quickly and causes inflammation in the respiratory system. Chest imaging is important for diagnosing lesions and evaluating the extent of lesions. It also helps to accurately observe changes in patient follow-up. CT has been reported as an important tool to help diagnose and manage patients with COVID-19

IMAGING RESULTS

Chest radiograph

Chest radiography is the first imaging method used in patients with suspected COVID-19 infection. It is advantageous that it can be used in low transmission risk and follow-up even though its sensitivity is low compared to CT. Results on chest radiographs are often normal in the early stages of COVID-19 pneumonia and mild cases. Lung results may also become apparent on posteroanterior (PA) chest radiographs on approximately the 10th day. Ground-glass densities observed in CT may be overlooked in retrocardiac and diaphragm locations on PA chest radiography. Widespread patchy radiopacities, which can be seen as opaque lungs on chest radiography, can be observed in severe disease or critical disease stages. Accompanying pleural effusion and consolidation can be seen on chest radiographs in severe patients. Wong et al. reported abnormal initial chest radiography results in 69% of PCR positive patients and 80% of hospitalized patients. Bandıralı et al. found a 58.8% rate of chest radiographs with abnormal results in PCR-positive patients who did not need to be hospitalized. Pakray et al. found abnormal chest radiography results in 89.6% of PCR positive patients. PA chest radiography is recommended in pregnant or pediatric patients and in the follow-up of hospitalized patients even though the diagnostic sensitivity of chest radiography is low in COVID-19 patients.

Computed Tomography

Computed Tomography (CT) plays an important role in the diagnosis of COVID-19 and the imaging of its possible complications. Chest CT sensitivity

was reported as 98% in the diagnosis of COVID-19. CT may be normal in the early stages of the disease process. The most common results detected in CT are ground-glass densities and consolidations. Crazy paving, interlobular septal thickening, bronchiectasis, and halo results are less frequent. Pleural or pericardial effusions, mediastinal lymphadenopathy, and pulmonary nodules are rarely observed compared to other results.

Ground-glass densities

Ground-glass densities are the most common result in CT images of COVID-19 patients. The prevalence of ground-glass densities was found to be between 34-91% in studies with a high number of patients. The definition of ground-glass densities is a hazy, increased lung attenuation area by preserving bronchial and vascular borders (**Figure 1**).

It shows peripheral localization and multilobed involvement close to the pleural surface, including fissures. Chest CT often involves the middle/lower lobes and posterior section. Pure ground-glass densities can be seen in 0-4 days after the onset of symptoms.Consolidations may accompany ground-glass densities, and the number of ground-glass areas may increase in the days

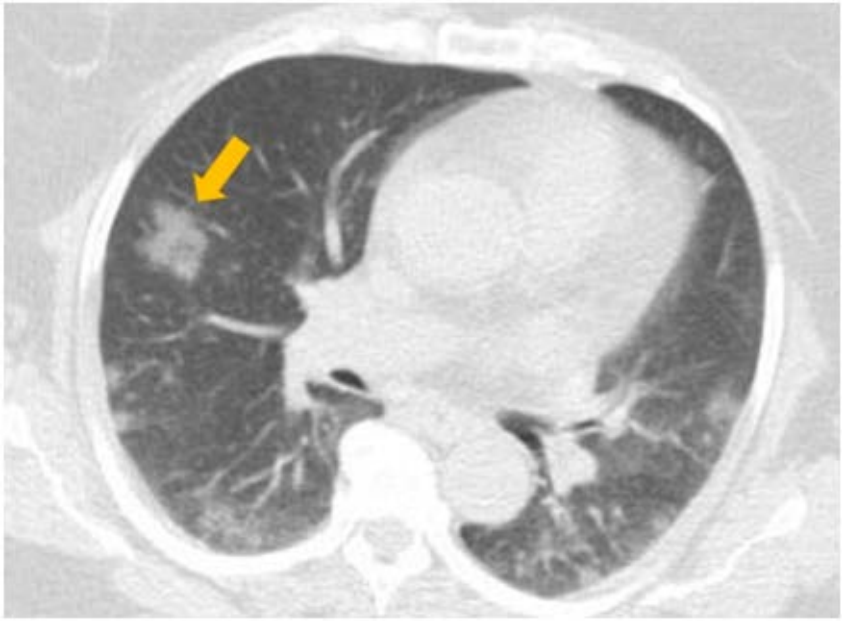

Figure 1. Ground-glass density in a 48-year-old female with COVID-19 patient presenting with fever and cough. Axial CT scan shows bilateral groundglass density (yellow arrow) in the middle and lower lobes.

ahead (days 6-13). It has been reported that focal ground-glass area accompanying fibrotic band or subsegmental atelectasis can be seen while ground-glass densities contract during the recovery period of the disease.

Consolidation

In chest imaging, COVID-19 patients had progressive opacities and consolidation during the course of the disease. Various chest CT results were present in 10-70% of COVID-19 cases proven by the RT-PCR test and consolidation was reported as 51.5%. The most common chest CT results are bilaterally distributed ground-glass density/consolidation (without subpleural preservation) in peripheral areas.

Air bronchograms are usually present within these areas as consolidation areas grow. As the disease progresses, fibrous exudate will increase in the alveolar space, air bronchograms and bronchial enlargement, secondary to this, diffuse consolidation of varying intensity in the lungs is observed on chest CT (**Figure 2**). With some curvilinear opacities compatible with fibrosis in the lungs, the gradual dissolution of the ground glass density and the formation of consolidation are seen during the dissipation phase.

It was reported that the number of absolute lung findings increased from the onset of symptoms in a study of 51 patients. Ground glass density and consolidation in the lungs are the main findings on the CT image. Con-

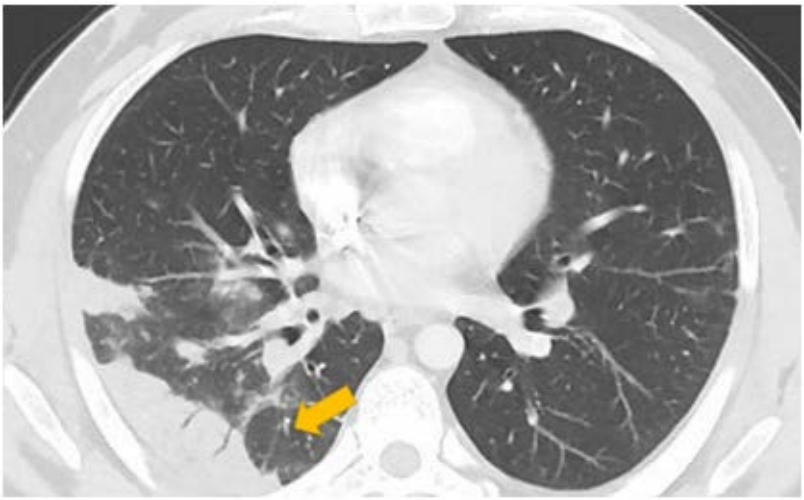

Figure 2. A 52yearold male coronavirus disease 2019 patient presenting with fever and cough for 10 days. Axial CT scan shows a groundglass density with consolidation of the right lower lobe (yellow arrow).

solidated lesions, including consolidated ground-glass opacities, and isolated consolidation correlated slightly positively with the time between the onset of symptoms and CT. In a prospective analysis of 41 patients, 98% of patients admitted to the intensive care unit (ICU) showed bilateral lung involvement on chest CT images. Imaging abnormalities in the form of multiple lobular and subsegmental consolidation areas, the most common result on chest CT, were generally higher in those with ICU patients. Lesions are associated with developmental time compared to previous studies: mainly GGO in the early stage (0-4 days), increased crazy paving pattern in the progression stage (5-8 days), consolidation in the peak stage (9-13 days), and consolidation dissolution in the dissipative stage (≥14 days).

Crazy Paving Pattern

Interlobular septal thickening and prominent intralobular lines may show overlapping with ground-glass density . (**Figure 3**). This imaging finding is called the crazy paving pattern.

The crazy paving pattern in chest CT has been described with increased ground-glass densities (5-8 days after onset of symptoms) in the progressive phase, which is roughly one of the four stages of COVID-19. As previously reported, chest CT of patients with Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) may show crazy paving pat-

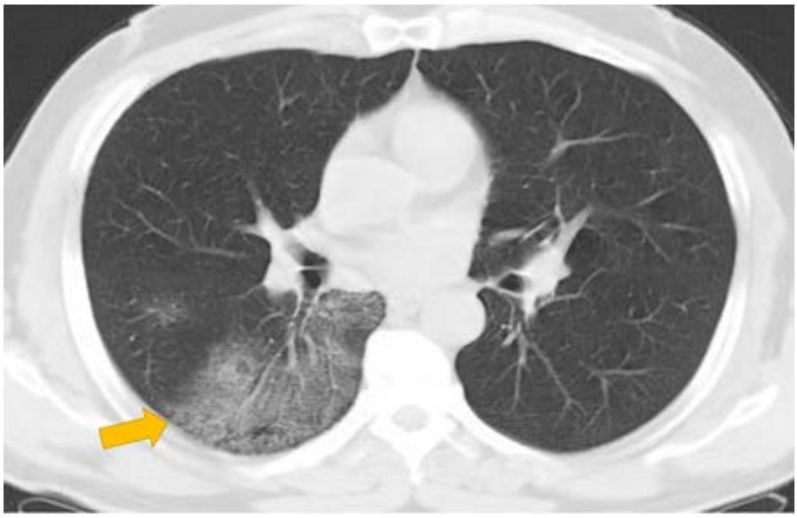

Figure 3. Crazy paving pattern in a 66-year-old man with COVID-19. Axial chest CT scan shows ground-glass density superimposed with interlobular septal thickening (yellow arrow), consistent with crazy-paving pattern.

terns. This pattern may be associated with interlobular and intralobular interstitial hyperplasia and may show interstitial inflammation and alveolar damage in lungs of COVID-19 patients. Various chest CT results were present in 10-70% of COVID-19 cases proven by the RT-PCR test and the crazy paving pattern was reported as 34.9% . The prevalence of the crazy paving pattern has been reported between 5% and 89%.

Most of the patients show more ground-glass density and fewer retained lobes than subsequent follow-up screenings in the early stages. However, the condensation of the crazy paving pattern over time, a rising in the number of related lobes, and consolidation densities occur in many patients. Tabatabaei et al. found in a selected cohort of 120 consecutive patients that intensive care unit patients had significantly greater consolidation, air-bronchograms, "crazy paving", and central involvement of the lungs compared to other hospitalized patients. On average, CT findings become evident on the 10th day of the disease. A reduction in the number of related lobes and an improvement in imaging results, including resolution of the crazy paving pattern and consolidated densities, were reported in 75% of patients after day 14. The most common results in follow-up CT have been reported to be an increase in consolidation densities and a loss in the crazy paving pattern in other published studies in the literature. The increase in the intensity of ground glass density occurs at the intermediate stages of the disease and indicates that these areas gradually transform into multifocal consolidation, septal thickening, and the emergence of crazy paving pattern. The combination of the crazy paving pattern with consolidation is considered the peak point of disease or progression.

Pulmonary vascular enlargement

Common pulmonary vascular abnormalities in COVID-19 pneumonia; can be described as vascular enlargement and regional mosaic perfusion patterns. The high prevalence of vascular enlargement and thickening in areas of pulmonary parenchymal opacity in COVID-19 patients is noteworthy and is evidence of the important role of vascular pathology in the pathophysiology of COVID-19 pneumonia. When there is a larger than expected vessel diameter within the point in the vascular tree, pulmonary vascular enlargement can be mentioned (**Figure 4**).

On CT, it is described as the enlargement of the subsegmental pulmonary vessel (pulmonary arteries and veins) with a diameter of more than 3 mm around and / or within the opacity. The vascular diameter greater than that of

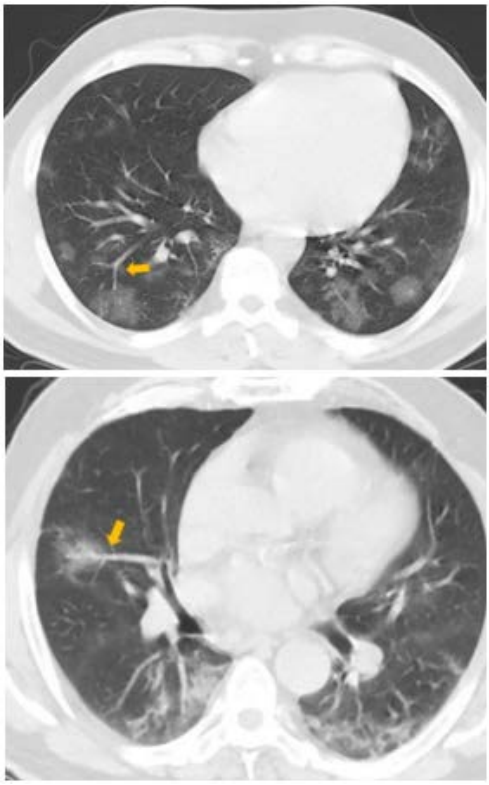

Figure 4. a) Vascular enlargement sign in a 38-year-old man with COVID-19 who presented with persistent fever and cough. Axial chest CT image shows multifocal bilateral areas of GGD with vascular enlargement (yellow arrow). **b)** 41-year-old man with COVID-19 patient presenting with fever. Axial CT scan shows bilateral ground-glass densities and vascular enlargement sign in the right middle and lower lobes (yellow arrow).

adjacent parts of the disease-free lung is characterized by a vascular diameter larger than that of the disease-free comparable regions of the contralateral lung or by the focal, continuous expansion of vessels towards the peripheral region of lungs. Quantitative methods will be more accurate since the evaluation of vascular enlargement and mosaic perfusion may be subjective.

It is reported to be positive in 70% of the cases. It is thought to be secondary to inflammation-related vascular involvement in this region even though the exact cause is not known. Ye et al. suggested that vascular enlargement may be due to proinflammatory factors. PVE is a potential diagnostic sign for COVID-19 even though the pathophysiology is not fully understood.

PVE has been reported in 45.2% to 89.2% of COVID-19 patients. In addition, Bai et al. reported that PVE was significantly associated with COVID-19 in a comparison of CT results in patients with COVID-19 pneumonia and non-COVID-19 pneumonia.

Halo and reverse halo (or atoll) sign

More atypical signs such as halo and reverse halo (or atoll) have been described less frequently in COVID-19 patients. These signs are not present at the onset of the disease and usually occur later. The reverse halo sign is surrounded by denser ring-like or crescent-shaped consolidation indicating a central ground-glass density and is also known as the atoll sign while the halo sign identifies a nodule or mass surrounded by ground-glass density (**Figure 5**).

Although this finding is known to be non-specific, reverse halo signs have been reported in several COVID-19 cases. Opportunistic invasive fungal infections in immunocompromised patients (e.g., aspergillosis, mucor mycosis), as well as in immunocompromised patients previously diagnosed withnon-fungal endemic infection, cryptogenic organized pneumonia, vasculitis, neoplasm, hypervascular pulmonary metastases, and inflammatory diseases. It should be kept in mind that it can also be seen in opportunistic

Figure 5. Halo sign in a 51-year-old man with COVID-19. Axial contrast-enhanced CT scan revealed ground-glass densities in both lungs and a nodule surrounded by ground-glass density consistent with a halo sign.

invasive fungal infections in immunocompromised patients (e.g., aspergillosis, mucor mycosis), non-fungal endemic infection, cryptogenic organizing pneumonia, vasculitis, neoplasia, hypervascular pulmonary metastasis and inflammatory diseases.

Reticular pattern

The reticular pattern is the pathological process of pulmonary interstitium or consists of fine subpleural reticulation without gross linear or curvilinear opacity or a significant amount of ground-glass density. It is characterized by interlobular septal thickening and prominent intralobular lines. (**Figure 6**).

The reticular pattern is seen in COVID-19 patients with a longer disease process and usually with pneumonia. The prevalence of reticular pattern and linear opacification is quite variable, between 1% and 81%. Also, in COVID-19 patients, subpleural curvilinear lines and fibrous bands are observed as a result of the replacement of cellular components and fibrosis.

Reticular opacities can accompany ground-glass density areas and can be well defined on standard chest radiographs. Fibrotic changes in the form of traction bronchiectasis, volume loss, structural distortion and, subpleural reticular opacity develop in the later stages of the disease. Generally, the peripheral and basal lungs are the areas where these reticular opacities are observed. On CT scans, it has been reported that COVID-19 patients with pneumonia may have persistent reticular opacities after treatment.

Figure 6. A 74yearold male COVID-19 patient presenting with persistent cough. Axial CT scan shows bilateral reticular pattern (yellow arrow) superimposed on the background of the groundglass density.

Pleural and pericardial effusion

Pleural effusion (5.2%) and pericardial effusion (2.7%) were rarely reported on chest CT in many COVID-19 cases. A recent study reported that 1 in 90 patients with COVID-19 pneumonia had pericardial effusion. The cardiac injury occurs in 12.5% to 19.7% of patients hospitalized with COVID-19 and is a risk factor that increases mortality. It has been reported that the frequency of pericardial effusion is higher in COVID-19 patients with serious disease than those without critical disease. Pericardial effusion may develop as a result of inflammation in the myocardium or pericardium in COVID-19 and may be a sign of cardiac damage. However, it should be kept in mind that elderly patients and those with heart failure may have pericardial effusion independent of COVID-19. Radiologists should consider the possibility of cardiac injury associated with COVID-19 in the presence of pericardial effusion on chest CT images even though pericardial effusion is a non-specific result.

Pleural effusion and focal pleural thickening, which may be associated with intense pleural inflammation, have been rarely reported among pleural pathologies, which are usually seen in the advanced stages of the disease. Furthermore, the addition of pleural effusion to COVID-19 pneumonia is thought to be associated with a poor prognosis. The prevalence of pleural effusion has been reported between 0% and 20% in COVID-19 patients.

Pulmonary thromboembolism

SARS-CoV-2 can induce coagulation cascade activation or local or systemic inflammation. Therefore, COVID-19 patients are at risk of developing increasingly defined thromboembolic complications. In pulmonary CT angiography, it has been reported that the incidence of pulmonary embolism (PE) in COVID-19 patients ranges from 17% to 35%. Patients with mild disease may also develop acute PE, but its prevalence is higher in critically ill patients. Regarding the location and distribution of the thrombus, PE is more common in the segmental and lobar branches and less frequent in the central pulmonary arteries. The need for mechanical ventilation is higher in COVID-19 patients with PE and D-dimer levels of patients with severe COVID-19 pneumonia are significantly increased. Although there is no age-adjusted D-dimer cut-off level in COVID-19 patients, it has been reported that D-dimer levels are associated with both the presence of PE and the degree of pulmonary artery occlusion.

Non-contrast chest CT is recommended by current guidelines in patients with risk factors and/or in patients with suspected COVID-19 whose clinical

findings are severe and critical. The definitive contribution of PE to mortality in COVID-19 patients remains unknown due to the lack of routine CT pulmonary angiography in all patients and the limited number of autopsy studies available. In addition, the risk of deep vein thrombosis and PE is increased, especially in those who receive treatment in the ICU and those who receive mechanical ventilation therapy (e.g., hemoptysis, unexplained tachycardia, or signs and symptoms of deep vein thrombosis and acute worsening of patient mobilization. Pulmonary CT angiography (CTA) should be considered to evaluate pulmonary parenchyma and vascular complications in patients with high clinical suspicion for PE with symptoms suggestive of hemoptysis, unexplained tachycardia, acute worsening of patient mobilization, or deep vein thrombosis. The British Society of Thoracic Imaging recommends that patients with COVID-19 undergo a non-contrast chest CT prior to CTA, as mosaic attenuation in CTA can cause difficulty in differentiating with ground glass density.

