The Clinical Implications and Evaluations of Pandemic Disease (COVID-19) in TURKEY

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PREFACE

It is obvious that technology, developments in the quality and quantity of researchers and scientific research are very important in the detection, control and treatment process of the clinical results and evaluations of the pandemic disease (COVID-19) in Turkey.

Every new scientific and technological innovation contributes to the more comfortable life of human history. We hope that this book, which includes chapters prepared by valuable scientists, will be useful to our country, all our colleagues, our dear students and all our people during the COVID-19 pandemic process we are going through difficult times.

We would like to thank everyone who contributed to the creation of this book, those who helped in the transfer of current information, our colleagues who acted as referees, the publishing house and its employees who gave us this opportunity to publish the book.

Regards…

Assoc. Dr. Hakan KAMALAK

Assoc. Dr. Aykut URFALIOGLU

CONTENTS

CHAPTER 1

POTENTIAL EFFECTS OF ELECTROMAGNETIC FIELDS USED IN CANCER THERAPY ON SARS-COV-2 INFECTION

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1. Introduction

Currently, the world is facing an unprecedented emergency pandemic caused by a novel coronavirus, which is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Because of their rapidly uncontrolled spreading and ability to evolve by a genetic mutation, viral infections can cause a significant threat to human health (2). The SARS-CoV-2, which causes a disease called COVID-19 (coronavirus disease 2019), is the most severe pandemic by coronaviruses after SARS-CoV in 2002-2003 and the Middle East respiratory syndrome (MERS-CoV) in 2012 (3). Therefore, scientists and medical professionals are making effort to establish efficient diagnostic strategies, vaccines, and antiviral drugs with appropriate procedures globally to combat the SARS-CoV-2 virus.

It has been confirmed that biophysical properties of cells, such as electrical, mechanical, and thermal, play essential functions in learning various biological activities consisting of disease progression at the cellular and molecular levels (4). The alterations of the electrical properties of cells in the disease state can render them valuable as potential markers in the detection or treatment of cancer (5). As the cell structure change with the cancer progression, the membrane capacitance and cytoplasmic conductivity adapt to reflect this alteration (6). It has been shown that normal, pre-cancerous, and cancerous cells have distinct electrical properties and membrane permeability (7). For instance, malignant tumors exhibited a higher conductivity (8), and lower impedance than surrounding normal tissues (9). These electrical differences also help to determine the displacement and density of electromagnetic (EM) current passing through the cell membrane (10). Therefore, the distribution of the absorbed EM energy between the different cells depends on their electrical conductivity related to their physiological and pathological forms (11).

The structure of many viruses consists of characteristic proteins dispersed at specific positions throughout their capsids and envelopes (12). The biophysical properties of these characteristic proteins provide new knowledge about the structures and functions of viruses (13). For example, since infected cells are physically more conductive, electromagnetic fields can selectively interact with infected cells and stimulate their membrane protein (14). Also, the selective interaction of the electromagnetic energy with the virus or virus-infected cells may support diagnostic and therapeutic processes of diseases. Therefore, it would be meaningful to investigate whether the EMF may contribute to the inactivation process of SARS-CoV-2 or its infected cells.

2. The structure of the SARS-CoV-2 virion

SARS-CoV-2 contains an envelope and a helical capsid, which is constituted by nucleocapsid (N), membrane (M) and envelope (E) proteins, covered with spike (S) proteins (15). The viral genomic structure of coronaviruses consists of several open reading frames (ORFs) (16), encoding replicase/ transcriptase polyprotein, major structural proteins (S, E, M and N) and other proteins (17) (Figure 1).