Ultrasonography

Lung ultrasonography (USG) has been defined for the evaluation of lung involvement in patients with suspected COVID-19 in cases where other imaging sources are not available or appropriate. Exposure decreases with a single operator, bedside examination, and easy disinfection, and the spread rate of infection decreases. Intensive care units reduce mortality and morbidity rates by providing rapid and critical clinical decision-making in emergency triage, obstetrics, and pediatric clinics and in rural areas where transportation and accessibility are limited. Repeatable and portable, easy to disinfect, radiation-free, and low-cost are other advantages of US. Lung ultrasonographic characteristics of patients with COVID-19 have been identified as follows:

1. Thickening with irregularity in the pleural line;
2. B lines in patterns that vary focally, multifocally, and confluently under the pleura;
3. Consolidations in varying patterns in translobar form with multifocal small, non-translobar, and mobile air bronchograms;
4. The emergence of A-lines during the recovery phase;
5. Pleural effusions are not common.

The results of lung USG characteristics vary in relation to the stage of the disease and the severity of the lung injury. The interstitial pattern may be

slightly alveolar or bilateral. In addition, consolidated areas can be observed. These two main findings, which differ in relation to the stage of lung injury, are the dominant pattern. Thickening of the pleural line in the inferior and posterolateral regions is the most common symptom in pneumonia or ARDS. In cases of bacterial pneumonia or superinfection or congestive heart failure, it should be considered in the differential diagnosis due to the presence of pleural effusion. The accuracy of USG in detecting pleural effusions was 93%.

In the early stages of COVID-19, the changes seen in the subpleural regions of the lung are more localized. Subsequently, air loss involving multiple lobes and consolidation of some lesions surrounded by the B line is observed. A white area is observed in which neither A-lines nor separated B-lines are visible on the USG in ARDS, including ARDS caused by COVID-19. This image is called the "white lung".

Whether pulmonary edema is of cardiogenic origin can be distinguished by careful examination of the pleura with USG. The presence of pulmonary USG changes in COVID-19 in both lungs is helpful in distinguishing from influenza and bacterial pneumonia but is not specific to any infection. In addition, the difficulty in detecting lesions deep in the lungs due to reduced transmission in the ventilated tissues is a known limitation of lung USG. Chest CT will be a good solution to detect pneumonia that does not extend to the pleural surface.

DIFFERENTIAL DIAGNOSIS

Other viral pneumonia factors (influenza, parainfluenza, adenovirus, respiratory syncytial virus, rhinovirus, etc.) are primarily present in the differential diagnosis of COVID-19. CT results are similar to other viral pneumonia. H1N1 virus pneumonia has ground-glass densities, interlobular septal thickening, and accompanying centrilobular nodules. Adenovirus pneumonia often has lobar or segmental consolidations that accompany ground-glass densities. Peribronchial thickening and centrilobular nodules are distinguishing results from other viral pneumonia in parainfluenza pneumonia. Small centrilobular nodules with asymmetric distribution on CT and asymmetric consolidation areas can be observed in respiratory syncytial virus pneumonia. Influenza pneumonia CT result is usually in the form of irregular ground-glass densities that may be associated with focal consolidation areas in the lower lobes. Similar results can be found in SARS and MERS pneumonia since they are from the same virus family. A definitive diagnosis can be made as a result of

laboratory examinations in which the virus is isolated in viral pneumonia. Chlamydia pneumonia is among the differential diagnoses of infectious origin of COVID-19 in mycoplasma pneumonia and bacterial pneumonia. Other diseases in the differential diagnosis include acute interstitial pneumonia, connective tissue-related lung disease, and cryptogenic organized pneumonia.

TEMPORAL CHANGES IN COVID-19 PNEUMONIA

Changes in lung results develop over time in COVID-19 pneumonia. The final stage of COVID-19 lung involvement is acute respiratory distress syndrome as with severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). Four different stages have been identified for COVID-19. 1. The most common result in the stage (0-4 days) is Ground-Glass Densities. The square and size of ground-glass densities increase, and it is observed that the result of crazy paving is accompanied in the second stage (5-8 days). 3. Consolidations are seen to be more dominant in the stage (days 9-13) and the result of crazy paving with ground-glass areas begins to regress. It has been reported that consolidation areas begin to regress in the final 4th stage and are accompanied by fibrotic batches. It was reported in another study that pure ground-glass densities were the most common result with the onset of symptoms. Ground-glass densities and accompanying linear densities have been reported to peak between the 6th and 11th days. Consolidations may extend and expand to the upper lobes, pleural or pericardial effusion, pneumothorax, and cavitation may develop in the late period. Secondary infections, sepsis, cardiac and multi-organ failure, and ARDS are the causes of mortality (**Figure 7**).

CT SCORING SYSTEM

CO-RADS

Four categories for COVID-19 pneumonia were identified by the Radiological Society of North America (RSNA) for standardization of CT reports of suspected COVID-19 subjects (negative for typical appearance, vague appearance, atypical appearance, and pneumonia). In addition, the Radiological Society of the Netherlands (Nederlandse Vereniging voor Radiologie) developed a classification indicating suspicion in patients suspected of COVID-19

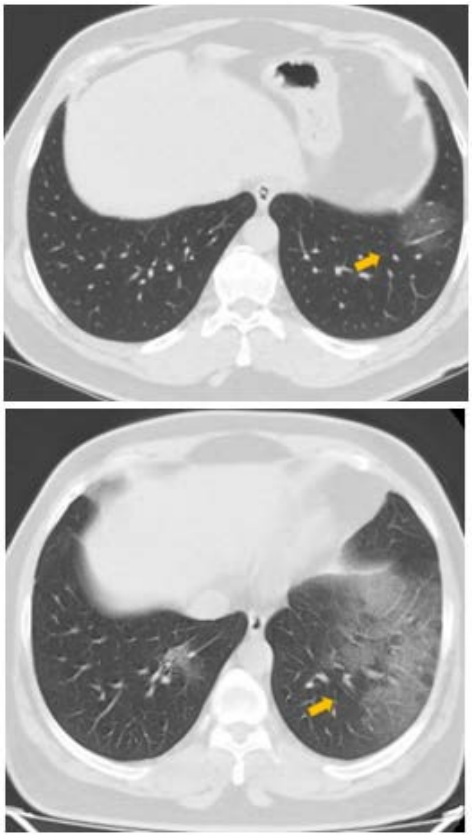

Figure 7. Axial CT scans in 49-year-old man with COVID-19. (a) Scan obtained on day 5 of illness shows diffuse ground-glass densities that affected left lower lobe. (b) Scan obtained on day 11 of illness shows that an increase in the areas of ground glass densities is observed (yellow arrow)

on April 7, 2020. CO-RADS is used to evaluate suspicion in the evaluation of pulmonary involvement (**Table**).

Table . CO-RADS Categories

	CO-RADS Category	Level of suspicion for pulmonary involvement
0	Not interpretable	Scan technically insufficent for assigning a score
1	Very low	Normal
2	Low	Typical for other infection but not COVID-19
3	Equivocal/unsure	Features compatible with COVID-19 but also other diseases
4	High	Suspicious for COVID-19

5	Very High	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

CO-RADS Category 0: This category should be reported when there is a common artifact in CT images and insufficient quality CT images.

CO-RADS Category 1: This category is defined for normal CT results or noninfectious CT results. Noninfectious results include emphysema, perifissural nodules, lung tumors, and fibrosis.

CO-RADS Category 2: This category is used due to results that are considered infectious and are not compatible with COVID-19. This category should be selected in results suggesting non-COVID-19 infection such as lobar pneumonia, tree-in-bud sign, and an abscess.

CO-RADS Category 3: Category 3 indicates suspicious results of COVID-19 in terms of lung involvement, such as non-infectious causes (such as perihilar ground-glass densities, presence of pleural effusion, and interlobular septa, organized pneumonia), and other viral pneumonia results.

CO-RADS Category 4: This category is reported as a high suspect in the presence of pulmonary results that may overlap with other viral pneumonia causes along with typical results for COVID-19.

CO-RADS Category 5: Category 5 should be selected in the presence of COVID-19 typical results indicating high suspicion for lung involvement. The presence of patchy ground-glass densities, crazy paving, multifocal involvement, and other accompanying typical results is significant for Category 5.

CO-RADS Category 6: It is used for patients with proven COVID-19 with coronavirus positive PCR results.

Severity Score

COVID-19 has been clinically classified as mild, common, severe, and critical. Patchy ground-glass densities with multilobar involvement are the most common results in chest CT, and ARDS and death may develop in severe and critical cases. Some scoring was performed semiquantitative in order to contribute to the prognosis. Pan et al. scored the involvement of each of the five lung lobes as less than 5% 1 point, 5-25% 2 points, 26-50% 3 points, 51-75% 4 points, and 76-100% 5 points. They reported that the total score increased until day 10. Yang et al. scored 20 pulmonary segments as 0, 1-50%, and more than 51% with 0.1 and 2 points. They proposed the threshold value as 19.5 points in order to distinguish between severe and mild cases in this study. Yang et al. evaluated the performance of a semi-quantitative score that calcu-

lated the degree of pulmonary opacification in 20 pulmonary segments as a surrogate for 33 disease burdens. Each lung opacity was given a score of 0, 1, or 2 based on whether parenchymal opacity was less than 0.50%, equal to, or greater than 50% of each region (total score: 0-40 points). A threshold of 19.5 was identified to distinguish between 83% sensitivity and 94% specificity between severe and mild cases. The severity of lung parenchymal involvement, which is visually scored, is calculated as a percentage in similar studies.

CONCLUSION

COVID-19 early diagnosis is very important for filiation efforts and prevention of transmission. With imaging methods, especially patients with pulmonary involvement are diagnosed with high sensitivity and specificity. Imaging will also have an important place in the diagnosis of viral infections targeting multiple organ systems and the late-stage complications of this disease.

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CHAPTER 16

THE INTENSIVE CARE MANAGEMENT OF PATIENTS WITH COVID-19

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INTRODUCTION

Coronavirus Disease-19 (COVID-19) has become a serious health problem since it was first defined in Wuhan, China in December 2019 and it has also given rise to a global crisis in all its economical, sociological and psychological aspects. Consequently, World Health Organization (WHO) declared this epidemic as a pandemic on March 11,2020. Besides its being severely infectious, the most feared aspect of this disease is that it causes serious pulmonary infection in almost 20% of the patients and it requires intensive care and respiration support for 5-10% of these patients. Therefore, the primary and most important factor determining mortality in countries is the healthcare system and that the resources meet the demands especially with the limited number of intensive care beds. During this process, the most important duties of health practitioners are on one hand to fulfil the increasing demands and on the other hand to follow scientific literature along with clinical and experimental studies every day and to benefit from the experiences of clinicians dealing with pandemic all over the world. Since there are limited studies about COVID-19,

recommendations for treatment were generally acquired from the experiences in China, Italy, the USA and the UK. In this section, we aimed to summarise the essential points in the intensive care management of the patients with COVID-19.

ICU INFRASTRUCTURE

Suspected or confirmed COVID-19 intensive care patients should be followed in airborne infection isolation room (AIIR) with negative pressure so as to protect other patients and healthcare professionals. However, it was determined in a survey carried out in 335 intensive care units (ICUs) in 20 Asian countries that only 12% of the rooms were AIIRs. Therefore, the patients could be taken into single rooms that are ventilated enough in ICUs without AIIRs. In an another survey conducted in Asia, it was stated that only 37% of the available rooms in intensive care units were single rooms and 13% of intensive care units did not have single rooms. The number of single rooms and AIIRs are highly low generally in the low-income countries. Cohort intensive care could be considered as an alternative in places where single intensive care rooms do not exist. Available evidence suggests that even if COVID-19 infection transmits through droplets rather than air, concerns about nosocomial infection in cohort intensive cares continue especially when aerosol-generating procedures are carried out. Therefore, personal protective equipment (PPE) should be taken into consideration for the patients in shared rooms. Oxygen masks with HEPA filter could provide even a little protection for the patients who are not intubated.

ICU Staffing

It is known that high workload of intensive care staff is in closely associated with high mortality. So, the number of the staff should require to be increased with the staff from other ICUs or other departments except ICU. It is quite significant the staff recruited from other departments should be trained about intensive care management and especially COVID-19 protocols. The risk of being infected with SARS-CoV-2 should be taken into account for intensive care unit staff. It is important to minimise the infection risk because not only does it directly cause the loss of manpower but also it has a devastating effect of being infected on morale of the staff. Mental health problems such as depression and anxiety are more common among healthcare professionals in

intensive care units due to the constant fear of being infected and difficult workload. Measures should be taken to prevent these kinds of problems. For this purpose, the necessary support should be given in order to prevent the spread of the infection, to communicate with the administration of the hospital and ICU doctors, to limit shift hours, to provide resting areas if possible and to relieve the staff with a multidisciplinary team including psychiatrists and psychologists.

ICU capacity

It is difficult but possible to take the spread of COVID-19 under control in the society and it is highly significant to maintain the capacity of intensive care. National and regional modelling of the requirement for intensive care is quite important. Let alone isolation or single rooms, many countries could not have sufficient intensive care beds at first stage. Most of the countries cannot show success in building new hospitals or intensive care units as China did in Wuhan during COVID-19 pandemic. The increases in the number of critically ill patients with COVID-19 could be sudden and rapid; therefore, ICU doctors, hospital administrators and governments should do planning for the increase in the capacity of intensive care beds in advance. Although it is possible to add beds to available intensive care units, the risk of nosocomial infection limits this choice as a result of the contraction of existing area. Converting the areas except the available intensive care into intensive care units and transfer of the patients to other determined hospitals and ICUs are among the other choices. Though centralising the resources and experts increase the result and efficiency, these benefits should be considered well against the risks during the transfer of the patients among hospitals. The fact that being dependent on a few centres could not solve the problem in case of the rapid increase in the number of patients during pandemic should also be taken into consideration. Gradual increases in ICU capacity also requires the increase in the number of not only beds but also equipment, consumables, medicine and staff. To reduce the density in ICUs, elective surgeries should be postponed and the patients with lower-acuity should be transferred to other departments for the treatment of the patients with COVID-19 who will need isolation.

ICU triage

If intensive care beds become in short supply for COVID-19 patients in despite of the strategies that will be carried out in intensive care, the necessity to apply triage in intensive care units could arise for these patients. This situation is valid for patients with and without COVID-19 since both groups can need the same ICU at the same

time. Triage in intensive care unit is an ethically complex and emotionally devastating process. The ideal thing is its being coordinated by national or regional healthcare systems. Some countries published guidelines for such cases during COVID-19 pandemic. Extensive physiological result-prediction scoring systems could be misleading in predicting the course of the disease. For old patients with comorbidity in COVID-19, it was determined that the results were worse in high D-dimer and C-reactive protein concentrations and the number of lower lymphocyte.

GENERAL CHARACTERISTICS OF COVID-19 PATIENTS ADMITTED TO INTENSIVE CARE

The criteria for admission to intensive care unit may vary according to countries and institutions. The patients' needs for ICU varies between 5-32%. Severe disease could emerge with the symptoms of severe acute respiratory infection (SARI) and it is stated that 60-70% of these patients could have severe pneumonia and acute respiratory distress syndrome (ARDS); 30% could have sepsis and septic shock, 20-30% may have myocarditis, arrhythmia and cardiogenic shock and acute renal failure may develop in 10-30% of them.

Although respiratory failure is often hypoxemic, hypercapnic respiratory failure mainly results from mucus plugging. It is indicated male gender is more with M/F ratio of 2/1 in severe cases. Moreover, according to the recent data in Italy, the ratio of male gender was determined to be 82%. Though hypertension and diabetes are the most frequently reported comorbidities, advanced age is also a risk factor for the development of severe disease. The duration between the onset of clinical symptoms and the development of pneumonia is almost 5 days and the time for admission to ICU after the development of hypoxemia is 7-12 days. The mortality rate due to COVID-19 in ICU is stated as 16-78% in various studies. In latest multicentre studies in Italy, the mortality rate was reported to be 26%. Advanced age, hypertension, diabetes, cardiovascular disease, chronic pulmonary disease, cancer, high D-dimer and C-reactive protein, low lymphocyte levels were found to be related to high mortality.

SEVERITY OF DISEASE AND INDICATIONS IN ADMISSION TO INTENSIVE CARE

The patients with severe pneumonia in COVID-19 disease are taken into intensive care and followed.

Severe forms of the disease:

- Severe pneumonia,
- Acute respiratory distress syndrome (ARDS),
- Sepsis,
- Septic shock,
- Myocarditis, arrhythmia, cardiogenic shock,
- Multiple organ failure tables,

Severe pneumonia

The patients in this group come up with radiological and laboratory findings accompanied by such symptoms as fever, dyspnoea and cough. These are the patients with respiratory distress symptoms like tachypnea with a respiratory rate of >30 /min, use of accessory respiratory muscles and thoracoabdominal respiration and with oxygen saturation ($SpO_{2)}$ <%90 in the room air or with PaO2/FiO2 ratio of <300. The course of COVID-19 pneumonia is severe in the patients with comorbidity and decompensated heart failure and chronic pulmonary disease exacerbation could accompany the table in these patients.

ARDS

ARDS that may occur in patients with severe pneumonia and progresses with a high mortality is defined according to the criteria below:

1. Respiratory distress which has occurred or got worse for the last week
2. Bilateral opacities that cannot be explained with radiologically volume overload, lobar or pulmonary collapse or nodules
3. Inexplicability of respiratory failure alone with heart failure or fluid overload
4. Hypoxemia
   a. Mild ARDS: 200 mmHg< PaO_2/FiO_2 ≤300 mmHg (PEEP ≥5 cmH_20)
   b. Moderate ARDS: 100 mmHg< PaO_2/FiO_2 ≤200 mmHg (PEEP ≥5 cmH_20)
   c. Severe ARDS: PaO_2/FiO_2 ≤100 mmHg (PEEP ≥5 cmH_20)

Sepsis

This is the syndrome in which suspected or confirmed infection is accompanied by the symptoms of organ failure. To determine the symptoms of organ failure, Sequential Organ Failure Assessment (SOFA) score is suggested. A

suspected or confirmed infection is defined as sepsis when there is an increase rate of ≥2 in SOFA score.

Septic shock

This is the vasopressor need in sepsis patients due to persistant hypotension to fluid treatment (<90 mmHg systolic blood pressure, >40 mmHg decrease in normal systolic blood pressure or <65 mmHg mean arterial pressure); and blood lactate level is over 2 mmol/L.

Besides the fact that severe pneumonia, ARDS and sepsis are the main clinical forms for COVID-19 in intensive care, it should also be remembered that multiple organ failures such as arrhythmia, myocarditis, kidney and liver function disorder, thrombocytopenia and confusion could emerge.

MONITORIZATION AND LABORATORY

COVID-19 is a multisystem disease affecting notably the respiratory system, cardiovascular, renal and gastrointestinal and even central nervous system. Therefore, clinical and laboratory monitarization requiring close follow-up of all systems is of great importance during the intensive care follow-up of the patients with the disease. Monitarization methods according to severity of the disease, involvement of the systems, accompanying comorbidities could be carried out with a broad extent from non-invasive to invasive. In addition to standard monitoring techniques, end-tidal CO_2 measurement and constant follow-up of body temperature should be done for the patients having serious respiratory failure on mechanical ventilator. If severe pneumonia, sepsis, septic shock and cardiac failure are accompanied with hemodynamic failure, monitoring dynamic parameters measuring cardiac output through invasive and non-invasive methods is of great importance. Echocardiography and pulmonary ultrasonography are also important clinical tools to guide the treatment. Arterial blood gas measurement includes very valuable parameters about tissue perfusion, fluid, sepsis, septic shock management and about oxygenation, ventilation, acid-base balance, blood lactate level and therefore ensuring the management of respiratory support of the patient appropriately. Measurement of advanced procalcitonin values should represent that bacterial infection could have been added to the table. Distinct increases in AST level in serious COVID-19 cases is associated with mortality. The kidneys are the organ system that should be closely monitored for possible perfusion disorders

during critical disease and shock processes as well as being another organ containing ACE receptors affected by coronavirus. The incidence of probable renal failure in these patients has increased. In terms of cardiovascular exposure, EKG and troponin and ProBNP monitoring could be useful for patients. Coagulation parameters are important in terms of following the clinic of secondary haemophagocytic lymphohistiocytosis(HLH) and processes like coagulopathy and vasculitis that could develop in these patients. PT, APTT, Fibrinogen, D-dimer and ferritin monitorization are suggested. As bronchoscopy increases infection risk during diagnosis, tracheal aspiration samples, bronchial or bronchoalveolar lavage should be preferred.

RESPIRATORY SUPPORT

Early diagnosis of hypoxemic respiratory failure is significant. In despite of conventional oxygen therapy, increase in respiration and hypoxemia could get worse progressively. Oxygen support should be given with low-flow oxygen delivery systems (nasal cannula, simple face mask, non-rebreather mask). Venturi and diffuser masks should be avoided as they can cause oxygen toxicity. High Flow Nasal Cannul (HFNO) and non-invasive mechanical ventilation (NIMV) support could be applied to the selected patients with hypoxemic respiratory failure. However, hypoxemia and tachypnea do not improve in the first few hours, these patients should be monitored closely in terms of clinical deterioration. It should not be applied to the patients who cannot control NIMV secretions, have a high aspiration risk and impaired mental status, are not hemodynamically stable and have multiple organ failure. Prolonged spontaneous ventilation could lead to a similar damage to pulmonary damage caused by ventilator by increasing negative intrathoracic pressure in these patients. Therefore, this should be prevented by performing endotracheal intubation as soon as possible. Invasive mechanical ventilation is required for almost 10% of these patients need. Endotracheal intubation should be applied by trained people by using rapid-sequence intubation protocol. If possible, intubation should be performed with video-laryngoscope. Intubation with flexible bronchoscopy carries a high risk of aerosolisation. Balloon-mask ventilation should be avoided during preoxygenation. Preoxygenation could be applied through non-rebreather masks. If it is needed to use balloon-mask, filter should be used. Neuromuscular blockers could be applied in order to suppress the cough before intubation. Positive-pressure ventilation should not be started before inflating the cuff of endotracheal tube. Closed system suctioning methods and bacteria-virus exchanger filters (HME) could be used. If it is not strictly required, bronchoscopic intervention should be

avoided and metered dose inhaler (MDI) should be used instead of nebulizers for bronchodilator therapy.

For patients with ARDS, low tidal volume (4-6 ml/kg), low inspiratory pressure (plateau pressure <30 cm H_2O) and <14 cm H_2O driving pressure should be performed. Deep sedation can be necessary to reach target tidal volume. In cases of pH <7. 15, tidal volume can be increased up to 8 ml/kg. In addition, permissive hypercapnia should also be allowed when needed. If there are no symptoms of tissue hypoperfusion, conservative fluid therapy should be applied. PEEP titration should be carried out at pressures which will prevent atelectotrauma and excessive distention. There are no available data for recruitment manoeuvre. If there are ventilatory dyssynchrony, resistance hypoxia and hypercapnia in patients with mild and severe ARDS in spite of deep sedation, neuromuscular blockers could be used in the first 24-48 hours of mechanical ventilation. For patients who have the value of PaO_2 / FiO_2< 150 and were applied conventional mechanical ventilation, prone position could be performed for more than 12 hours. It has been suggested that prone position is also useful for the patients who are not intubated and can spontaneously inhale. Routine use of corticosteroids is not suggested. Extracorporeal membrane oxygenation (ECMO) could be taken into consideration for the patients with refractory hypoxemia in despite of lung-protective ventilation and eligible patients should be transferred to experienced centres. Due to lack of evidence about this virus and disease, the advantage of ECMO is not clear. There are also studies stating that ECMO is not a frontline therapy method considered in case of major pandemic.

There are 2 phenotypes of respiratory failure in COVID-19 patients. In the phenotype characterized with low elastance (high compliance) and called Type-L, the perfusion rate, lung weight and recruitability are low. In the phenotype characterized with high elastance (low compliance) and called Type-H, right-left shunt fraction, lung weight and recruitability are high. Severe hypoxemia in lungs with high compliance could be explained by the loss in lung perfusion regulation and hypoxic vasoconstriction; increasing FiO_2 could be a solution to hypoxemia in these patients. Early intubation can cause transition to Type-H. In addition, in patients who are intubated and have hypercapnic Type-L, ventilation from 6 mL/kg to 8-9 mL/kg does not lead to the risk of pulmonary damage induced by ventilator. However, performing high PEEP for the non-recruitable lungs in Type-L patients could cause hemodynamic deterioration and fluid retention. Type-H phenotype is similar to moderate ARDS; therefore, high PEEP, prone position and even extracorporeal support are among the conventional therapy methods to choose. These sug-

gestions have not been proved by large-scale studies and in severe hypoxemia, delaying intubation and increase in respiration could make the situation worse. In patients who do not respond to conventional O_2 therapy, early intubation or short term NIMV and HFNO are suggested. It should be ensured that the need for oxygen has reduced ($FiO_2 < 40$, PEEP < 8 cmH_2O), the patient is hemodynamically stable and conscious and cough reflex has been maintained for weaning. Instead of T-tube weaning trials, weaning with pressure-assisted ventilation could be preferred as it emits less aerosol. It is also not clear whether cuff-leak test will be carried out in weaning. In patients with weaning failure, tracheotomy indication accepted as a high-risk procedure for aerosolization could occur.

COAGULOPATHY AND VENOUS THROMBOEMBOLISM

In the studies carried out, coagulopathy has been found to be associated with mortality and it has been suggested that mortality significantly decreased by heparin utilization in patients with COVID-19. As well as anticoagulant effect of heparin, it has been shown that binding inflammatory cytokines, inhibiting neutrophil chemotaxis and leucocyte migration, sequestration of acute-phase proteins through peptide C5a neutralization play role in decreasing mortality. Therefore, though thromboprophylaxis is not a specific therapy to COVID-19, when pathophysiology of the disease is taken into account, it is considered to be important. Low molecular weight heparin (LMWH) is used as prophylactic in intensive care units. Microvascular thrombosis due to increased endothelial injury may develop in COVID-19 patients. Increased fibrinogen and D-dimer levels and hypercoagulability also increase depending on the severity of the disease. The risk of pulmonary embolism development is considered to be high for these patients. So, it is required to apply LMWH to every patient in prophylactic dose and to patients with high risk of clinical thrombosis at therapeutic dose.

- thrombosis prophylaxis in patients with D-dimer <1000 ng/ml
- CrCl>30 ml/min.
  - BMI <40 kg/m^2 Enoxaparin 40 mg/day subcutaneous
  - BMI >40/kg/m^2 Enoxaparin 40 mg 2 × 1 subcutaneous
- CrCl<30 ml/min.
  - As low molecular weight heparin is not generally suggested, standard heparin 5.000 U subcutaneous 2 × 1 or 3 × 1 can be applied.
- the patients with D-dimer >1.000 ng/ml or severe disease
- CrCl>30 ml/min.

  - Enoxaparin 0,5 mg/kg subcutaneous in every 12 hours
- CrCl<30 ml/min.
  - Standard heparin 5.000 U subcutaneous 2 × 1 or 3 × 1 or reduced dose low molecular weight heparin are suggested.

FLUID MANAGEMENT AND RENAL REPLACEMENT TREATMENT

When the patients apply to the hospital for COVID-19 symptoms, they are generally on the 7-14th day of the disease and they may be dehydrated. A careful fluid evaluation is required for all the patients when applying to hospital because preload response such as passive leg raise test should be considered given the high incidence of myocardial dysfunction in COVID-19. The reason for myocardial dysfunction is thought to result from strong binding affinity of SARS-CoV-2 spike protein to human angiotensin converting enzyme 2 (ACE2). The findings of troponin, beta natriuretic peptide concentrations and echocardiography are important for the early detection of myocardial involvement. Conservative or resuscitative fluid management strategy and administration of inotrope or vasopressors should be accordingly decided. It could be more useful to avoid from excessive positive fluid balance instead of targeting negative fluid balance in the early period. Negative fluid balance is especially aimed for the patients with ARDS. It has been shown that conservative fluid strategy improves oxygenation and increases the number of days spent without ventilator. This situation could be ensured by diuretic treatment; however, in some cases, renal replacement therapy can require to be started so as to get negative fluid balance. Such electrolytes as sodium, potassium, magnesium and phosphate should be kept at their normal values. In spite of appropriate fluid replacement, the first preferred vasopressor agent is norepinephrine for the patient with hypotension (<65 mmHg mean arterial pressure). Norepinephrine with the dose of 0.05 mcg/kg/min. when mean arterial pressure is over 65 mmHg is administered and could be increased when necessary. Alternative agents except noradrenaline should be vasopressin or adrenaline. It can be necessary to reduce noradrenaline dose so as to minimise the possible side effects during high-dose noradrenaline use and in this case, vasopressin is recommended. Dobutamine could be involved in the treatment for the patients with hypotension and symptoms considered as cardiac dysfunction.

Conventional indications to start renal replacement therapy are hyperkalaemia, refractory acidosis, uraemia and fluid overload. Renal replacement therapy could also be performed for patients with COVID-19 and acute kidney injury to provide negative fluid strategy. In COVID-19 patients who have been performed renal replacement therapy, there is anecdotal evidence suggesting that the frequency of filter thrombosis is more though known anticoagulation methods are used in filter circuit; therefore, the use of continuous systemic unfractionated heparin infusion should be considered instead of citrate and/or low molecular weight heparin (LMWH) for anticoagulation in COVID-19 patients to be operated renal replacement therapy. It is stated that anti-Xa measurements are more reliable than APPT in order to evaluate the efficiency of UFH in preventing filter thrombosis.

PHARMACOLOGICAL TREATMENTS IN COVID-19 DISEASE

Supportive care is the essential point of intensive care management of COVID-19 patients. Very few of pharmacological operations are evidence-based. Researches in this field continue today.

Antivirals

Early use of favipiravir considered more secure than other antivirals in terms of side-effect potential and drug interactions is suggested for the patients with severe pneumonia. 2x1600 mg favipiravir loading and 2x600 mg maintenance treatment are recommended.

Remdesivir is an RNA-dependent polymerase inhibitor and adenosine analog blocking a viral replication. FDA has allowed remdesivir use in children and adults with severe COVID-19 in the USA. Studies on its efficiency in treatment continue. Although preliminary results present its possible efficiency in COVID-19 patients, the knowledge about selection of patients have not been clear yet. Remdesivir is not suggested for patients with five times more alanine aminotransferase (ALT) level than the normal level. If ALT level exceeds this value, the drug should be discontinued. The drug should not be administered to the patients with GFR <30 ml/min.

Antimicrobial treatment

Routine antibiotics use is not recommended for uncomplicated COVID-19 patients; however, since the diagnosis of COVID-19 takes time and the dis-

tinction of the disease from other bacterial and viral pneumonia is difficult, empirical antibiotics are frequently used. In addition, as atypical community-acquired pneumonia will develop in most of the patients, antibiotic treatment will be administered to these patients. Antibiotic requirement should be checked daily and discontinued if it is culture-negative. In intensive care units, the participation of microbiologists is suggested for multidisciplinary approach.

Steroid treatment

Corticosteroids, especially dexamethasone and hydrocortisone, are frequently used in the management of COVID-19 patients

WHO has two suggestions regarding corticosteroids;

1. A strong suggestion for systemic corticosteroid therapy (intravenous or oral) for severe or critical COVID-19 patients
2. A conditional suggestion about not performing corticosteroid therapy in COVID-29 patients who are not acute.

Dexamethasone and hydrocortisone should be applied for severe or critical COVID-19 patients in cases below;

1. Acute respiratory distress syndrome (ARDS)
2. Sepsis or septic shock
3. In other cases needing supportive therapies like ventilation or vasopressor therapy
4. In cases with severe respiratory distress
5. In patients with O_2 saturation of < 90 in room air
6. Increased respiratory rate (> 30 /min)

Dexamethasone may be discontinued if the patients are to be discharged from the hospital in 10 days. For the patients who could take them orally and who are not considered to be of great concern with enteral absorption, oral tablet forms should be given. Intravenous administration should be used only when tablet or oral solution is not appropriate or available. While prescribing dexamethasone, it should be paid attention to the effect of proton pump inhibitors on protecting gastric ulcer. Hydrocortisone could be performed 50 mg intravenously three times a day for 7-10 days. Administration of it with a

low dosage for longer time could be considered for the patients with septic shock.

Treatment for Cytokine storm

Makrophage activation syndrome (MAS) or secondary haemophagocytic lymphohisitocytosis (HLH) is a hyperinflammatory syndrome that may progress to fulminant multiple organ failure and could develop in the course of severe infections as well as rheumatic diseases, as a result of excessive release of pro-inflammatory cytokines such as IL-6. Among the clinical and laboratory findings are persistent fever, serious elevation in acute phase reactants like CRP, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hyperfibrinogenaemia, increased AST, increased ferritin, haemophagocytic syndrome in bone marrow aspiration or biopsy and immunosuppression. They are seen in almost 5% of the critical patients and these patients should be treated in intensive care units. It is indicated that steroid, intravenous immunoglobulin (IVIg), Tocilizumab, Anakinra and JAK inhibitors could be used in treatment. However, it should be taken into consideration that these drugs have significant side effects in terms of intensive care. First, they could cause immunosuppression. High-dose corticosteroids are not recommended for COVID 19 patients except specific cases mentioned above. Since IgA deficiency is a contraindicated situation for IVIg, it is suggested to be administered by looking at IgA level in IVIg treatment. Moreover, it is stated that, with IVIg, there are risks of anaphylaxis, aseptic meningitis, pulmonary damage associated with thromboembolism and transfusion, overload symptoms, acute renal failure and hyponatremia. Even though administration of 400 mg IV Tocilizumab and its repetition in 12-24 hours are recommended, it should be remembered that in patients with the history of diverticulitis, a picture similar to ARDS could cause gastrointestinal perforation. Pregnancy is contraindicated in neutropenia ($<500/mm^3$), active tuberculosis, active hepatitis B or C, allergy and hypersensitivity.

There is no clear evidence about the use of extracorporeal treatments based on the removal of cytokines in Covid-19 pneumonia. A specifically processed type Oxiris that is also used as Sepsis adsorption column HA380 (Jafron© Biomedical Co., China), Cytosorb© sepsis column (CytoSorbents Corporation, NJ, USA) and AN-69 membrane sepsis column are extracorporeal cytokine removal methods that could be used. However, its efficiency in COVID-19 patients is not known. Whereas therapeutic plasma exchange may be used in removal of cytokines in patients with sepsis, it is not recommended

routinely in COVID-19 pneumonia. All these practices have not been included as evidence-based in manuals but they have been recommended in case studies more. In addition, in patients developing hemodynamic renal failure requiring continuous renal replacement therapy, it should be kept in mind that cytokine removal can be performed through filters having sepsis column features and a protocol including a convection method. Intensive care management of COVID-19 patients are summarized in **Figure 1**.

CARDIOPULMONARY RESUSCITATION (CPR)

In case of cardiac arrest, CPR should be carried out by the people with personal protective equipment. Chest compression or airway procedure should not be performed without wearing full personal protective equipment. Chest compression in CPR should be started with automatic resuscitators if possible. Pre-oxygenation could be employed by non-rebreather masks so as to avoid aerosol contamination. If pulsatile rhythms are diagnosed and intervened as soon as possible, circulation could be maintained and need for more respiratory support like intubation could be prevented. In need of bag valve mask ventilation and endotracheal intubation, at least two physicians should perform this procedure through video laryngoscopy and oropharyngeal airway.

CONCLUSION

COVID-19 pandemic is the biggest global public health crisis today. No specific treatment has been shown to be effective from the first time it was determined until today. Though public health politics aiming at prevent COVID-19 cases are much more important than developed medical Technologies, both administrators of the countries and hospitals should cooperate with ICU practitioners in order to overcome the difficulties of ICU care. In the light of COVID-19 pandemic and the data obtained from the intensive care follow-up of these patients, the need for intensive care units that are well-organized and have well-trained health professionals has come up once again. Intensive care science has a leading role in the management of such epidemics. The contribution of intensivists dealing with complex organ failures is highly significant in terms of training of health professionals during the planning of these epidemics. While organizing these planning, to support health professionals emotion-

ally, increase motivation by using available communication tools and minimise the fear and anxiety are quite important to prevent burnout.