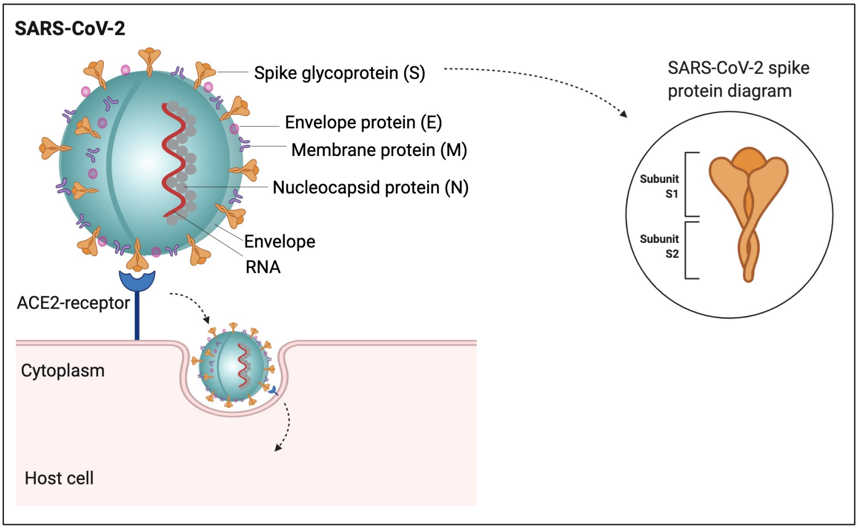

Figure 1. A schematic representation of the structure of the SARS-CoV-2 virus (created with BioRender.com).

SARS-CoV-2 utilizes the surface homotrimeric S protein as a substantial route of cellular infection (18). The SARS-CoV-2 spike glycoprotein contains two functional subunits, S1 and S2 (19). The S1 subunit includes the receptor-binding domain (RBD), which is known to bind the angiotensin-converting enzyme 2 (ACE2) receptor on host cell surfaces, whereas the S2 subunit facilitates viral and cellular membranes fusion, leading the entry of the virus into the host cell (20). In brief, SARS-CoV-2 uses the S protein to bind the ACE2 receptor and trigger a cascade of events leading to cellular uptake (21). Therefore, since the S protein is responsible for viral infection and inducing host immune response, it has been considered the primary target for viral inactivation approaches (22).

2.1. Electrical properties of SARS-CoV-2 virion

SARS-CoV-2 virion is spherical shaped and with an average diameter of 80–120 nm (23), and petal-shaped surface spikes are ~20 nm long (24). The genome size of coronaviruses ranges between 26 and 32 kilobases (25). Coronavirus is an enveloped virus surrounded by a lipid bilayer with spike proteins, where both the envelope and the spike protein are vulnerable to heat (26). Furthermore, virus inactivation occurs due to the thermal denaturation of the proteins that comprise each virion (27). SARS-CoV-2 infected cells include metabolic processes in their own unique hypermetabolic state (28). A higher metabolic rate produces a high ionic concentration in the microenvironment of viral-infected cells, as in cancer cells. The high ionic concentration produces greater electrical conductivity in the near vicinity of cells, which elevates the current density in the region (29).

Electrical impedance is a well-defined physical principle by which the impedance of many specific cells can be measured against alternating current applied at increasing frequencies (9). Dielectric behavior of cells changes when cells undergo from a healthy to a pathological state (30). Also, membrane capacitance (C_{mem}) can be used as an electrophysiological marker to diagnose disease, track disease progression, and support treatment strategies (10). The characteristic molecular composition of the capsid, envelope proteins and RNA of the many viruses confer them different specificity and infectivity (31). Also, the dielectric characteristics of specific proteins have influence upon the total dielectric constants of viruses; therefore, each virus can have a specific impedance value (12). Nakano et al. measured the electrical impedances of adenovirus and rotavirus and reported that these two viruses have different impedance values (32). MacCuspie et al. measured the capacitance of five species of viruses: modified vaccinia Ankara (MVA), herpes simplex virus type 1 (HSV1), cowpea mosaic virus (CPMV), simian virus 40 (SV40), and adenovirus type 5 (AV5). They indicated that these viruses could be clearly distinguished based on their capacitance spectra (12). It has also been shown that cytoplasmic conductivity and specific membrane capacitance of enveloped viruses (lentivirus, influenza virus, baculovirus) change throughout the virus infection cycle (33). Therefore, these different values of capacitance, conductivity, and impedance could be used in the selective-interactions of viruses or virus-infected cells.

3. The potential interaction of the EMF with SARS-CoV-2

Many researchers have investigated EMF exposure systems for cancer therapy, including but not limited to modulated electro-hyperthermia (mEHT) (34, 35), tumor treating fields (TTFields) (36, 37), and pulsed electromagnetic fields (PEMF) (38, 39). The common point of these systems is that the therapeutic effects of EMF have been clinically validated (Table 1). Therefore, considering its strong potential in cancer therapy, we hypothesize that EMF may also affect viruses or virus-infected cells. The potential inactivation effects of EMF on viruses or virus-infected cells are examined in detail in the subsections.

Table 1. EMF-derived devices and their potential effects.

Device	Frequency	Potential effects
mEHT	13.56 MHz	thermal or non-thermal anti-tumor effects
PEMF	1–50 Hz	anti-inflammatory effects
TTFields	100–300 kHz	impairing rapidly dividing cells, anti-mitotic effects

Abbreviations: mEHT: modulated electro-hyperthermia, **TTFields:** tumor treating fields **PEMF:** pulsed electromagnetic field, **Hz:** hertz, **kHz:** kilohertz, **MHz:** megahertz.

3.1. The effects of RF-hyperthermia on SARS-CoV-2

The concept of 'hyperthermia' as a medical term refers to a rise in temperature in the human body, which is one of the most prominent symptoms of many diseases (40). However, in therapy, hyperthermia refers to the induction of temperature increase in the desired area (41). It is widely acknowledged that radiofrequency hyperthermia (RF-HT) has a thermal-killing effect on tumor cells which is considered its main working mechanism (42). In cancer treatment, RF-HT is accepted as an alternative method that either devastates the tissues (≥47 °C) or renders the cancer cells more susceptible to radio-chemotherapy (41–45 °C) (43, 44). Also, RF-HT induces various changes on cell membrane such as protein denaturation and aggregation, leading to apoptosis (≥41 °C) (45). These temperature increases are effective in tumor cells but are not sufficient for SARS-CoV-2 virus inactivation. However, complete inactivation of the SARS-CoV-2 requires a high temperature, it can be inactivated at 56 °C for 30 min or at 65 °C for 10 min (46). Nevertheless, increased temperature with hyperthermia could partially neutralize or inactivate the viral infection (14).

RF-HT not only creates a heat effect but also modifies the biophysical features of the cell membrane (47). However, the potential non-thermal efficacy of RF-HT, which has been generally ignored by most researchers, has been confirmed on the cell membrane lipid bilayer (34). This interaction between the RF and cell membrane can alter the ionic gradient of the cell membrane, creating a non-thermal efficacy concerned with ion fluxes (42). There is growing clinical evidence that alternating electric fields and amplitude-modulated EMF (AM-EMF) are suitable for preventing tumor growth (48). The mEHT is used in complementary anti-tumor therapy in oncology (49). The RF current with a frequency of 13.56 MHz cannot penetrate into the cell, as the cell membrane is an excellent electrical insulator (34). In addition, RF-HT can create localized hot spots due to the inhomogeneity of the electrical permeability and conductivity of the cell membrane (50). The energy of the AM-RF current is absorbed mainly through the cell membrane (34). Andocs et al. showed that capacitively-coupled RF-fields interacted with the microdomains of the cell membrane (34) (Figure 2a).

Lipid membranes are a significant preliminary point of interaction for viruses, which can utilize microdomains of cell membranes entitled lipid rafts for some processes of their replication cycle (51). These tightly packed microdomains have dynamic structures that may play a crucial role in coronaviruses and host cell interactions (52). The membrane rafts absorb more RF energy than any other lipid bilayer part of the cell membrane due to their different dielectric properties (34). The higher RF energy absorption means a higher local temperature of the membrane rafts during RF current transmission to the cell (34). In addition, lipid rafts facilitate the interaction between the spike protein and its ACE2 receptor and the endocytosis that occurs in the early stages of the internalization of coronaviruses (53). These rafts are the focus of intense research in the field of infection, and it may be considered to target certain lipid raft components to inhibit virus infection at the cellular level (54).