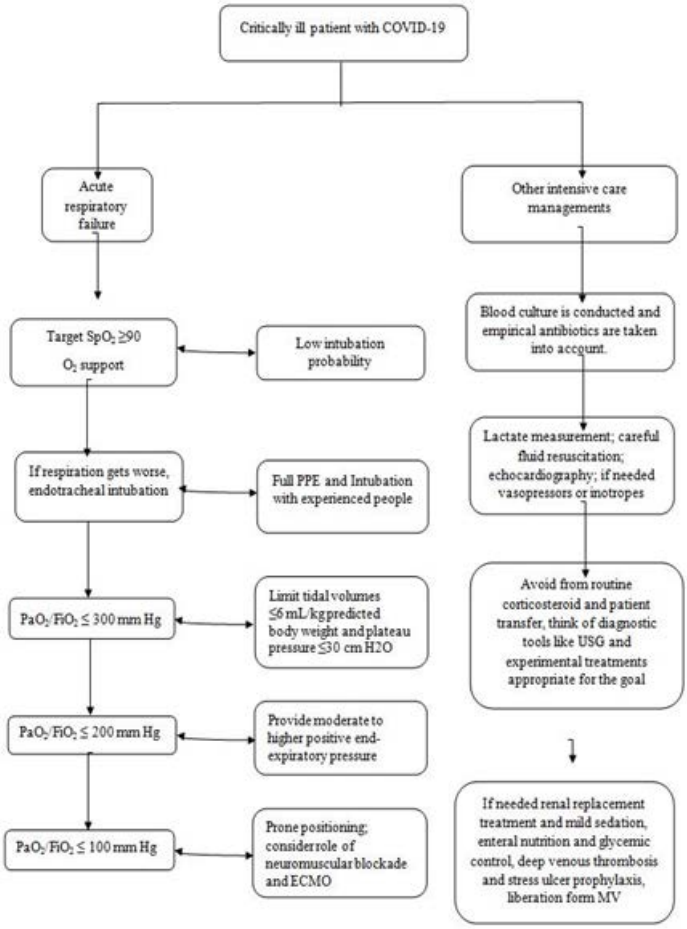

Figure-1: Clinical management of critically ill patients with COVID-19

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CHAPTER 17

COVID-19 AND PREGNANCY

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INTRODUCTION

Covid-19 disease is caused by SARS-CoV-2, an enveloped, non-segmented and single-stranded RNA virus. SARS-CoV-2 virus is included in the β subgroup of the coronavirus family. Covid-19 disease caused by the SARS-CoV-2 virus was declared as a pandemic by WHO on March 11, 2020. The virus is transmitted by droplets and the first entry point is the epithelial cells in the mucous membranes of the respiratory system such as the mouth and nose. Although there are studies showing that Covid-19 infection increases the risk of preterm birth in pregnant women, low birth weight, and postnatal intensive care needs of newborns, clear information about pregnancy loss, preeclampsia and vertical transition has not been reported definitively in the studies so far. Although it has been shown in previous studies that viral infection during pregnancy causes disorders such as fetal malformation and psychiatric disorder, there is no clear information so far that Covid-19 infection increases fetal malformations and long-term psychiatric and neurological disorders in the newborn.

Even though it has been reported that immunological, physiological and anatomical changes actually reduce the protection against viral infections during pregnancy, pregnant women experience Covid-19 infections with a

frequency and severity similar to other individuals due to unknown mechanisms. However, there is no clear and precise information on this matter yet. Covid-19 infection is seen in various spectra during pregnancy. They are either asymptomatic or can undergo a severe and fatal infection. Covid-19 infection can cause both morbidity and mortality and may lead to obstetric complications such as preterm birth and low birth weight during pregnancy. The transfer of the newborn to intensive care and the disadvantages of prematurity in cases such as preterm delivery and low birth weight contribute to the morbidity and mortality of the fetus. However, the role of Covid-19 infection in obstetric complications such as pregnancy loss and preeclampsia is not clearly known.

EPIDEMIOLOGY

Although the exact number of Covid-19 cases in pregnancy is not known, there are very few studies on this subject. In a study in the USA, the frequency in pregnant women admitted to the hospital was found to be 15.4%. In another study, the frequency of Covid-19 in pregnant women was reported as 12.2%. In a study evaluating the mortality rates during pregnancy, no change was observed in the mortality rate of pregnant and non-pregnant women and the mortality rate was found to be 0.2%.

PHYSIOLOGICAL CHANGES OBSERVED DURING PREGNANCY

Changes occur in all systems during pregnancy, especially physiological, immunological and anatomical changes. Pregnant women are considered to be more susceptible to viral infections because of these changes compared to other individuals in the society, because pregnant women, compared to other individuals, have been observed more affected by diseases caused by viruses from the same virus family including H1N1, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). However, there is no study in the literature showing that pregnant women are affected more than other individuals due to some unclear factors. No significant clinical difference was observed between pregnant women with Covid-19 infection and pregnant women without Covid-19 infection. The following major system changes are important for Covid-19 infection during pregnancy.

Immunological Change

Immunological mechanisms vary according to trimesters during pregnancy and accordingly cause changes in pro-inflammatory and anti-inflammatory responses. Proinflammatory process is dominant in the first trimester to allow blastocyst implantation and to prepare for delivery in the third trimester while anti-inflammatory response is dominant in the second trimester to ensure fetal growth. Therefore, during the first and third trimesters of pregnancy, the body is more vulnerable to viral infections. It can be considered that Covid-19 infection may progress more severe during these periods. Proinflammatory immune response in pregnant women with Covid-19 infection has been reported to be similar to non-pregnant patients with Covid-19 infection. TH1/TH2 balance generally tends to shift towards TH2 during pregnancy. A shift towards TH2 leads to a decrease in TH1 cellular immunity. Due to this decrease, the body cannot react adequately against microorganisms that have to live inside cells, such as viruses, and becomes more vulnerable to viral infections. The balance of regulator T (Treg)/TH17 cells ratio is important for embryonic implantation and a healthy pregnancy. Decreased Treg levels and increased TH17 levels are considered to be associated with miscarriage, pre-eclampsia, and preterm delivery during pregnancy. Studies have shown a decrease in Treg cells and an increase in TH17 cells in Covid-19 infection. The increased number of TH17 cells and their activation is blamed for the release of many proinflammatory cytokines into the body. This situation, called cytokine storm, is seen as an important cause of damage in maternal and fetal tissues.

The Covid-19 infection enters the body through droplets from the respiratory system. The SARS-CoV-2 virus enters the mucosal cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) receptor, which are mainly found in the respiratory tract and then in the intestinal mucosa, kidneys, endothelial cells, fetomaternal junction and some fetal tissues. Stimulation of the ACE2 receptor causes an increase in angiotensin 2 (AT2) release and a decrease in angiotensin 1-7 (AT1-7) release. After AT2 binds to the angiotensin 1 receptor (AT1R), the nuclear factor beta pathway is activated and, thus, causes an abnormal increase in IL-6, IL-1β, IL-10, TNF-α cytokines. The reduction of AT1-7 also causes the inflammatory response to decrease. Inflammatory cytokines such as IL-1 β, IL-2, IL-6, IL-7, IL-8, soluble TNF receptor1(sTNFR1), TNF-α, procalcitonin, C-reactive protein (CRP), ferritin, D-dimer, GM-CSF, IL-17, macrophage inhibitory factor 1-α (MIF1-α) have been reported to increase in Covid-19

patients. The number of Natural Killer (NK), CD4 and CD8 T cells and lymphocytes are decreasing in both Covid-19 infection and pregnancy. This leads to susceptibility to infection and increases the risk of transmission during pregnancy. It has been shown that IL-1β, IL-6, IL-8 and sTNFR1 are closely related to the severity of Covid-19 disease. The levels of CRP, IL-6, procalcitonin, ferritin and D-dimer have been found to be increased in proportion to the severity of Covid-19 infection. All of these immunological changes point to increased sensitivity to Covid-19 infection during pregnancy.

Covid-19 and Changes in Respiratory System During Pregnancy

Due to the increased estrogen and progesterone hormone levels during pregnancy, edema, hyperemia, increased mucus secretions and a decrease in mucus clearance capacity occur in the respiratory tract mucosa. Increasing estrogen level during pregnancy leads to an increase in the amount of hyaluronic acid in the mucosa and causes hydration and edema in the mucosal tissues. During pregnancy, the capacity of the lungs also changes due to the upward elevation of the diaphragm secondary to the expansion of the uterus. Functional residual capacity, decrease in expiratory reserve volume and residual volume, increase in inspiratory capacity and tidal volume are the reasons for these changes. Total lung capacity, lung compliance and first second expiratory volume do not change. During pregnancy, the need for oxygen also increases and the amount of oxygen consumed is 10% more than normal. This causes shortness of breath and dyspnea during pregnancy. Shortness of breath and dyspnea cause compensatory respiratory alkalosis secondary to frequent breathing of the mother. In addition, as the capacity of the lungs of pregnant women to clear mucus is reduced, this leads to lower respiratory tract infections. Due to all these changes in the respiratory system during pregnancy, it is predicted that Covid-19 infection may cause more serious clinical pictures.

Coagulation Changes and Endothelial Damage During Pregnancy

Thrombin production increases during pregnancy due to intravascular inflammation and this leads to a tendency to coagulation. Blood volume, cardiac output, stroke volume and heart rate increase and vascular resistance decrease during pregnancy. In addition to Covid-19 being a disease that mainly affects the respiratory tract, it has been reported that the SARS-CoV-2 virus binds to the ACE2 receptor in platelets and endothelium, causing the release of coagu-

lation factors, the secretion of inflammatory cytokines and the formation of leukocyte-platelet aggregates and, thus, thrombotic complications. Complications such as thrombotic disorders, sepsis and disseminated intravascular coagulation (DIC) have been reported in patients with severe Covid-19 infection. In large-scale studies, it has been shown that thrombocytopenia is concomitant to 18.8% to 36.2% of severe Covid-19 patients. Therefore, pregnant women should be followed carefully in terms of thrombotic complications and appropriate treatments should be planned. During pregnancy, due to the changes in the cardiovascular system, platelets and endothelial cells, the cytokine storm caused by binding of SARS-CoV-2 to ACE2 receptors in the endothelial cells in platelets tends to thrombosis and increases the incidence of clinical pictures such as thrombotic disorders (myocardial infarction, cerebrovascular occlusion, etc.), sepsis, DIC, multiple organ failure.

CLINICAL COURSE OF COVID-19 IN PREGNANCY

The clinical course of Covid-19 infection during pregnancy is similar to the clinical course in the community. It causes a wide range of clinical pictures from asymptomatic situations to situations requiring intensive care. During pregnancy, Covid-19 cause clinical symptoms such as fever and cough mainly, and myalgia, fatigue, dyspnea, sore throat, chest pain, weakness, headache, diarrhea, impaired taste and smell, nausea, vomiting, nasal congestion, muscle and joint pain, intrapartum and postpartum fever.

Covid-19 exhibits a clinical course in 5 subgroups over a wide range. These 5 subgroups include asymptomatic cases, mild and moderate cases, severe cases, critical cases and mortal cases. Symptomatic cases of Covid-19 disease are evaluated in 3 stages. Patients included in stage 1 exhibit flu-like symptoms. Stage 2 is divided into 2 subgroups as 2a and 2b and patients in stage 2a show signs of viral pneumonia, tachypnea, cough and fever while stage 2b includes hypoxia additionally. Patients with cytokine storm syndrome in which cytokines are released excessively, lung damage and multi-organ failure syndrome are included in stage 3. The presence of comorbid diseases such as diabetes, hypertension, chronic obstructive pulmonary disease and obesity in Covid-19 disease causes the clinical picture to become more serious. Tendency to gestational hypertension, gestational diabetes mellitus, thrombosis, preeclampsia, eclampsia, hemolysis, HELLP syndrome, asthma, hypothyroidism and obesity occurs, which can increase Covid-19 morbidity and mortality. The maternal and fetal effects of Covid-19 infection in pregnancy have not been

clearly understood yet. However, due to the fact that the infections caused by viruses such as SARS, MERS, H1N1, which are included in the coronavirus family, have more severe course during pregnancy, it has been considered that Covid-19 disease will also lead to more severe infections in pregnant women in the days when the first cases were observed. In the studies so far, it has not been clearly and definitively demonstrated that Covid-19 causes serious maternal and fetal morbidity and mortality in pregnancy as much as the disease caused by previous coronaviruses. Since the first case was heard, clinical courses similar to other individuals in the society have been observed in pregnant women. Although pregnant women with Covid-19 have been observed to have clinical courses similar with non-pregnant women, it has been observed that Covid-19 was more morbid in the presence of elderly maternal age, black race and comorbid conditions, according to some other studies. In studies comparing pregnant women with Covid-19 infection and pregnant women without Covid-19 infection, no significant difference has been observed in terms of mortality in pregnant women. Maternal mortality and the need for more intensive care have been reported in some studies. No clear and definite conclusion has been reached in the studies so far on this subject.

OBSTETRIC COMPLICATIONS IN PREGNANT WOMEN WITH COVID-19

There are still situations that are not fully clarified in the obstetric results of Covid-19. When the obstetric complications of Covid-19 are evaluated, no finding showing that it increases the complications in the first trimester has been detected until now. When the pregnant women with Covid-19 infection and those without Covid-19 infection have been compared in the first trimester, it has been observed that the pregnancy loss rates did not change. In a recent systemic study, it has been observed that pregnant women with Covid-19 infection increased the incidence of preterm delivery by 63.8%, low birth weight incidence by 42.8% and fetal distress frequency by 61.6%. In another study, it has been noted that pregnant women with SARS-CoV-2 infection had an increased possibility of preterm delivery and low birth weight, but the reason for this has not been clearly understood. In a study investigating pregnancy loss rates in pregnant women with SARS-CoV-2 infection, it has been found that pregnancy loss rate in pregnant women with Covid-19 infection was 2%. Pregnant women with positive Covid-19 and those without Covid-19

infection have been compared in terms of pregnancy loss and similar pregnancy losses have been found in another study. It has been found that the rates of Cesarean section increased in pregnant women with Covid-19 infection. Applications of the Cesarean section in pregnant women for reasons other than obstetric indications such as respiratory problems, risk of transmission and worsening of the clinical course that may occur in pregnant women with Covid-19 infection are the reason of this. However, Cesarean section should be decided according to the clinical condition of the mother and obstetric reasons. Covid-19 infection with no complication alone should not be considered an indication for Cesarean section.

Preterm Delivery

There are clues in systematic reviews that preterm delivery is increasing in pregnant women with Covid-19 infection. However, some studies have observed that preterm delivery does not increase. Preterm delivery can be induced or occur spontaneously in pregnant women with severe Covid-19 infection. There is no clear information in the literature about why preterm delivery occurs and why it is increasing in pregnant women with Covid-19 infection. In general, it can be predicted that preterm delivery may increase in pregnant women with Covid-19 infection. It is a known fact that preterm delivery increases morbidity and mortality in the newborn in the short, medium and long term. The likelihood of respiratory distress, respiratory distress syndrome, retinopathy of prematurity, bronchopulmonary dysplasia, sepsis, metabolic diseases, necrotizing enterocolitis, intraventricular hemorrhage and periventricular leukomalacia increases in premature babies. It should be kept in mind that preterm delivery may also lead to long-term complications such as cerebral palsy, learning difficulties, vision and hearing abnormalities, psychological disorders, growth disorders and chronic diseases. Therefore, care should be taken in terms of preterm delivery in pregnant women with Covid-19 infection.

Low Birth Weight

Low birth weight indicates births below 2500 grams. Low birth weight usually occurs due to intrauterine growth retardation and preterm delivery. Since preterm delivery and intrauterine growth retardation are more common in pregnant women with Covid-19 infection, the possibility of low birth weight in pregnant women exposed to Covid-19 infection also increases. Most of the

various studies on this subject report that low birth weight is more common in pregnant women with Covid-19 infection, while some studies state that it does not increase. Comorbid conditions such as high neonatal mortality, neurological disorders, psychological disorders, cardiovascular diseases and diabetes mellitus may develop due to low birth weight.

As a result, low birth weight is observed more frequently in pregnant women with Covid-19 infection compared to pregnant women without Covid-19 infection, and this increases neonatal morbidity and mortality. Pregnant women with Covid-19 infection need careful follow-up in terms of low birth weight.

Pregnancy Loss

There is no clear information on whether viral infections cause pregnancy losses and the mechanism that causes pregnancy loss is not clearly understood. It has been suggested that pregnancy loss may occur as a result of direct effect or as a result of the immunological response that occurs after the affection of trophoblasts and placenta by viral infections. The balance between TH1 and TH2 is crucial for a successful pregnancy and implantation. The change in Treg/TH17 ratio is also important for a successful pregnancy and implantation. It has been suggested that the increased tendency towards TH2 in pregnant women with Covid-19 infection may be a reason for pregnancy loss. It has been reported in most studies that no significant difference has been seen when pregnant women with and without Covid-19 infection were compared in terms of pregnancy loss. In contrast, some rare studies have argued that the rate of pregnancy loss and miscarriage increases in women with Covid-19 infection. As a result, although it has been considered that the increase in cytokines and inflammation that will occur due to the maternal immune response can theoretically lead to pregnancy loss because of detecting SARS-CoV-2 virus in placental and fetal cells in Covid-19 infection, most studies did not report a significant difference in terms of pregnancy loss and miscarriage.

Vertical Transmission

Since the presence of ACE2 receptors in placental and fetal tissues is known, it has been investigated in many studies whether Covid-19 infection is transmitted to the fetus vertically. In some studies, researchers observed that although the SARS-CoV-2 virus has been detected in placental villous stroma

and placental membranes, the possibility of vertical transmission has been found to be low. In some studies investigating vertical transmission, researchers detected the presence of the SARS-CoV-2 virus in the spinal cord blood, placental tissues and rectal swab samples of newborns. To date, there is no study on whether the newborn leaves a neurological sequel in the long term in maternal infections caused by coronaviruses. In maternal infections caused by other viruses, it has been found that neurological sequels develop in the baby in the long term, although the viruses have not passed the placenta and transmitted to the fetus. Therefore, there is concern that the babies of pregnant women with Covid-19 infection may develop neurological sequels in the long term. A clear reason for the mechanisms that cause these neurological disorders has not been found yet. These mechanisms are thought to be caused by direct tissue damage in the fetal nervous system by viral infection during pregnancy and indirectly due to the released cytokines due to fetal immune response. There are studies showing that viral infections that do not pass through the placenta cause brain damage in the fetus. It was stated in these studies that due increased amounts of cytokines, neurotransmitters and excitotoxic metabolites secreted from the placenta infected by the virus, there may be damage to the nerve cells of the fetus. Therefore, pregnant women with Covid-19 infection should be followed up carefully after delivery in terms of neurological sequels that may occur in their babies.

Psychological Disorders

In previous studies, it has been shown that some psychological disorders can be acquired by viral infection during pregnancy. It has been observed that disorders such as schizophrenia and psychotic disorders can occur after maternal viral infections. Although the cause of these psychological disorders is not known exactly, it has been argued that they may occur following changes in local gene expression of the placental and maternal viral transmission, changes in placental serotonin release, and changes in the release of Dopamine and Gamma Aminobutyric Acid (GABA) in fetal brain cells. Increased levels of TNFα, IL-8 and CRP in the maternal blood have been found to increase the risk of schizophrenia and psychotic disorder. Therefore, it should be kept in mind that in pregnancies infected with SARS-CoV-2 virus, cytokines, hormones and neurotransmitters, which are secreted after placental and possible fetal transmission and whose secretion amounts change, cause changes in the baby's brain and these may also lead to conditions such as schizophrenia and psychotic disorders.

It has also been shown that the risk of autism spectrum disorder is increased in babies of mothers with viral infections. Increased levels of serum IL-17a and IL-6 have been reported in mothers of babies with autism spectrum disorders. Since serum IL-17a and IL-6 levels are increased also in pregnant women with Covid-19 infection, they should be followed up carefully for the presence of autism spectrum disorder in their babies.

COVID-19 DIAGNOSIS DURING PREGNANCY

The diagnosis is made after the Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test of the smears of the symptomatic and asymptomatic pregnant women suspected of having SARS-Cov-2 infection taken from the nasal, nasopharyngeal or oral mucosa. For differential diagnosis, P-A lung radiography, computed tomography of Thorax, Thorax US and hematological parameters are evaluated to support the definitive diagnosis. In Covid-19 infection, laboratory findings such as lymphopenia, leukopenia, leukocytosis, thrombocytopenia, increased erythrocyte sedimentation rate, anemia, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatinine kinase (CK), increased levels of bilirubin, CRP and ferritin levels. In addition, increased respiratory rate, decreased oxygen saturation and decreased PaO2/FiO2 ratio can be seen in the later stages of the disease. Besides, P-A lung radiography, computed tomography of Thorax, Thorax US can be performed for visualization of pulmonary lesions to support the diagnosis. However, computed tomography and radiographic images do not present a specific appearance and diffuse hyperechoic areas in the form of viral pneumonias involving the lung, ground glass appearance and thickened pleural bands and pleural effusion can be seen.

DELIVERY METHOD

There is no clear information in terms of delivery method for Covid-19-positive pregnant women. It has been reported that delivery method should be determined according to the clinical condition of the pregnant woman. Delivery time can be adjusted according to the severity of Covid-19 infection. It has been reported that normal delivery time should be expected in those with mild Covid-19 infection and delivery can be done at week 32 in those with severe Covid-19 infection. While planning the delivery method, it is

recommended to prefer Cesarean delivery according to obstetric indications, and if there is no indication, vaginal delivery should be preferred.

ADMINISTRATION OF ANTENATAL STEROID IN PREGNANT WOMEN WITH COVID-19 INFECTION

It has been stated that the administration of ACOG antenatal steroid will not change the clinical course of Covid-19 in pregnant women with positive Covid-19 between weeks 24 to 36 in the presence of routine indications, therefore it would be more beneficial to use it to reduce fetal morbidity. In order to prevent the increase in morbidity and mortality that may occur in conditions such as preterm delivery and low birth weight, corticosteroids should be administered based on the clinical condition of pregnant women with the risk of preterm delivery.

COVID-19 VACCINATION IN PREGNANT WOMEN

There is no clear information about vaccination to prevent pregnant women from Covid-19 infection. WHO does not recommend vaccination of pregnant women since there is no study in terms of side effects and fetal effects of vaccine in pregnant women. Although there is no clear information on the vaccination of pregnant women who work or are in risky positions, such as health care professionals, it has been reported that vaccination should depend on the common opinion of the patient and the physician.

BREAST MILK AND BREASTFEEDING

The nutrients in breast milk have many effects on growth factors, immunological factors, and on the growth of the baby and immune and neurocognitive development. Immunoglobulins in breast milk protect the baby against viral infections in the neonatal period. In pregnant women with Covid-19 infection, it has not been clearly shown whether a viral infection is transmitted to the baby through breast milk. However, the mother should be warned to take the necessary precautions during breastfeeding and breastfeeding should be encouraged, as it may be possible for the mother to infect her baby with the SARS-CoV-2 virus through droplets. Even if pregnant women with Covid-19

infection are taking medication, the mother should be encouraged to breastfeed the baby, as the drugs penetrate too little into the milk.

CONCLUSION

It is known that 66% to 88% of pregnant women with Covid-19 infection are asymptomatic. It should be kept in mind that pregnant women, even if they are asymptomatic, can be infected with the SARS-CoV-2 virus and infect those around. Therefore, appropriate screening programs should be carried out in pregnant women who admitted to the clinic. Pregnant women with Covid-19 infection should be followed up carefully in terms of conditions such as preterm delivery and low birth weight. Pregnant women with Covid-19 infection should be followed up in terms of psychological and neurological complications that may occur in their babies in the medium and long term.

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CHAPTER 18

THE CLINICAL FEATURES IN PEDIATRIC PATIENTS WITH COVID-19

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INTRODUCTION

Chinese scientists identified the pathogen as Coronavirus after the first serious pneumonia cases were discovered in Wuhan, China, in December 2019. In January 2020, it was understood that the world encountered an acute respiratory distress virus that had not been encountered before. At first, it was named novel coronavirus 2019. However, it was later dubbed SARS-CoV-2 after it was discovered that the virus's genetic structure was close to that of the SARS coronavirus. On January 30, 2020, the World Health Organization declared a global emergency. On March 11, 2020, the epidemic was declared a pandemic . It has been announced that it is a new type of coronavirus that has typical features of the coronavirus family such as SARS-CoV and MERS-CoV, causes severe respiratory failure, and is classified in the Beta coronavirus genus. People in the seafood wholesale industry were the first to be infected with Covid-19. This virus, like SARS-CoV and MERS-CoV, is a zoonotic infection, meaning it can be transmitted from animals to humans. Because of its ability to spread from person to person, the disease spread quickly. SARS-CoV-2 is spread through droplets or inanimate surfaces contaminated by these droplets.

Although other transmission routes such as fecal-oral spread have not been fully clarified, pediatric cases with persistent PCR positivity in fecal samples have been reported despite regression of symptoms, and it has been suggested that it may be beneficial to expect PCR negativity in nasopharyngeal swabs as well as rectal swabs and stool samples in orderto determine the duration of isolation in children. Although infected symptomatic people are the primary source of transmission, the contribution of asymptomatic carrier people to the transmission has resulted in a rapid spread. The contagiousness of people infected with SARS-CoV-2 in the presymptomatic period may pose difficulties for disease control. In a study conducted in Singapore with 243 patients over a period of two months, it was found that there was contagiousness before 1–3 days from the onset of symptoms in the epidemiological clusters, and the importance of social distance in preventing SARS-CoV-2 transmission was emphasized.

CLINICAL FINDINGS

COVID-19 disease is effective in all age groups and the incubation period is between 1 and 14 days. Symptoms occur within 5-6 days on average. Most cases occur after contact with family members or sick people. The symptoms of COVID-19 in children and adults are similar but may differ in frequency. Most children are asymptomatic and severe illness is uncommon. Also, most children experience mild to moderate illness. The disease heals after seven to fifteen days. The number of severe cases is low. Severe clinics are more popular in immunocompromised children and the young age groups. In a review of 61 studies involving all age groups, at least one-third of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections were asymptomatic . In a study conducted on children with COVID-19 under the age of 20, it was reported that both genders were affected equall. In another study involving 7480 children with PCR-positive COVID-19, the weighted mean age was 7.6. Fever and cough were among the most common complaints in children admitted to the hospital, accompanied by gastrointestinal symptoms such as sore throat, fatigue, muscle pain, trouble breathing, headache, runny nose, and, in some cases, vomiting and diarrhea. Symptoms in infants include feeding difficulties and undetectable fever. The most common gastrointestinal symptoms in children are diarrhea, vomiting and abdominal pain. Cutaneous manifestations are rare and include urticarial, maculopapular, vesicular eruptions, and transient livingo reticularis.

In a study of 17877 patients aged 0-19 years conducted in the United States of America, the symptoms were listed according to age groups as follows: frequency of symptoms in children aged 0 to 9 years; Fever, cough, or shortness of breath 63% (Fever 46%, Cough 37%, Shortness of breath 7%), Myalgia 10%, Rhinorrhea 7%, Sore throat 13%, Headache 15%, Nausea/vomiting 10%, Abdominal pain 7%, Diarrhea 14%, Loss of smell or taste 1%. Among children aged between 10 to 19 years, the frequency of symptoms was as follows: Fever, cough, or shortness of breath 60%, Fever 35%, Cough 41%, Shortness of breath 16%, Myalgia 30%, Rhinorrhea 8% Sore throat 29%, Headache 42%, Among children aged between 10 to 19 years, the frequency of symptoms was as follows: Fever, cough, or shortness of breath 60%, Fever 35%, Cough 41%, Shortness of breath 16%, Myalgia 30%, Rhinorrhea 8%, Sore throat 29%, Headache 42%, Nausea/vomiting 10%, Abdominal pain 8%, Diarrhea 14%, Loss of smell or taste 10%.

The hospitalization rate of pediatric cases is between 6–20%, and the rate of admission to intensive care is 0.58–2%. The effect of comorbid diseases on the course of infection in children has been stated in some publications. In a study involving eight patients between the ages of 2 months and 15 years, it was stated that only one of the patients had an underlying acute lymphocytic leukemia. In a study involving 25 pediatric patients diagnosed with COVID-19 and hospitalized, 2 patients had a severe course. These two patients were between 0-1 years old. In addition, these patients had congenital heart disease and metabolic diseases. In another study, it was reported that among 171 pediatric patients, three of them required follow-up in the intensive care unit; and hydronephrosis, acute leukemia, and intussusception were comorbid in each of them. COVID-19 infections were examined in the clinics of 7480 children under the age of 18 with PCR positive, and 1475 of them were classified for the severity of symptoms. Of these classified cases, 15 percent were asymptomatic, 42 percent mild, 39 percent moderate (pneumonia without hypoxemia), 2 percent severe (dyspnea, central cyanosis, hypoxemia), and 0.7 percent critical (acute respiratory disorder syndrome, respiratory failure, shock).

Different hypotheses describe the mild path of COVID-19 infection in children. One of them is that SARS-CoV-2 uses ACE-2 receptors, and these receptors decrease with age, as detected before in animal studies. The other is that children's airways are healthier, children do not smoke, are less exposed to toxic gases, underlying diseases are less common, and have a more active innate immune system. Another theory is that the younger age group has

frequent viral infections, and the immune system responds more effectively to SARS-CoV-2 with these stimuli.

LABORATORY FINDINGS

Laboratoryfindings are variable in COVID 19 cases. In a report evaluating blood parameters in children, 69.6% of the patients had normal leukocyte counts, while an increase in the leukocyte count was observed in 15.2%, lymphopenia was detected in only two patients. In another study with PCR-positive COVID-19 cases younger than 18 years of age, it was found that most of the children had normal complete blood counts, but 17 percent had lymphopenia and 13 percent had neutropenia. High C-reactive protein (CRP) and procalcitonin were found in about one-third. High levels of serum aminotransferases and lactate dehydrogenase (LDH) levels were one of the common abnormalities. Kidney dysfunction can occur in children with severe illness. In a study involving 52 children, serum creatinine was higher than the upper reference range (ULRI) in 24 of them (46%). Of these patients, 15 met the criteria for acute kidney injury (AKI). Most of these 15 cases were seen in children with Multisystem inflammatory syndrome in children (MIS-C) admitted to the intensive care unit. However, these patients did not need transplantation and returned to normal levels with treatment.

DIAGNOSIS

Taking the rightsample at the right time with the appropriate technique increases our success for the diagnosis of COVID-19. Because it is difficult to distinguish SARS-CoV-2 from viruses acquired from other populations with a single symptom or symptoms, and co-infection is common. Much work is needed to increase the reliability of polymerase chain reaction (PCR) in diagnosis. The detection percentage of the virus was found to be higher in nasopharyngeal samples than in oropharyngeal samples. It was stated by the Centers for Disease Control and Prevention that nasopharyngeal samples should be preferred primarily. If an oropharyngeal sample is to be taken, it would be appropriate to take it in combination with a nasopharyngeal swab. Samples, if possible, from the lower respiratory tract should be repeatedly taken from patients whose first RT-PCR sample taken from the upper respiratory tract is found to be negative, but whose clinical suspicion persists. It is

quite difficult to produce SARS-CoV-2 in vitro and is often used for vaccine and drug studies research. Detection of antibodies caused by COVID 19 in the blood is very important in detecting past infections and determining their epidemiology. It has been stated that serology should not be used as the only diagnostic test. In another study, high sensitivity and specificity were determined by examining nucleocapsid protein from nasopharyngeal samples of RT-PCR positive patients by fluorescent immune chromatographic method.

Radiological Diagnosis

Imaging findings may differ. It may occur before the patient's complaints. In radiological diagnosis, plain radiographs in children may not show abnormal findings in the early period or mild involvement. In a review of 674 PCR-positive, COVID-19 infected children who were imaged, approximately 50 percent had abnormalities. In COVID-19, predominantly bilateral, rarely unilateral, subpleural ground-glass opacities and consolidation areas can be detected in tomography. In a study conducted to show the differences of imaging findings in children from the adult age group, involvement was found bilateral in 10 patients and unilateral in six patients. Subpleural involvement was detected in all patients with tomography findings, and consolidation surrounded by 50% air crescent sign, 60% ground glass image, 20% and 15% small nodules were detected, as well . In the same study, co-infection was found in 40% of the patients. The presence of co-infection in children with COVID 19 may change imaging and the use of imaging alone may be insufficient for diagnosis. In a study involving 107 pediatric patients, the radiological findings were listed as ground glass in 33%, local patchy involvement in 19%, bilateral patchy involvement in 12%, and interstitial changes in 1%. Typical signs of other respiratory viral infections (hyperinflation, peribronchial signs) have not been reported.

RISK FACTORS FOR SEVERE ILLNESS IN CHILDREN

Children with concomitant medical problems are at higher risk of severe illness than healthy children. These risk factors are obesity, severe genetic disorders, severe neurological disorders, hereditary metabolic disorders, sickle cell anemia, congenital heart disease, diabetes, chronic kidney failure, asthma, and other chronic lung diseases, down syndrome, malignancy, or immunosuppression due to drugs that weaken immunity. In one study, 42 percent of

children hospitalized with COVID-19 had less than 1 underlying condition, the most common of which were obesity, chronic lung disease, and premature. In another study, 22 percent of patients had comorbidity in the evaluation of 587 PCR-positive children. The most common comorbidities are asthma (45%), congenital heart disease (23%), immunosuppressive (12%), hematological or oncological diseases (6%), and chronic lung disease.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

In international studies, different concepts and case definitions are used for multisystem inflammatory syndrome (MIS-C) in children associated with COVID-19. The case definition for MIS-C is still unclear. Other clearly defined inflammatory syndromes such as Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome in children have clinical features that are both similar to and different from MIS-C cases. MIS-C can cause shock and multi-organ failure.

The European and US Centers for Disease Prevention and Control (CDC) provides a case definition, clinical findings, severe disease and multi-organ involvement (two or more), exclusion of differential diagnoses, and within four weeks before the onset of symptoms or the newly proven SARS-CoV- 2 infection or COVID-19 exposure.

The incidence of MIS-C is not yet clear. COVID-19 is assumed to be a rare complication in children. In one study, the incidence of SARS-CoV-2 infection was 322 per 100,000, and the incidence of MIS-C was detected as 2 in 100,00. It is assumed to be caused by an uncontrolled immune response to the virus in Kawasaki disease (KD), macrophage activation syndrome (MAS), MIS-C, and cytokine release syndrome. It appears to have a different immune phenotype than KD and MAS. Most of the affected children have positive serology while the PCR test for SARS-CoV-2 is negative; this result suggests that MIS-C is associated with an immune abnormality that occurs following an acute infection. Refractory fevers (median duration of four to six days) 100%, gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) 60-100%, rash 45-76%, conjunctivitis 30-81%, mucous membrane involvement 27-76%, neurocognitive symptoms (headache, drowsiness, confusion) 29-58%, respiratory symptoms 21-65%, sore throat 10-16%, myalgia 8-17%, edema in hands and feet 9-16%, lymphadenopathy 6-16% were present. Most patients go to the hospital due to fever for 3-5 days. In a study, 10% of 186

patients had a three-day fever, 13% had a four-day fever, and 78% had a five-day fever.

Gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea are more common and distinct and may mimic appendicitis in some children. Terminal ileitis has been found on abdominal imaging and/or colonoscopy in some children.

Respiratory symptoms (tachypnea, dyspnea) are often due to shock. Some children may need free oxygen or positive pressure ventilation, but severe pulmonary involvement (acute respiratory distress syndrome) is uncommon. Neurocognitive symptoms are common and may include headache, drowsiness, confusion, and irritability. A minority of cases go to the hospital with more severe neurological symptoms such as encephalopathy, seizures, coma, meningoencephalitis, muscle weakness .

At admission, 59 (66%) of 89 of the patients with suspected or proven MIS-C had lymphopenia; high proBNP levels in 74 out of 82 (90%), high troponin levels in 63 out of 89 (71%), high C-reactive protein levels in 98 out of 98 and high d-dimer levels in 86 out of 94 (91%) was observed. Laboratory findings of inflammation appear to be related to the severity of the disease. Children with shock had higher CRP, neutrophil levels, lymphocyte counts, and serum albumin values, as well as higher cardiac markers than non-shock pediatric patients, according to a study.

Chest radiographs of many patients were normal. Abnormal findings included pleural effusions, patchy consolidations, focal consolidation, and atelectasis. Chest CT (when available) usually has findings similar to those on a chest radiograph. Few patients had nodular ground glass opacification. Abdominal ultrasound or CT images included free fluid, ascites, ileitis, mesenteric lymphadenopathy/adenitis, and pericholecystic edema.

In one study, 10 (10%) of 79 MIS-C patients hospitalized in the intensive care unit required mechanical ventilation. The median time from symptom onset to hospitalization was four days. Intravenous immune globulin (IVIG) treatment was given to 69 patients, systemic glucocorticoid therapy to 63 patients) and vasopressor therapy to 61 patients; systemic glucocorticoid and IVIG treatment was given to 48 patients.

TREATMENT

After the SARS-CoV-2 epidemic was declared, treatment became very important. Antiviral treatments and vaccines have become mandatory. Also, the

development time for new agents was very short. For this reason, it has been tried to find an effective agent against COVID 19 among the drugs used for different indications. Among antiviral agents, lopinavir/ritonavir, interferon, arbidol and oseltamivir have been tested in different patients. However, evidence-based information in the pediatric age group is insufficient and these treatments should not be used routinely, except in critically ill patients, since most of the infection is asymptomatic or mild.

Antiviral Treatments

Hydroxychloroquine, chloroquine

It has been stated that chloroquine and hydroxychloroquine, which are used in the treatment of malaria and autoinflammatory diseases, inhibit viral and endosome fusion in vitro studies by affecting the endosomal pH and glycosylation of host receptors, and their anti-inflammatory effect may have a positive effect on the clinical course. The efficacy of hydroxychloroquine in treating COVID-19 is uncertain. Hydroxychloroquine is not licensed for this indication, and its emergency use authorization for the treatment of COVID-19 has been revoked in the United States. It is ideally used only in the context of clinical research with hospitalized patients. Due to the insufficient data on the use of hydroxychloroquine in children and the risk of life-threatening side effects such as QT prolongation, our national guideline states that it should be used in severe cases and children with accompanying risk factors, accompanied by ECG monitoring.

Favipiravir

Favipiravir is an RNA polymerase inhibition agent known to be effective on ebola and influenza. It is known from studies on ebola that this drug, whose side effects are known to be mild and self-limiting, is more effective at high doses. In the comparison between 120 patients using arbidoland 116 patients using favipiravir, there was no difference in the clinical recovery time of favipiravir compared to arbidol. It has been reported that the most common side effect is hyperuricemia. Data on the use of favipiravir in children with COVID-19 are insufficient. In cases where treatment is required, the Favipiravir tablet can be crushed and given by mixing with foods, making it easier for children to use.

Remdesivir

It is a broad-spectrum antiviral agent developed against RNA viruses such as flavivirus and coronavirus. remdesivir is a prodrug of a nucleotide analog that

inhibits RNA-dependent RNA polymerase and has activity against coronaviruses. Reported side effects of remdesivir include nausea, vomiting, and transaminase elevations. Studies on its use in the treatment of COVID-19 are ongoing. In a multi-center study conducted in China, 158 of the patients diagnosed with microbiologically and radiologically proved COVID-19 were given remdesivir and 78 placebo patients were included. Faster clinical improvement was observed in the group receiving remdesivir, but no statistically significant difference was found. In the United States, remdesivir has been approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19 requiring hospitalization in adults and children aged 12 years weighing 40 kg; with an emergency use permit, it is also available to other children hospitalized with suspected or laboratory-approved COVID-19 weighing 3,5 kg . The normal duration of treatment for children with severe illness is up to 5 days; the period can be extended up to 10 days for critically ill children who do not recover after five days. Remdesivir should not be co-administered with hydroxychloroquine or chloroquine because co-administration may reduce the antiviral activity of remdesivir.