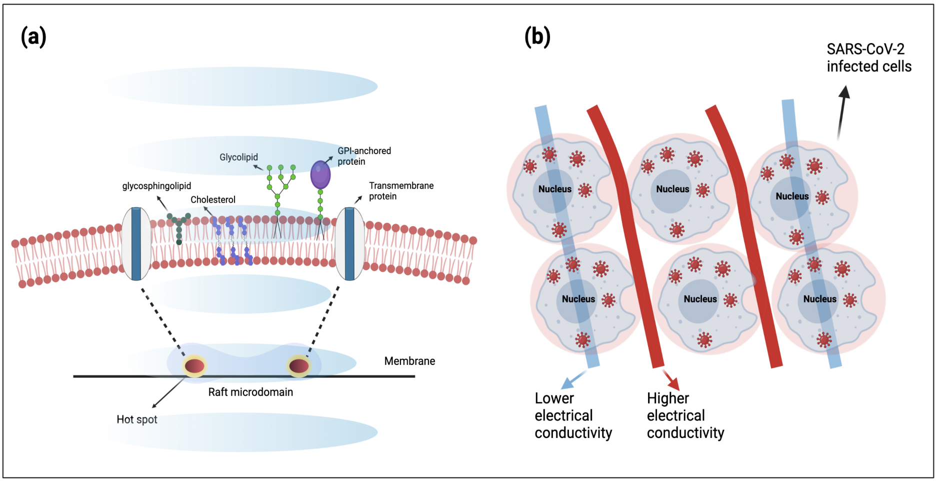

Figure 2. (a) Schematic representation of the lipid raft in the plasma membrane and localized hot spots in the RF exposure, **(b)** the primary selection of virus-infected cells by RF-current flowing through the tissue. The microenvironment of infected cells is highly electrical conductivity (created with BioRender. com, adapted from (34, 55)).

SARS-CoV-2 infected cells can cause biophysical dissimilarities that may facilitate their selection and recognition (14). The infected cells have a higher metabolic rate than uninfected ones, and they need a high amount of energy to support the virus replication process (56). The higher metabolic rate produces a higher ionic concentration in the microenvironment of infected cells, and this higher concentration generates better conductivity with an increased electrical current (29). Therefore, externally applied EMF prefers to flow predominantly through the virus-infected cells due to its relatively higher ionic electrical conductivity (14) (Figure 2b). It would be insightful to investigate whether RF-HT can contribute to the inactivation process of SARS-CoV-2 infected cells (Figure 3).

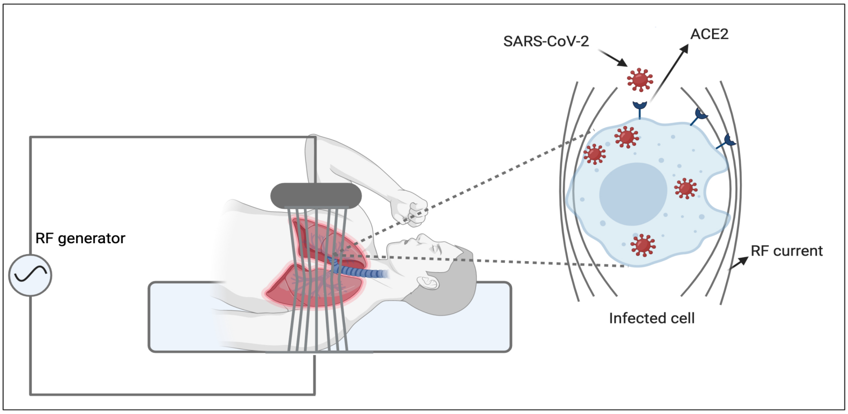

Figure 3. Schematic representation of the potential selective effect of the RF-field on SARS-CoV-2 infected cells. Externally applied RF-field prefers to flow through the virus-infected cell because of its comparatively higher ionic electrical conductivity (created with BioRender. com, adapted from (14)).

3.2. The effects of PEMF on SARS-CoV-2

The PEMF involves low-frequency pulsed energy waves (1-50 Hz) and has been utilized by the Food and Drug Administration (FDA)-registered device for many therapeutic purposes due to its anti-inflammatory effects (38, 57, 58). Immune system dysregulation or excessive inflammatory reply to SARS-CoV-2 causes systemic complications of COVID-19 (59). The clinical deterioration is associated with a hyper inflammation with excessive release of proinflammatory cytokines (e.g, TNF-alfa, IL-6), resulting in cytokine storm (60, 61). It has been reported that PEMF significantly reduces the levels of interleukin-1b, known as a principal inflammatory cytokine (38), and increases the release of anti-inflammatory cytokines (e.g., interleukin-6 and interleukin-10) in tissue (39) (Figure 4).