Lopinavir/ritonavir

The first publications about the use of lopinavir-ritonavir in the treatment of SARS-CoV2, a protease inhibitor used in HIV treatment, are not reliable since they were made on a small number of patients. In a study of 199 adult patients, lopinavir-ritonavir and standard supportive therapy were compared and lopinavir-ritonavir was not found to be effective. Giventhe lack of efficacy and adverse pharmacodynamics, the routine use of lopinavir-ritonavir is not recommended.

Other Treatments

Corticosteroids

The use of glucocorticoids for immune-mediated complications of COVID-19 is made on a case-by-case basis based on the severity of the disease. There are reservations about the side effects of corticosteroids, the risk of secondary infection and decreased viral clearance, and the use of steroids. It is not routinely recommended for COVID-19 treatment, except for some critical patients. Although glucocorticoids have decreased mortality in adult patients, studies are ongoing in children. The benefits and risks are uncertain. In a series of eighth cases published on COVID-19 pediatric patients, it was reported that

supportive treatments and corticosteroids were used in five patients, three of these patients recovered completely, and two patients continued their treatment. In the "Infectious Diseases Society of America" COVID-19 treatment guideline, the dosage schedule for steroid use is given.

Antisitokine and immunomodulatorytherapies

Other adjunctive treatments for COVID-19 immune-mediated complications are determined on a case-by-case basis, in conjunction with the rheumatology and infectious diseases departments, depending on the severity of the disease and when indicated. In the treatment of children with COVID-19, immune modulators (IL-6 inhibitors (Tocilizumab), interferon-beta 1b, plasma obtained from recovering patients can be given. In severe clinical COVID-19 patients, an increase in proinflammatory cytokines and cytokine storms have been reported to worsen the clinical picture. IL-6 plays a key role in this pathway. Tocilizumab, effecting through IL-6, is an agent used in the treatment of rheumatological diseases. In a study conducted on 20 patients, clinical improvement was reported in 91% of the patients with a single dose of tocilizumab treatment . There is a need for large-scale, controlled studies on the use of these agents.

Immunoglobulin, convalescent plasma

It has been stated that plasma taken from donors who recovered from COVID-19 infection was transfused to critically ill patients, patients had a clinical benefit in a case series of five patients, and it may be beneficial to conduct further research on this subject. It is emphasized that there should be an increase in the number of patients who have had COVID-19 infection and recovered in the donor pool for immunoglobulin treatment. In another study, three critically ill patients who received high-dose immunoglobulin showed clinical improvement.

Monoclonal antibody therapy

Bamlanivimab, or casirivimab/imdevimab is recommended for monoclonal antibody therapy for COVID-19. Bamlanivimab, casirivimab/imdevimab are highly neutralizing monoclonal antibodies produced by recombinant DNA technology. Risk factors should be considered in children being treated. The benefits and risks in children are uncertain. Children treated with bamlanivimab or casirivimab/imdevimab should continue to isolate themselves and follow infection control measures. The US Food and Drug Administration has

granted emergency use for 12-year-old children diagnosed with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Bamlanivimab and casirivima/imdevimab can be used in patients older than 12 years and weighing 40 kg with certain risk factors for mild, moderate, severe disease and hospitalization.Bamlanivimab and casirivimab/imdevimab should be administered as soon as possible after a positive SARS-CoV-2 test and within 10 days of symptom onset. In a study of 452 patients, bamlanivimab reduced the risk of hospitalization compared to placebo. Nausea and infusion-related adverse effects (itching, flushing, rash) have been reported, but these are uncommon and mild. An interim analysis of the first 275 patients in a multicenter, randomized, placebo-controlled study, casirivimab-imdevimab reduced the viral load, and the rate of medically attended visits (e.g., emergency room, telemedicine, and face-to-face visits; hospitalization) over 29 days.

HOW SHOULD CHILDREN BE MANAGED AT HOME?

Children with documented or suspected Covid-19 and mild symptoms (e.g fever, cough, pharyngitis, other respiratory symptoms) should usually be treated at home unless they have a chronic condition that increases the risk of serious illness. Management focuses on preventing infection (isolation), monitoring clinical deterioration, and supportive care.

CONCLUSION

As a result, COVID-19 seems to have a mild course in the pediatrics age group, but it is important to distinguish these children from COVID-19 infected adults, as severe clinical follow-up can be observed in children with chronic diseases, malignancy, or immunosuppression. Careful follow-up of this age group gains importance as a significant portion of severe cases are reported in infants. Since the patient group, which has an asymptomatic and mild clinical course, including children, has a very important role in the spread of the disease, it is important to pay attention to social distance in the society, to take preventive measures and to eliminate new sources of infection by screening contact cases.

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CHAPTER 19

THE NEUROLOGICAL COMPLICATIONS IN PATIENTS WITH COVID-19

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INTRODUCTION

Coronaviruses are single stranded, enveloped, RNA viruses. In December 2019, an epidemic started related to a new coronavirus (2019-nCoV) that had never been detected before in humans. Later, the name of 2019-nCoV disease was accepted as COVID-19 and this coronavirus has been named SARS-CoV-2.

The common symptoms of infection include fever, cough, and dyspnea. In severe cases, pneumonia, severe acute respiratory failure, renal failure, and death may develop. The rate of neurologic complications is too high to ignore. In an observational study conducted in Wuhan, the rate of Covid-19 patients with neurological involvement has been determined to be 36.4% .

In fact, the coronavirus is not a neurotropic virus, it targets the respiratory epithelium. However, angiotensin converting enzyme 2 (ACE 2), the target receptor for virus binding and entry into cells, is also found in glial cells in the brain and spinal cord. Therefore, it can bind, multiply, and damage neuronal tissue. It can directly invade the brain parenchyma through the nasal mucosa, lamina cribrosa, olfactor bulb or retrograde axonal transport. Another

way to reach the nervous system is through the direct entry of the virus into the brain with the disruption of the blood brain barrier in the viremia phase of the disease . It is thought that SARS-CoV-2 is also affect the central nervous system (CNS) through these mechanisms. After Covid-19 invades the CNS, it causes neurological destruction, possibly due to hypoxia due to pneumonia and immune-mediated damage due to cytokine storm.

CNS involvement and complications of Covid-19 can be divided into two parts as central and peripheral.

CENTRAL NERVOUS SYSTEM INVOLVEMENT

Acute transverse myelitis

There are case reports of transverse myelitis associated with Covid-19. Valuiddin et al. have reported a 61-year-old female patient who completed numbness and weakness in the extremities about 1 week after a runny nose and tremor and an expansile lesion was found on cervical magnetic resonance imaging (MRI). The patient did not benefit from methylprednisolone, partially benefited from plasmapheresis. Munz et al. have detected a hyperintense lesion at T9 level in the T2 sequence in thoracic MRI approximately 1 week after the onset of Covid-19 symptoms in a 60-year-old patient. The common feature of MRI lesions in both patients is that they are in patchy style. The patients of Chow et al. who had transverse myelitis after Covid-19 have benefited from 1 g/ day methylprednisolone treatment for 3 days.

Postinfectious inflammation is probably responsible for the pathogenesis of transverse myelitis after Covid-19. There is no guideline on treatment, it has been seen that the reported cases had benefit mostly from methylprednisolone use.

Cerebrovascular events

Our knowledge of Covid-associated cerebrovascular disease is based on case series and retrospective observational studies. Although ischemic stroke is more common among the reported cases, intracranial hematoma and venous sinus thrombosis cases are also seen. Li et al have identified 11 patients with cerebrovasculer events, 10 ischemic and 1 hemorrhagic, in 219 patients with Covid-19 in a retrospective, single center, observational study.

Advanced age, Covid-19 disease severity, underlying diseases (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking and alcohol

consumption), high D-Dimer levels are risk factors for cerebrovascular diseases in patients with Covid-19. Renal failure is more common in cerebrovasculer disease with Covid-19 than without. These patients should be evaluated carefully for renal function.

The choice of treatment (antiaggregant / anticoagulant) in terms of ischemic stroke should be made according to Trial of ORG 10172 in acute stroke(TOAST) classification, clinical syndrome and laboratory findings.

Dhamoon et al have detected Covid-19 infection in 38% of 277 stroke patients admitted during the Covid-19 epidemic period. National Institutes of Health Stroke Scale(NIHHS) scores at the beginning of the stroke have been found to be higher in patients with Covid-19. Accompanying inflammatory events, hypoxia due to pneumonia and further increase in cerebral edema may be factors that increase the severity of ischemic stroke.

The underlying etiology in cerebrovascular disease is thought to be endothelitis.

Headache and dizziness

Headache and dizziness are the most common neurological manifestation among the Covid-19 patient series. The frequency of headache has been found to be approximately 12-64% in studies and case series. Headache due to systemic viral infections can be seen. Although there is no definite information about the character of headache, it can be seen in migraine, tension headache, cough headache phenotype. The most common is the migraine phenotype. Pain usually begins on the first day of viral infection symptoms and it is bilateral, and in the migraine phenotype. It can be included in 9.2.2 Headache can be included in the attributed to systemic viral infection group, in the International Classification of Headache Disorders (ICHD-3).

The pathophysiology of headache is thought to be the invasion of trigeminal nerve endings by SARS-CoV-2 virus in the nasal cavity, trigeminovascular activation with increased ACE2 expression in endothelial cells, or the release of proinflammatory mediators such as IL-1 beta, PGE2, NO and cytokines.

Dizziness is a symptom that should not to be underestimated for Covid 19 patients. In a review of 141 patients, dizzeness was found in all patients. It may accompany infectious conditions or be a symptom of cerebrovascular disease (cerebellar infarction or bleeding). Anamnesis should be taken well, neurological examination should be done in detail, imaging should be requested if necessary.

Encephalopathy

Encephalopathy is a diffuse brain dysfunction with different levels of impairment of consciousness. Infection is one of the encephalopathy etiologies. In addition, encephalopathy can be seen also in sepsis, electrolyte imbalance, hypoxia and renal failure, which are complications of Covid-19 infection. Severe underlying viral infection increases the risk of encephalopathy. The rate of encephalopathy reported in literatures is between 7.5-31%.

Correction of the underlying infectious, inflammatory, hypoxic and metabolic condition will help improve the encephalopathy picture.

Encephalitis / Meningitis

Viruses are the common cause of infectious encephalitis. Encephalitis cases related to other coronaviruses are encountered. Poyuiadji et al have published a case of acute necrotizing encephalopathy due to Covid-19.

Seizures

There are case reports about patients with covid 19 who had a seizure. These seizures may be due to electrolyte imbalance, hypoxia, CNS infection, renal failure and cerebrovascular events. There is no evidence that covid 19 infection causes an acute symptomatic seizure. However, there are case report. To determined incidence of new onset acute symptomatic seziure in Covid-19 patients, 304 patient were observed. They had no epileptic seziure during the follow up period.

Myoclonus

Generalized myoclonus cases developing after Covid-19 infection have been reported. Symptomatic drugs such as levetiracetam, clonazepam, valproic acid or immunotherapy such as corticosteroids and IVIG can be used in the treatment.

PERIPHERAL NERVOUS SYSTEM INVOLVEMENT

Guillanne Barre Syndrome

Guillain Barre Syndrome is ascending, symmetrical, inflammatory polyradiculoneuritis, which is mostly seen after bacterial and viral infections. There

are also cases seen after Covid 19 infection. Male gender and being over the age of 50 are risk factors for the development of Guillain Barré Syndrome. In Caress et al's 37 patients with Covid 19 and Guillain Barre series, two patients applied with Guillain Barre syndrome and Covid 19 was detected in their tests. For other cases, Guillain Barré Syndrome symptoms begin an average of 11 days after the onset of Covid-19 symptoms, with pain, paresthesia and weakness in the extremities, the most common initial finding. In the electrophysiological examination of these patients, the most common type of acute inflammatory demyelinating (AIDP), followed by Acute motor sensory axonal neuropathy (AMSAN), Miller Fischer syndrome, and acute motor axonal neuropathy (AMAN) were found, respectively. Thirty-three of 37 patients received 0.4 g/kg/day intravenous immunoglobulin (IVIG), three plasma exchange, and one symptomatic treatment. Plasma exchange (PLEx) was applied to two of the IVIG patients later. One patient died due to respiratory failure.

Myalgia / Myositis

Myalgia is one of the most common conditions in Covid-19 infection. There is a case series reporting its frequency as 52%. It is a finding that adversely affects the general condition of the patient, and care should be taken in terms of rhabdomyolysis complication. There are cases with rhabdomyolysis due to Covid-19 and it is a fatal complication. It is recommended that patients with myalgia should be followed up for rhabdomyolysis and evaluated frequently with renal function tests.

Anosmia/ Ageusia

Smell and taste disorders related to coronavirus have been reported frequently. When Covid 19 positive patients were compared with negatives, loss of sense of smell was found to be 68% to 16%, loss of sense of taste was found to be 71% to 17%. In the study, the viral load in the nasal cavity of both symptomatic and asymptomatic patients was found to be higher than the viral load in the pharynx. This suggests that the nasal cavity is the entry point of the virus. Viruses entering the nasal cavity, enter the CNS through the branches of the trigeminal nerve, causing anosmia and ageusia by damaging the peripheral extensions of the trigeminal and olfactory nerves . In one study, it was found that 27% of patients with anosmia who had Covid-19 recovered in an average of 7.2 days.

CONCLUSION

Sars-CoV-2 infection, which emerged in Wuhan in 2019, may have many neurological complications. These complications are too much to ignore. Both central and peripheral nervous systems are involved. Neurological complications may occur after the diagnosis of infection, or patients may present with neurological findings before Covid-19 infection is diagnosed. Every Covid-19 patient should be evaluated in detail in terms of neurological complications. In addition, Covid-19 infection should be considered while investigating the etiology of the neurological symptoms and diseases we encounter.

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CHAPTER 20

AN OVERVIEW OF THE EFFECTS OF THE COVID-19 OUTBREAK ON MENTAL HEALTH

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INTRODUCTION

COVID-19 infection which is first seen in Wuhan, China in December 2019, being caused by the zoonotic RNA virus spread rapidly throughout the world and it was declared as a pandemic by the World Health Organization in March 2020. Most common symptoms are fever, malaise and dry cough. Apart from fever and respiratory system symptoms, there are many findings relating with the disease causing organ failure and even multi-systemic involvement which may lead to death. Most common form of transmission is bymeans of the respiratory system through droplets. Virus enters host cells via surface proteins. Angiotensin convertingenzyme 2 (ACE2) has been determined as the entry receptor. Main entrypoint of thevirus is the respiratory system, but the virus may also infect the digestive, urinary, neurological and hematological systems. Infection can be transmitted from animals to humans and from person to person. Other possible routes of transmission are fecal-oral and mother-to-child. It is known that the incubation period changes between 5 and 14 days, rarely being longer. Severity of the disease varies depending on the age and presence of other accompanying chronicdiseases. Heart diseases,

asthma, obesity, HIV, liver and kidney diseases are defined as comorbid conditions which may affect the course of the disease negatively. The disease is more common in men than in women.

Against the COVID-19 pandemic, scientists and managers focus on pathogen and biological risk in order to understand the pathophysiological mechanisms involved, and to prevent, control and treat disease. At the same time, psychological and psychiatric comorbid conditions that occur due to the disease at both individual and collective levels are being neglected. This situation creates gaps in people's coping strategies and increases the burden of relevant diseases.

Entireworld has beenfighting against COVID-19 pandemic for more than a year. And this process affects people's mental health negatively in many ways. When impact of COVID-19 on mental health is evaluated systematically, primarily, th eimpact of pandemic process on mental health regardless of whether there is disease transmission or not, secondly comorbid spiritual disorders developing in patients catching COVID-19 disease and finally, mental disorders experienced by patients who had psychiatric disorder and got treatment during pandemic period and during when they had COVID-19 disease are being evaluated.

IMPACT OF PANDEMIC ON MENTAL HEALTH

Early in the epidemic process, managers provided suspicious and false information about the transmission route, incubation period, geographic spread, number of infected people, and actual mortality rates. This situation has caused insecurity and fear in societies. Inadequate control measures and lack of effective treatment made the situation worsen. Many physiological, cognitive, emotional and behavioral reaction shave been observed with the triggering of the stress situation in the society due to reasons such as this uncertainty, limitation of information, and the contagious nature of the disease, and these had direct effects on mental health. In a study conducted in China, where the pandemic first came out, it was shown that depression, anxiety and perceived stress levels were higher than they were another times.

Effects of pandemic on human psychology include many individual differences. In Turkey and other countries in the world, mask use to control the epidemic, social distancing, hygiene, prevention of collective bargaining, closing schools and workplaces, travel ban and curfew restrictions are being implemented. These affect societies both socially and economically. Disaster

that has occurred disrupts the daily routines of people and requires them to adapt to new conditions. Adaptation to new situations is not the same for every individual. Social and cultural characteristics of a person may vary according to socioeconomic conditions, psychological well-being and individual characteristics.Variables such as the insufficiency of the basic needs of individuals such as security, accommodation, nutrition, incomplete or misinformation about what happened, prolonged quarantine period, lack of social support, financial losses in the epidemic, developing COVID-19 symptoms or contacting with COVID-19 positive individuals in this process make people psychologically more risky during the epidemic process.

Furthermore, in a study conducted in China, it was reported that individuals under the age of 18 and over 50, individuals with low education levels, divorced or widowed individuals, agricultural workers, and minority persons had more obsessive-compulsive symptoms, interpersonal sensitivity, phobic anxiety and psychotic symptoms in this process. In other similar studies, people who may experience more negative consequences in the COVID-19 outbreak were determined to be the elderly, young people, women, students, immigrants, prisoners and homeless people. In this process, it has been reported that living with the family, having a fixed / regular income of the family, and living in urban areas rather than rural areas are protective against the development of psychological disorders in individuals.

Diseases are seen as traumatic negative events that can cause post-trau-matic stress disorder (PTSD) in people. The experiences and reactions of the people during the pandemic process can be evidence of this. A study con-ducted asserted that the COVID-19 epidemic had a negative impact on mental health, stating that one fourth of thesubjects experienced acute stress and more than a quarter experienced depression, anxiety and sleep problems. Another study reports higher rates. More than three quarters of the subjects had moderate to severe anxiety, two thirds had moderate to severe depression, and one third had post-traumatic stress disorder symptoms. In this process, the prevention of socialization, which is associated with the mental well-being of the person, and the disruption of daily routines have been associated with the development of acute stress disorder symptoms. Especially, it has been observed that quarantine has negative effects on mental health, and approxi-mately 35% of people under quarantine experience psychological distress. This situation was found to be associated with stigma, sleep problems, fear, low self-esteem, depression and PTSD in individuals. It has also been shown that female gender, young age, low education level, low income level and prolonged

social isolation areas sociated with higher levels of anxiety, depression and PTSD.