The biophysical effect of PEMF occurs on the cell membrane, which undergoes a transient depolarization (62). This depolarization activates specific transmembrane ion channels, among which the voltage-dependent calcium channels that are permitting an influx of calcium ions (Ca^{2+}) (57). The entry of Ca^{2+} into the cell and its binding with calmodulin triggers a whole set of biochemical pathways, including various enzymatic activation in the cytoplasm (62). When Ca^{2+} is activated, it binds to calmodulin, an enzyme responsible for the synthesis of nitric oxide (NO), and NO triggers to the production of cyclic guanosine monophosphate (cGMP) (57). As a result, PEMF may activate the calmodulin-dependent NO/cGMP signaling pathway, leading to an anti-inflammatory response (63). Therefore, PEMF can be a practical approach in the SARS-Cov-2 inactivation process.

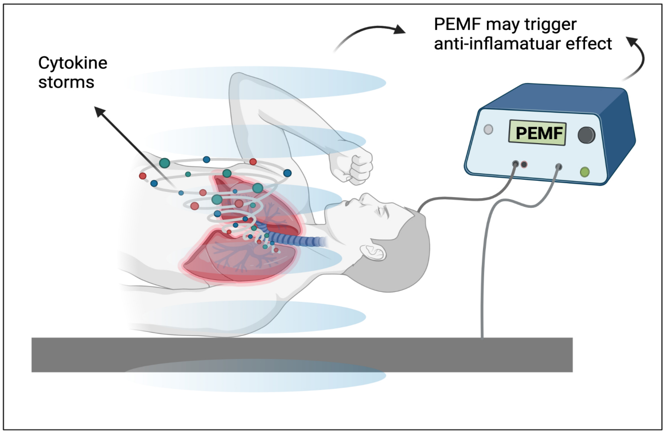

Figure 4. Schematic representation of the potential eff ect of the PEMF on SARS-CoV-2 infected cells to provide targeted therapy to the specifi c area (created with BioRender. com)

When the virus enters into the target cell, the host immune system identifi es the entire virus or its surface epitopes and evokes the host immune response (64). In diff erent immune cells, mitochondria can arrange immunity by regulating both metabolic and physiologic states (65). The immune regulatory eff ects of mitochondria play a substantial role against viral infection (66). In addition, many viral proteins have been identifi ed that regulate mitochondrial ion permeability or membrane potential (67). Mitochondrial antiviral protein, a signaling receptor with the antiviral characteristic on the mitochondrial membrane, is critical for host defenses against viral infection (68). Moreover, mitochondrial dysfunction caused by the virus, such as the loss of mitochondrial membrane potential (MMP), contributes to the progression of COVID-19 (69). The loss of MMP causes energy disproportionation, and triggers reactive oxygen species (ROS) (70), which is considered one of the major reason behind COVID-19 (66). It is particularly critical in patients with respiratory disease as excessive ROS production can damage lung epithelial cells (71). However, ROS production is benefi cial to the host via the immune response (72), but excessive ROS production can attend to the inflammatory storm that damages the host and causes inflammation (73). Therefore, using an antioxidant system to eliminate this excessive ROS would be benefi cial in symptomatic COVID-19 patients (74). However, it is essential to keep free radicals at a critical physiological homeostatic level (75).

3.3. The effects of TTFields on SARS-CoV-2

The non-thermal effects of RF-EMF (TTFields, Novocure Inc, Israel) were clinically approved by the FDA to treat recurrent and newly diagnosed glioblastoma in 2011 and 2015, respectively (76). Also, TTFields was recently approved for first-line treatment of unresectable malignant pleural mesothelioma in 2019, and clinical studies are ongoing in many types of cancer (77). TTFields uses alternating electric fields (1–3 V/cm, 100–300 kHz), which disrupts mitosis on tumor cells, thereby reducing tumor growth (78). In addition, the 100–300 kHz RF field regulates ion channel gates by changing cell membrane potential (79) and mitochondrial membranes (80). Neuhaus et al. showed that TTFields stimulates the voltage-gated calcium channel, trigger Ca^{2+} entry, contribute to the cellular stress response (81), and disrupts the MMP (82). Moreover, the biophysical effects of TTFields include the forced dipole alignment, dielectrophoresis, and delay in cell division of actively dividing cells (76). TTFields has been shown to disrupt the proliferation of tumor cells by interfering with mitosis in rapidly dividing tumor cells (83). Similarly, during SARS-CoV-2 infection, the gradual increase in viral replication rate in infected cells can be considered (84). Therefore, whether TTFields support the SARS-CoV-2 inactivation process is a question worth investigating.