Additionally, it is predicted that mental problems experienced during the process may lead to suicidal behavior. Nowadays, there are no systematic studies on the COVID-19 pandemic and suicides, but experiences in pastepidemics such as Plague, Spanish Flu, SARS, Ebola have shown an increase in suicide attempts and suicide rates as well as psychiatric comorbidities. With the COVID-19 epidemic, an increase in panic, fear, depression, anxiety disorder, PTSD and sleep disorders has been observed in societies. Quarantine measuresled to social isolation and economic difficulties in closed workplaces. The anxiety that patients with the disease will have the disease again and the limitations of the treatment possibilities have increased the fear. These are all characteristics that may pose a risk for suicidal behavior.

When effects of the pandemic process on mental health are examined, healthcare workers should be evaluated as a separate group. Because they are at the forefront of this process and face higher levels of psychological problems compared to other people due to high risk of infection, inadequate working conditions, long working hours, physical fatigue, loneliness and separation from their families. In a study, it has been shown that the levels of depression and anxiety observed in health care workers are high, mainly due to stress, insomnia, and anxiety about contamination. It has been reported that health care workers dealing with the diagnosis, treatment and care of patients diag-nosed with COVID-19 more frequently show symptoms of depression, insom-nia and stress.

Increase in mental disorders occurring due to the process causes people to receive professional support in this sense. But since frequent visits of patients to the hospital during the pandemic process will increase the risk of contami-nation, patients' access to healthcare practices has been restricted with the measures taken. In this case, telepsychiatry applications were recommended for patients to receive psychiatric support by evaluating the current pandemic conditions. Telepsychiatry enables remote psychiatric examination by using electronic communication and information technologies. Although face-to-face interviews have the advantages of detecting body language and gestures, examination without physical contact reduces the possibility of transmission to healthcare workers and the risk of spreading asymptomatic viruses during the epidemic process. And besides physical isolation, it offers people living in social isolation the opportunity togetther support they need.

Role of the psychiatrist in supporting people spiritually during the pandemic process was determined as educating individuals about common negative psychological symptoms and encouraging mental health-enhancing behaviors; to integrate the applied treatments into existing health services and to facilitate problem solving. In this context, telepsychiatry applications with accurate and reliable information to reduce the fear and panic of COVID-19; plays an important role in raising awareness for psychiatric comorbidities and in the treatment of these comorbidities. It also offers mental health professionals the opportunity to undertake psychological interventions, including cognitive behavioral therapy and other forms of psychotherapy.

MENTAL HEALTH IN COVID-19 PATIENTS

One of the difficulties that is experienced during the pandemic process is the psychiatric disorders accompanying the COVID-19 disease. Being infected with the virus adversely affects the mental health of the individual by causing the fear of death, health anxiety, anxiety that it will transmit to relatives, and a feeling of stigma in addition to physical complaints.

Anxiety and depression symptoms were found to be significantly higher in hospitalized patients. Female gender, advanced age, being alone in the hospital increase this risk. For these patients it has been found that staying in the same room with family members who test positive for COVID-19 can reduce the levels of anxiety and depression observed in people, indicating that social support has significant contributions to the mental health of people in the process.It has been shown that neuropsychiatric effects such as fatigue, widespread muscle pain, headache, shortness of breath and concentration difficulties may continue in patients who have survived the COVID-19 disease and recovered from the infection. Another study showed that patients continue to have psychological distress approximately 50 days after being diagnosed with COVID-19. While PTSD symptoms are reported in approximately one quarter of these patients, it is emphasized that 40% of the mare accompanied by depression. The anxiety levels of the patients were also found to be high, and it was shown that they had shortened sleep times and difficulty falling a sleep.

COVID-19 process has brought up various difficulties for both physicians and patients in terms of measures that can be taken and practices to protect the mental health of these patients. It is predicted that anxiety disorders, depression, PTSD, sleep disorders, psychotropic drug use and drug abuse increase with the pandemic. While the pandemic has increased the need for

safe prescribing of psychotropic drugs, it has made it difficult to prescribe safe drugs due to both the limitation of face-to-face out patient services and drug side effects and interactions. The systemic effects of the COVID-19 infection itself and the drugs used in its treatment should be taken into account when choosing drugs in these patients. Knowing about possible side effects is of great importance in the management of the disease.

EFFECTS OF SYSTEM INVOLVEMENT OBSERVED IN COVID-19 DISEASE ON PSYCHOTROPES

It is known that COVID-19 infection does not only affect t here s piratory system but also many organs including the heart, liver, kidney, immune and hematological system. This situation is in the use of psychotropic drugs can cause drug interactions by affecting the absorption, distribution, metabolism and excretion of drugs.

It has been reported that lymphopenia and leukopenia developed in 63% of patients in COVID-19 infection. Lymphopenia, which is among the poor prognostic factors, has been observed in severe cases of COVID-19. In the course of the disease, it may be necessary to avoid drugs that can increase lymphopenia and leukopenia. Among the psychotropic drugs, especially carbamazepine, clozapine and olanzapine, although there is a high risk, first and second generation antipsychotics, tricyclicantidepressants (TCA) and benzodiazepines can adversely affect white blood cell production.

Coagulopathy and diffuse intravascular coagulation are commonly seen in COVID-19 patients. In addition, anticoagulants are used in treatment due to the increased thrombotic risk. In this case, it is necessary to be careful in the use of drugs that disrupt the blood platelet function and may increase the risk of bleeding (such as valproicacid, selective serotonin reuptake inhibitors, serotonin-neuradrenaline reuptake inhibitors).

Impact of COVID-19 infection on the cardiac system can be in the form of arrhythmias, myopericarditis, acute cardiac syndrome and heartfailure. And the drugs used in treatment may have cardiac side effects. It is known that chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir increase the risk of torsades de pointed (TdP) by prolonging QT. Antipsychotics (eg. thioridazine, intravenous haloperidol, ziprasidone, iloperidone, aripiprazole and lurosidone), citalopram, tricyclicantidepressants are drugs that can increasethe risk of QT prolongation and TdP. These drugs are known to increase the risk of QT prolongation. In particular, patients with a history of

cardiac disease, female gender, family history of heart disease, electrolyte imbalance and substance abuse are in the risk group for this side effect.

The risk of liver damage is particularly increased in severe cases. In acute liver failure, an increase in alanine aminotransferase, aspartate aminotransferase and bilirubin is observed in the laboratory findings. In this case, chlor-promazine, carbamazepine, valproate, duloxetine and nefazodone should be avoided in preferred drugs to protect the patient from drug-induced liver damage. Dose adjustment is required when its use is necessary.

Acute kidney injury has been observed in patients with chronic kidney disease and acute respiratory distress syndrome (ARDS) in COVID-19 infection. Renal functions of these patients should be closely monitored and dose adjustment of drugs eliminated from the kidneys, especially lithium, gabapentin, topiramate, pregabalin, paliperidone, and duloxetine, should be made. Potential nephrotoxic drugs should be avoided.

COVID-19 infection is primarily a respiratory disease. Cough and shortness of breath are the first clinical symptoms observed. Pneumonia and acute respiratory distress syndrome may be observed in severe cases. In these patients, the side effect of benzodiazepines, which can cause respiratory depression, especially at high doses, should be considered. While prescribing benzodiazepines (especially preferred in anxiety and panic disorder patients), it is recommended to make a choice of drugs by evaluating the benefit and loss situation.

Corona viruses are viruses with neurotropic properties. ACE2 receptor functional for COVID-19 is also found in neurons, microglia cells, astrocytes and oligodendrocytes. Anosmia, mouth and neuropathic pain due to peripheral nerve involvement of the virus; Headache, dizziness, ataxia, confusion, delirium, epileptic seizures and acute cerebrovascular diseases can be observed due to central nervous system involvement. It is thought that direct invasion of the virus may play a role in the formation of these clinical symptoms, as well as inflammatory cytokines. Among the neurological symptoms, delirium is the clinical picture that concerns us the most in terms of psychiatry and creates difficulties in treatment. The prevalence of neuropsychiatric symptoms in COVID-19 patients was found to be 22.5%. This rate increases in those who are taken to intensive care due to ARDS and it has been shown that 84.3% have delirium and neurological symptoms. Manyetiological factors play a role in causing delirium. In addition to organic reasons such as organ failure, hypoxia, sepsis, drug effect, metabolic disorders, long-term adherence to the ventilator; Prolonged immobility and social isolation

contribute to delirium etiology. In the management of delirium, firstly conservative approaches and then drug therapies are recommended. In conservative approaches; It is neces-sary to provide ambient lighting compatible with the circadian rhythm, to regulate night sleep, to establish communication that will ensure the orienta-tion of the patient to time, person and place, and to ensure physical activity as quickly as possible. In the medical treatment of delirium; melatonin can be used to regulate the sleep-wake cycle. Trazodone alone or in combination with ramelteon is one of the other alternative drugs that can be recommended for sleep. Benzodiazepines are not recommended as they can deepen delirium (except delirium tremens). It was found that haloperidol, olanzapine, quetiap-ine and arirpiprazole were effective in delirium pictures accompanied by behavioral disorders.

MEDICINES USED IN TREATMENT OF COVID-19 AND THEIR INTERACTION WITH PSYCHOTROPES

Chloroquine and hydroxychloroquine (HCQ)

HCQ, a synthetic form of quinine used in the treatment and prophylaxis of malaria, is considered a possible treatment for COVID-19 infection. Neuropsychiatric side effects such as psychosis, delirium, agitation, depression, sleep disorders, suicidal tendency and personality changes can be observed due to the use of the drug. Having a family history of psychiatric disease, female gender, low body weight and high doses increase this risk. HCQ is metabolized in the liver by cytochrome 2C8, 3A4, 3A5 and 2D6 enzymes. Use of these enzymes together with inhibitors or inducers can change the plasma concentration. In addition, since chloroquine and HCQ are moderate inhibitors of cytochrome 2D6 and P-gp, caution should be exercised in their use with drugs that are metabolized by these enzymes and have a narrow therapeutic index. Chloroquine and HCQ can increase the risk of TdP by prolonging the QT interval. This situation increases the risk of TdP by making an additive effect when used together with the antidepressants citalopram and escitalopram. Therefore, although their use is not recommended, ECG monitoring is recommended in mandatory situations.

It is known that among antipsychotic drugs, haloperidol, iloperidone, pimozide, sulprid, ziprasidone cause QT prolongation and increase the risk of TdP. Thioridazine and zuclopenthixol are metabolized by cytochrome 2D6. When used with HCQ, plasma concentrations of drugs increase, increasing

the risk of QT prolongation and TdP. Combination of these drugs is not recommended.

In addition, chlorpromazine, risperidone, aripiprazole, clozapine, paliperidone, zotepine, amisulpride, quetiapine also increase the risk of QT prolongation and TdP. It is suggested that these drugs can be used together with chloroquine and HCQ by ECG monitoring.

Tocilizumab

It is a recombinant humanized monoclonal antibody that is an interleukin-6 receptor antagonist used in the treatment of autoimmune arthritis. No drug-related neuropsychiatric side effects have been reported. No significant interaction has been reported when used with psychotropes.

Favipiravir

It is an antiviral that is an RNA-dependent RNA polymerase inhibitor. It is used in influenza and other RNA virus infections. No neuropsychiatric side effects have been reported due to favipiravir use. No significant interaction has been reported when used with psychotropes.

Remdesevir

It has been identified as a potential treatment for Ebola. It is a nucleoside analog used to inhibit the RNA polymerase effect. No drug-related neuropsychiatric side effects have been reported. No significant interaction has been reported when used with psychotropes.

Oseltamivir

It is an antiviral used in the treatment of influenza. It is a sialic acid analog that inhibits neuraminidase activity. Neuropsychiatric side effects such as sleep disturbance, headache and dizziness related to drug use have been reported. No significant interaction has been reported when used with psychotropes.

Azithromycin

It is a broad-spectrum macrolide antibiotic used in the treatment of respiratory, enteric and genitourinary infections. It has been reported that it may

prolong the QT interval and increase the risk of cardiac arrhythmia in patients using the drug. It has been associated with toxic effects on the liver. ECG monitoring is recommended when used with psychotropes that cause QT prolongation.

Plasmatherapy

Plasma from patients who have recovered from COVID-19 infection is used especially in patients with severe respiratory failure. No specific neuropsychiatric side effects related to plasma transfusion have been reported. No significant interaction has been reported when used with psychotropes.

C Vitamin

Vitamin C, an antioxidant, is used in the treatment of Covid-19 to increase the immune response at high doses intravenously. No neuropsychiatric side effects have been reported with the use of high doses of vitamin C. However, although vitamin C deficiency is seen as a risk factor for delirium, it can lead to depression, confusion an danger. Combined use with barbiturates may reduce the effectiveness of vitamin C.

Corticosteroids

It was not recommended in the treatment of viral infections, considering that it would increase the severity of the disease. However, clinical experience has shown that it is effective against cytokine storm and hyper inflammation in COVID-19 infection. It is known to have neuropsychiatric side effects such as depression, mania, agitation, mood disorder, anxiety, sleep disorders, catato-nia, depersonalization, delirium and psychosis due to corticosteroid use in the past. It induces cytochrome 3A4 and 2C19 enzymes in the liver. Psychotropes metabolized by these enzymes may decrease plasma level.

Interferon (IFN)

IFNs, being glycoproteins with immunomodulatory, antiproliferative and hormone-like activities, have been recognized as a potential treatment for COVID-19. It is warned that IFN use may have side effects related to fatigue, mood disorders, increased risk of suicide, anxiety, emotionall ability, apathy, sleep disorders and cognitive impairment. Close psychiatric follow-up of patients using IFN is recommended. A pharmacokinetic interaction has not

been reported regarding its combined use with psychotropes, but when used with carbamazepine, valproate and clozapine, warning is made about the risk of bone marrow suppression.

Our knowledge about the interactions between psychotropic drugs and Covid-19 infection and drugs used in its treatment is limited. The information we have is presented to us in the light of the findings revealed to date.

IMPACT OF PANDEMIC ON CHRONIC PSYCHIATRIC DISEASES

Pandemic process has also negatively affected individuals with chronic psychiatric diseases and caused them to experience many disruptions in their treatment process. These patients have higher risk of catching and transmitting COVID-19, having severe process of COVID-19 disease, need to get in patient treatment and risk of death with respect to average risk of community. The reasons for this situation include the difficulties of patients receiving psychiatric treatment in adapting to self-care, hygiene, nutrition, sleep and other necessary measures, inadequacy in impulse and behavior control, cognitive disorders, and access to treatment. In addition, metabolic diseases that develop due to the side effects of psychiatric treatments and inflammatory processes associated with psychiatricdiseases increase this risk.

Life expectancy in psychosispatients is shorter than the population average. This difference is about 15 years and the cause of death is 90% physical diseases such as cardiovascular diseases, diabetes and respiratory diseases. It has been shown that the risk of deep vein thrombosis and pulmonary embolism increases 2-3 times in patients with psychotic disorders such as schizophrenia. Frequent observation of smoking and less physical activity in these patients are also factors that increase the disease burden and deteriorate their general health status.

It is not emphasized that there is a need to change the treatment strategies of these diseases during the pandemic process. However, new applications are suggested for the use of clozapine and depot antipsychotics. These are as follows;

USAGE OF CLOZAPINE

Clozapine, which is frequently preferred in the treatment of resistant schizophrenia, is a drug recommended to be used by monthly complete blood count

against the risk of agranulocytosis. However, this practice increases the risk of COVID-19 transmission in patients during the pandemic process. A new consensus has been published by Siskind et al in 2020. According to this report, it is stated that frequency of neutrophil count could be reduced to once in a quarter in patients

1. a. Patients having been on clozapine therapy for more than 1 year. b. Patients whose neutrophil count had never fallen below 2000 before. c. Patients without safe and practical access to neutrophil count analysis. It is said that the frequency of checking the neutrophil count in these patients can be reduced to every 3 months (if medicine for 3 months can be obtained).
   For patients who are just starting clozapine treatment, it is recommended to follow country-specific protocols for the first 6 months. It is stated that for patients who are on clozapine treatment continuously for 6-12 months, decisions regarding complete blood count follow-up can be made on a case-by-case basis, and regardless of hemogram follow-up, patients using clozapine should continue to receive regular mental status and potential drug side-effect assessments through face-to-face or online interviews.
2. Clozapine is associated with an increased risk of pneumonia. This risk increases due to sialorrhea and aspiration side effects. Therefore, patients using clozapine should be informed about applying to a health care institution in case of signs of infection. And upon application, detailed systemic examination and detections of the patient, including complete blood count, should be done.
3. During the course of COVID-19 infection, an increase in the plasma level of clozapine can be seen. In a fever and flu-like picture, it is recommended to reduce the clozapine dose to half against the risk of clozapine toxicity. After the fever subsides, the lower dose should be continued for 3 days and then the dose should be increased gradually. Clozapine should be discontinued in case of toxicity.

Clozapine use can lower the seizure threshold. In case of seizure during acute infection, the dose of clozapine should be reduced, and an antiepileptic should be added to the treatment if necessary.

It is recommended that patients using long-acting depot antipsychotics can switch from 1 month injectionto 3 months injections if the clinical course is stable for more than 4 months.

CONCLUSION

As a result, the COVID-19 pandemic affects the entire world, including our country, both physically and spiritually especially health care workers, those with chronic physical illnesses, children, the elderly, immigrants and those with chronic mental illness come out to be groups that are much more risky. COVID-19 besides the effects of acute infection, restrictions applied to prevent spreading of disease, quarantine, closure of schools and workplaces, socialisolation, economic burdens give rise to fear, worry, sleep disorders in people and increase risk of anxiety disorder, depression and TSSB. It has also increased the psychological burden of patients who had previously had a psychiatric disorder and received support, and caused many disruptions in their treatment. In this process, it may be necessary to use COVID-19 drugs and psychotropes together. In this case, it is necessary to be careful about drug interactions.

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CHAPTER 21

ANOSMIA and COVID-19

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INTRODUCTION

In December 2019, the Coronavirus outbreak first occurred in Wuhan of China. Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), a part of the Coronavirus family, caused a pandemia in all over the world. On February 12, 2020, the World Health Organization (WHO) defined the disease which is caused by a new version of coronavirus as COVID-19.

Coronaviruses are enveloped, single-stranded RNA viruses. They affect humans, bats, cats and rodents in the environment. Alpha (α) and beta (β) coronaviruses are often the cause of respiratory diseases in humans and gastroenteritis in animals**.** SARS-CoV-2 is a coronavirus belonging to the β-coronavirus subgroup.In one study, it was reported that SARS -CoV-2 is a chimeric virus between bat coronavirus and an unknown coronavirus. Furthermore, snakes were found to be the most likely habitat for SARS-CoV-2.

In the early stages of the epidemics symptoms such as fever, shortness of breath and cough are observed. In addition, headache, nasal congestion, runny nose, tonsil swelling, sore throat, fatigue, conjunctivitis, smell and taste disorders (dysgeusia) are also observed during COVID-19 disease. In the course of

the disease, many organs, especially the lungs, may be affected. In COVID-19 disease, the disease is mild or asymptomatic in 80-90 % of the cases. The mortality rate varies according to studies, but it is in the range of about 2-5 %.