4. Conclusion and future perspective

COVID-19 has become a global risk, and scientists are attempting to investigate antiviral strategies, vaccines, or drugs. Currently, supportive therapeutic approaches and measures remain the best weapons in the combat to control COVID-19. However, the most appropriate therapeutic strategy to combat COVID-19 and associated lung infections remains unclear.

It is known that EMF has a significant impact on clinical cancer treatment, and has potential anti-tumor, anti-mitotic and anti-inflammatory activity. Since EMF exposure is known to contribute to cancer treatment, regardless of the precise mechanism of this interaction, we can try these treatment options for the combat against SARS-CoV-2 infections. In this chapter, we discussed the potential effects of some EMF-derived instruments (mEHT, PEMF and TTFields) on SARS-CoV-2 infection, whose therapeutic ability on tumors has already been approved clinically. Recent studies have been published describing a potential mechanism of EMF with abnormal tissues (8, 10, 12, 14, 29, 34, 42, and these studies have inspired us that EMF can also be used in viral infections. The RF-HT is an optimal supportive treatment for SARS-CoV-2 infections. It includes a special biophysical procedure to select virus-infected cells, depending on their altered electrical conductivity in the near vicinity of cells (14. Therefore, the specific RF-field absorption of the membrane raft may lead to a new therapeutic strategy to combat viral infected cells.

Although the exact mechanism of PEMF has not yet been clarified, its stimulation has shown anti-inflammatory effects. Current evidence suggests that cytokine dysregulation plays a part in the severity of disease causing SARS-CoV-2 (85. In addition, PEMF may have the potential to eliminate this severity induced by cytokine storms. Therefore, the interaction between PEMF and cytokine storm may contribute to future therapeutic research on COVID-19. The TTFields is a non-invasive antimitotic therapy that the FDA has recently approved to treat malignant pleural mesothelioma (MPM (77. Both MPM and COVID-19 affect the respiratory system, and they are similar in some respects, including symptoms (fever, loss of taste, shortness of breath, chest pain, etc. and psychological impact (86. Therefore, based on the treatment success of TTFields in MPM, we propose to apply it to the new COVID-19 challenge.

In conclusion, the well-designed protocol of electromagnetic therapy promises a non-invasive technique to fight viral infections, just as it has succeeded in cancer. We believe that if the non-thermal therapy efficacy of EMF can be further confirmed, it will open up a new and easy treatment strategy for SARS-CoV-2 and any future pandemics. However, as EMF therapy can be a treatment platform for many viruses that require specific frequencies targeting different viruses, time spent now will support all future pandemics.