Postinfectious olfactory dysfunction (OD) is a symptom that can be seen after viral and bacterial infections. It is thought that it results from neuroepithelial dysfunction. OD can be seen in different ways such as anosmia, hyposmia, dysgeusia, and phantosmia. It is known that anosmia that occurs after upper respiratory tract infection accounts for 40 % of cases and is generally associated with nasal obstruction and mucosal congestion. It was also accepted that it is occurred due to nasal mucosal swelling and conduction blockage to the olfactory cleft region. Postviral anosmia studies have shown absence of cilia. In addition, it showed that olfactory sensory neurons transform into metaplastic squamous epithelium. Fornazieri et al. have been reported the frequency of anosmia as 13-26 % due to upper respiratory tract infection. Additionally, Suzuki et al. detected coronavirus, rhinovirus, parainfluenza virus and Epstein-Barr virus in the nasal secretion of individuals with different diseases after viral infection. Various animal studies have also shown that viruses can damage central olfactory pathways and other brain regions.

At the onset of COVID-19, anosmia was not among the clinical symptoms. However, on March 26, the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) published a statement highlighting that anosmia with dysgeusia is a symptom associated with COVID-19 patients. The Academy has set up the COVID-19 Anosmia Reporting Tool, an online survey (COVID-19 Anosmia Reporting Tool for Clinicians) for patients to submit data around the World. On April 17 (Centers for Disease Control and Prevention), the CDC summarized and updated the most common symptoms of COVID-19, adding "new taste or smell loss" to the symptom list.

COVID-19 is a neurotropic virus. The virus not only affects the respiratory tract, but also causes neurological symptoms. Neurological symptoms are observed in 1/3 of the patients. Anosmia is also an accepted symptom among neurological symptoms. Anosmia may be an isolated symptom or associated with other general and otolaryngological symptoms. Among covid patients, the incidence varies between 30-88 %. In the study by Mao et al., 36.4 % of COVID-19 patients had central nervous system findings and anosmia was reported in approximately 5 % of these patients. It has been reported that it is more common in women and approximately 70% of the patients have sudden onset. A recent study found that 45% of COVID-19 patients had OD.

Anosmia is one of the most common symptoms seen in COVID-19 patients. In 5% of patients with COVID-19, the first symptom is anosmia. OD starts suddenly in most cases, usually lasts 1-3 weeks and is a temporary condition. One study found that patients generally develop anosmia in 8.96 days, 4.4 days after the SARS-CoV-2 infection, and found that 98 % of patients were able to recover within 28 days. The prevalence of taste and / or smell disorders in COVID-19 proved to be significantly higher than patients with influenza, at a frequency of 12.5 % and 39.2 %, respectively. An artificial intelligence study found that the prevalence of anosmia / taste disturbance was 28.6 times higher in COVID-19 positive patients than in COVID-19 negative patients.

PATHOGENESIS

Although the pathogenesis of COVID-19 anosmia is not completely described, it has been suggested that there may be obstruction, inflammation, and damage of the olfactory region. On the other hand, no significant association was found with symptoms such as nasal congestion and mucosal inflammation in COVID-19 anosmia. This result suggests that mechanisms other than sinonasal obstruction may play a role in COVID-19 anosmia. Another potential mechanism is direct damage to the olfactory nerves and retrograde invasion of the olfactory pathways. Anosmia is more widely accepted that the virus does not affect the olfactory neurons directly, but may be due to damage to the other cells of the olfactory epithelium.

SARS-CoV-2 can affect OD in several ways; such as parosmia, phantosmia, hyposmia or anosmia. In addition, taste disturbances may accompany OD. The pathophysiology of the effect of this disease on OD has not been fully established. However, it is reported that the virus reaches the olfactory bulb via the angiotensin converting enzyme 2 (ACE2) receptor located in the basal surface of the nasal mucosa.

The ACE2 receptor is intensely expressed in the nucleus tract solitarius and ventrolateral medulla, which are involved in the organizing of the respiratory period in the brain. Additional, ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) are very abundant in the olfactory bulb. In recent studies, ACE2 release was found to be higher in the olfactory mucosa. The high incidence of these receptors in the olfactory bulb may explain the high affinity of the SARSCoV-2 virus using the same receptor. Therefore, it has been accepted that the way the virus enters the human cell is through the ACE2 receptor.

DIAGNOSIS METHODS

Studies have found that patients with mild cases of COVID-19 are much more likely to develop anosmia than patients with moderate to critical cases. Studies have found the rates of anosmia up to 70 % of patients with the mild form of COVID-19.

Magnetic resonance imaging (MRI) of the olfactory pathway is an useful anatomical imaging method for evaluating olfactory function disorders associated with postviral infection, neurodegenerative diseases and trauma. Studies have shown that the width and volume of the olfactory cleft increase in patients with postviral anosmia**.** In studies conducted with Covid-19, various radiological results were obtained.Galougahi and Eliezer, reported normal olfactory bulbus volume with normal signal intensity in COVID-19 patients. Aragao et al. showed an abnormality of the olfactory bulbus as micro bleeding or an abnormal increase at MRI. Laurendon showed severe enlargement of olfactory bulbus with abnormally high signal intensity in T2, consistent with bulbus edema in a COVID-19 patient with anosmia. In the COVID-19 case with anosmia report by Li, MRI of the bilateral olfactory bulbus showed a decrease in the right olfactory bulbus volume and an increase in linear hyperintensities. In one case report of COVID-19 patient with anosmia by Politi at the MRI of the bilateral olfactory bulbus, it was accompanied by right gyrus and mild rectus hyperintensity was seen. The width and volume of the olfactory crest were found to be significantly higher in patients with anosmia caused by SARS-CoV-2.

Smell tests are used to determine OD. Smell tests are generally of two types, psychophysiological and electrophysiological. Psychophysiological tests can be grouped into 3 groups: smell detection, smell discrimination and identification. For identification, CCCRC (Connecticut Chemosensory Clinical Research Center Test), UPSIT (University Of Pennsylvania Smell Identification Test), B-SIT (The Brief Smell Identification Test), OSIT (Odor Stick Identification Test), Sniffin Sticks (SS) test are used. Electrophysiological tests are of two types: electro-electrography and evoked olfactory potentials. The most common SS test is used in Europe. Using the SS test, smell discrimination, smell threshold and smell identification tests can be performed. These tests can also be used in anosmia due to COVID-19.

TREATMENT

It is possible to treat anosmia due to organic causes such as tumor obstructing the nasal passage, polyps, infectious and mechanical reasons. When these reasons are absent, the results of the treatment are not satisfactory. Vitamin A and B treatments have been tried in the problem of smell. It is known that vitamin A provides epithelial regeneration. However, these vitamins have not been found to have a healing effect on smell. In additional, considering its positive effect on wound healing, zinc treatment was tried, but there was no clear clinical response on smell. Sharp smells and smell exercises are applied in the current treatment of anosmia due to COVID-19.

CONCLUSION

In the case of anosmia and hyposmia without any upper respiratory tract infection, it should be taken a symptom that requires caution in terms of Covid 19. In addition, a person presenting anosmia and hyposmia complaints may need an evaluation of the central nervous system involvement. However, it is obvious that larger studies are needed in this respect.

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CHAPTER 22

REHABILITATION IN COVID-19

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INTRODUCTION:

The rehabilitation process is focused on helping people suffering from a disorder to maximize functional ability, psychological health, and social cohesion. Rehabilitation is crucial for maximizing recovery for people after acute illness and maintaining function for those with chronic illness. The reha-bilitation process starts with the disease and continues in the subsequent recovery period. The goal is to improve the functional level.

The COVID-19 pandemic has led to a massive increase in the need for rehabilitation for the population, both directly and as a result of social isolation, mobility restriction and health system disruption. Although the need for rehabilitation has increased, rehabilitation processes in diseases other than COVID-19 have been interrupted by the pandemic.

COVID-19 patients need rehabilitation in many ways; cardiopulmonary complications, complications due to stay in intensive care, weight loss, loss of muscle mass, neuromuscular complications are the main ones. The rehabilitation protocol is personal and planned according to the needs of the individual. Here, the possible effects of the COVID-19 outbreak from the eyes of a physician were reviewed and the guidelines in the literature on rehabilitation were summarized.

COVID-19 PANDEMIC

Coronavirus is a large family of virus that cause illnesses from the common cold up to more serious diseases such as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV). In 2019 December, a new coronavirus was identified as the cause of a disease outbreak that originated in China.

The virus is now known as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to COVID-19 infection was first reported on December 31, 2019. In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. A period of 1.5 years has passed since the first emergence of the disease, and it always appears with different pathophysi-ological pathways and clinical features. Although COVID-19 primarily affects the respiratory system, it also causes serious and fatal disease with multisystem involvement. The long-term effects of COVID-19 are unknown.

COVID-19 CLINIC AND THE ROLE OF REHABILITATION

Current data show that it mainly causes cardiopulmonary complications, decrease in quality of life and emotional stress in most of the patients. It seems that there is a need for guides in determining rehabilitations after COVID-19.

COVID-19 can cause viral pneumonia with pulmonary infiltrates, deep shortness of breath and hypoxia. Hypoxia can be persistant and requires prolonged supplemental oxygen and effort desaturation. In those who are severely ill from COVID-19, a hyperinflammatory condition can cause multiple organ dysfunction, including myocarditis and heart failure. This hyperinflammatory condition combined with inactivity and inadequate food intake are risk factors for acute sarcopenia (loss of muscle mass and strength).

Rehabilitation medicine plays an important role in reducing the disability of COVID-19 survivors and ensuring their optimal functions. Patients hospitalized due to the COVID-19 pandemic may experience symptoms such as fever, muscle pain, fatigue, cough and shortness of breath. Older age groups and those with concomitant illnesses are at risk of developing more serious illness and physical fitness. Rehabilitation have an important role in support-

ing hospitalized patients with COVID-19 but also need to be aware of chal-lenges when treating these patients.

Rehabilitation is necessary both during and after the COVID-19 disease to reduce dysfunction and disability due to the disease. As before the pandemic, it is not easy to reach rehabilitation services. Especially the elderly population with accompanying disease and those with severe disease need more rehabilitation.

Various degrees of disturbances have been reported, particularly in respiratory, physical and psychological functions. Respiratory rehabilitation intervention may improve prognosis, maximize functional preservation and improve quality of life (QoL), but there lacks of studies worldwide exploring the outcome of this intervention. Liu K et al. observed that the 6-week respiratory rehabilitation program caused improvement in respiratory function, quality of life, anxiety and depression in patients with COVID-19. Rehabilitation has certain beneficial effect in the acute stage, and especially in the recovery stage, including improving respiratory function, exercise endur-ance, self-care in daily living activities, as well as psychological support, etc.

In the field of rehabilitation, necessary guides have begun to be created to address these patients in every period. First of all, these patients should be well defined and their needs should be determined before rehabilitation. These include comorbidities, complications due to hospitalization in intensive care, and the effects of the virus on cardiac, immune, neurological, and cognitive systems.

In addition, rehabilitation programs related to cardiopulmonary, mobility and function should be determined. Providing function, disability and return to daily life with a detailed, individual assessment and progressive treatment plan will positively contribute to the quality of life of the person. Determining the patient's needs quickly and directing them to appropriate rehabilitation programs will contribute to success. In the paper by Kiekens C et al.[11] rehabilitation and in particular respiratory management in the acute and immediate post-acute phases are summarized. In the post-acute phase, severe muscle weakness and fatigue, dysphagia, psychological problems, mobility, activities of daily living and impaired functions including work are frequently observed.

After COVID-19, many people experience various problems related to organ functions, and rehabilitation is necessary to maintain normal functions of these people. In addition, a large number of COVID-19 patients have been

deprived of rehabilitation services due to isolation and quarantines. Survivors of severe COVID-19 experience persistent weakness and cardiorespiratory failure. Feasibility and potential benefit of cardiopulmonary rehabilitation after COVID-19 remains unclear. Hermann M. et al.[13] retrospectively analyzed COVID-19 patients and they found that comprehensive cardiopulmonary rehabilitation after COVID-19 is safe, feasible, and effective. They found improvement in physical performance and general health.

Zha Lu et al.[14] worked on modified rehabilitation exercises for COVID-19 patients. These exercises focused on facilitating the pulmonary function and expectoration process. Additionally, they integrated acupressure into the exercises. They found that these exercises facilitated breathing and expectoration in mild case.

GUIDES ON COVID-19 REHABILITATION

This includes rehabilitation, safety recommendations, rehabilitation during treatment, discharge recommendations, and staffing recommendations. Rehabilitation includes respiratory support and active mobilization should be planned during the hospitalization period. Respiratory support includes breath control, thoracic expansion exercises, airway clearing techniques and strengthening the respiratory muscles. Active mobilization suggestions include in-bed mobility activities, active range of motion exercises, active extremity exercises, daily living exercises, transfer training, ergometer, gait training and ambulation etc….

Physical Medicine and Rehabilitation experts from eleven different countries in Europe and North America have published guidelines on the clinical experience of the rehabilitation processes of COVID-19 patients. According to this guideline, COVID-19 patients reported particularly 1) Respiratory 2) Cognitive 3) Loss of condition 4) Critical illness neuromyopathy 5) Dysphagia 6) Joint pain and stiffness 7) Severe sequelae and loss of function in psychiatric areas.

The pulmonary rehabilitation principles suggested by Chinese Rehabilitation services are; 1) Pulmonary rehabilitation for hospitalized patients, 2) Pulmonary rehabilitation is not recommended for serious / critically inpatients 3) Training with video or visual instructions for isolated patients 4) Evaluation and observation throughout the entire pulmonary rehabilitation 5) It includes adequate protective equipment.

PULMONER REHABILITATION

Pulmonary rehabilitation is the treatment of chronic respiratory disease, despite standard therapy. Respiratory diseases not only cause primary lung disease but also; includes peripheral muscle dysfunction, respiratory muscle dysfunction, nutritional abnormalities, heart failure, skeletal disease, sensory deficits, psychosocial dysfunction.

Pulmonary rehabilitation can be directly made or indirectly with printed materials, visual training, training videos or remote consultation approach for patients isolated due to COVID-19.

The main goals of pulmonary rehabilitation for the patients with COVID-19 are;

- To reduce dyspnea symptoms,
- Reduce loss of function,
- To prevent / reduce complications that may develop,
- Preserving / improving physical function,
- To reduce anxiety and depression,
- Ultimately to improve the quality of life.

POST-COVID SYNDROME:

We also see long-term post-covid prolonged findings in people who have had the disease. Post-COVID syndrome (known as 'long COVID') is a prevalent syndrome. It includes a plethora of symptoms (exercise intolerance, dyspnea, chest pain, chemosensory impairment, lymphadenopathy, rhinitis, appetite loss, palpitations and orthostatic intolerance) which may last for weeks or more. This condition seem to be related to a virus- or immune-mediated disruption of the autonomic nervous system resulting in orthostatic intolerance syndromes.

In post-covid period some of the patients may have long-term impairment and dysfunctions, including pulmonary fibrosis, heart, liver, kidney, nerve and immune system. It is not yet possible to know how much of post-intensive care syndrome symptoms and respiratory failure will remain in the late post-acute and chronic period. In the literature there are also studies reporting permanent symptoms and findings in patients with post-COVID period.

Therefore, patients with permanent complaints should be included in long-term rehabilitation plans.

WHAT IS TELEREHABILITATION?

Telerehabilitation serves to solve this problem by aiming to provide rehabilitation services for individuals in remote areas. Telerehabilitation systems of this type, which are easily assembled using a combination of low-cost technologies, can be a powerful tool in addressing the social struggle with this pandemic, regardless of their use in the hospital or community.

Telemedicine may also be used to follow-up with patients in the postacute period. Such clinical pathways should each involve dedicated multidisciplinary teams composed of pulmonologists, physiatrists, neurologists, cardiologists, physiotherapists, neuropsychologists, occupational therapists, speech thera-pists, and nutritionists. The widespread use of telerehabilitation will be beneficial in reaching health services in many areas of medicine.

COVID-19 IN TURKEY

In the first case it was identified as the first COVID-19 patient on 11 March 2020, in Turkey. Considering that the rate of patients developing sequelae associated with COVID-19 will rapidly increase, Physical Medicine and Rehabilitation (PMR) specialists have important duties in reducing disabilities and restoring, optimizing functions in the acute hospital environment. The COVID-19 pandemic affected seriously both the services and the PMR physi-cians as early as the first month. This effect is expected to become worse, when the duration of pandemic prolongs.

A group of physiatrist in Turkey, Ayür Y et. al.[27] declared clinical practice guideline includes pulmonary rehabilitation (PR) recommendations for adult COVID-19 patients which is developed in the light of the guides on the diag-nosis and treatment of COVID-19 provided by World Health Organisation (WHO) and Turkish Republic Ministery of Health, and recently published scientific literature, PR recommendations for COVID-19 regarding basic prin-ciples of pulmoner rehabilitation.

The organisations make recommendations for the initiation of the rehabilitation protocol for patients who are hemodynamically stable and PCR negative, especially in the acute period.

Because a patient who is not hemodynamically stable can easily enter dyspnea with the effort caused by exercise. We may face undesirable effects due to exercise.

It is also important for the practitioner to protect himself from infection with personal protective equipment. This should be the priority.

COVID-19 RHEUMATIC REHABILITATION

We know that many viruses (HAV, HBV, HCV, parvovirus, CMV, EBV, Influenza etc…) cause poly / oligoarthritis. These types of viral arthritis heal without any sequelae. In the literature, we see that clinical pictures of mono and oligoarthritis have been reported in the acute / subacute period due to COVID-19. These patients should be evaluated within the scope of rheumatic disease rehabilitation. The joint should be immobilized in the acute period, exercise program and joint protective interventions should be planned.

COVID-19 PHYSICAL ACTIVITY, EXERCISE AND IMMUNITY

Physical activity (FA) is an indicator of one of the primary conditions of healthy living and therefore one of the primary components of wellness medicine. Physical exercise has proven beneficial in preventing illness, adjunctive treatment of chronic illnesses, and psychological well-being. Moreover, the protective effect of exercise on the immune system is known and an optimal immune system is very important in the response against COVID-19. Considering the current social isolation recommendations in different coun-tries, it is essential to maintain the routine physically active lifestyle of people as a preventive health measure in these days when the virus spread is tried to be prevented. It is worth remembering that WHO recommends physical activ-ity for at least 150 minutes per week for healthy and asymptomatic adults and 300 minutes per week for children and adolescents. This time of physical activity should accumulate on the days of the week; it can be divided according to individual routine and preferably separately according to routine, and should preferably consist of medium andvigorous intensityactivity.

To elaborate the benefits of physical activity by showing the effect of regular physical activity in increasing immune function and reducing the risk of the severity or duration of viral infections with well-supported evidence. The most consistent evidence shows that moderate physical engagement (~ 150 minutes / week) is necessary for optimal immune support.

CONCLUSION

In summary, most of the patients recovering from COVID-19 are of advanced age and have accompanying multisystem problems. In addition, prolonged persistent symptoms and signs after COVID-19 are common. There is a need for rehabilitation services in different areas including cardiopulmonary, physical insufficiency, cognitive dysfunction, musculoskeletal symptoms, chronic pain, social isolation and difficulty in accessing health services.

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