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CHAPTER 2

OPERATING THEATERS DURING THE PANDEMIC IN TURKEY

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Introduction

The new Coronavirus disease (Covid-19) emerged in Wuhan, China in December 2019 and was declared a pandemic by the World Health Organization in January 2020. Covid-19 virus is a viral disease that is transmitted very quickly between people through close contact and droplets. The rapid spread from China to the whole world occurred easily and within a few months (1). The limitation of information about Covid 19 and its change in life routine has inevitably affected hospitals and many operating room arrangements, as it is everywhere and in all units of all countries. The priorities of the usual situations, the operations performed and the way they are done have necessarily changed; The priority has been to protect healthcare workers and to heal patients diagnosed with Covid 19 in both the service and intensive care units. In this chaotic period, the order of the operating rooms had to change; all priorities have changed (2). It is difficult and costly to manage employees and working environments in emergencies such as disasters or epidemics. With this Covid 19 epidemic, many details that need to be considered have entered our lives and added the new regular expression to our literature (2). In addition, the order of resource use in pandemic management, the health and organization of personnel has been a compelling process requiring detail with newly learned rules (3). Since all health workers and auxiliary personnel, especially physicians in general, are at risk, it has become challenging for these people to work in hospitals, and at the same time, the fact that physicians and health workers are a valuable workforce resource has come in view (4). The first case was reported in Turkey in March 2020 and this difficult process started very quickly. With the ongoing pandemic process, the issue of how to plan surgical procedures has created a difficult process in the management of the virus. Both the necessity of employing surgeons in different areas and the necessity of including the operating room team in the epidemic management forced the suspension of elective surgical procedures in the first period (5). In fact, the surgical team has to be stable; they are irreplaceable and in their absence the consequences can be even worse. Unfortunately, the pandemic has forced us to change this general order. However, deferring elective and postponed procedures during the pandemic process was unfortunately inevitable when the process first started (2). İf patients infected with Covid 19 have to undergo surgery, all necessary precautions must be taken. This puts a strain on the operating rooms and exposes employees to the risk of infection. All known or suspected COVID-19 positive patients requiring surgical intervention to minimize the spread of infection should be treated as positive until proven otherwise. Clearly defined means of personal and environmental protection should be provided for healthcare professionals caring for these patients. The use of specially trained personnel for critical management is most crusial to minimizing the spread of COVID-19. All personnel should be required to wear masks (a face mask with a level 2 or 3 filter (FFP) with a level 2 or 3 filter, depending on the level of aerosol-generating risk), eye protection, double non-sterile gloves, gowns, caps and stockings. However, the main point of attention is the necessity of protecting patients who do not have Covid 19 positivity but need emergency surgery. It should be the most important factor to be planned to take those with Covid 19 disease or suspected cases and those who do not have covid positivity to separate operating room rooms by separate roads. Personal protective equipment should be provided or at least masks should be worn for all non-COVID patients during transfer routes or during all hospital transfers in order to minimize the risk of infection by contact of the sick with others (6). These aforementioned details will be presented in the continuation of our article in the form of determined headings, how they were carried out in the operating rooms of our country during the pandemic process that lasted for more than a year.

What have we done in the operating theatres in Turkey during the last 18 months?

1. **How did we protect ourselves as healthcare professionals in the operating room?**

With the spread of the corona virus around the world, emergency meetings were held in centers where many surgeries were performed, and algorithms were organized to protect personnel with personal protection equipment (PPE) (7). Guidelines for the determination of these algorithms were made by considering the historical data of SARS virus and ebola virus (8,9). These guides have been prepared by the infectious diseases control committees in many countries, personal protective equipment has been listed, and methods accepted all over the world have been quickly implemented in our country. Recommended PPE for contact with critically ill patients with confirmed or suspected 2019-nCoV infection includes liquid resistant gowns, gloves, eye protection, full face shields, and suitably tested N95 respirators (10). In addition to these, caps and hair covers are among the preferred protection methods to cover the hair. Eye protection with side shields or goggles will also increase protection if exposure comes from the side. Full face shields can provide both eye protection and prevent facial and respiratory contamination. Worn shoes must be impermeable and disinfectable. Staff should wear operating room clothes under PPE (11). The most commonly used respiratory PPEs currently include surgical masks, N95 respirators, and electrical air-purifying respirators. Surgical masks are usually plentiful and disposable. They form a physical barrier between the wearer's mouth and nose and potential pollutants in the immediate environment. Masks vary in quality and level of protection. N95 respirators have the advantage of blocking at least 95% of aerosol (<5 μm) and droplet size (5-50 μm) particles. Their use requires initial and periodic fit testing and is associated with poor tolerance by users due to respiratory resistance and heat. N95 respirators comply with the European filter facepiece 2 standard with a filter capacity of at least 94% (12). Electric air blowers are battery operated blowers that provide positive airflow through a filter. The filter type is determined by the amount of pollutant exposure in the air; they provide head and neck protection and do not require fit testing, especially if there is no tight-fitting facepiece. However, these masks are generally associated with increased perception of dry eye and are by far the most expensive PPE (12). Since the beginning of the epidemic in Turkey, personal protection methods have been used at the same standard as the countries in the world, and these protection methods have been tried to be applied in all areas, whether in pandemic services, intensive care units and operating rooms (13). Although operating rooms are one of the important places of patient entrance and exit, aerosol spread and one-to-one respiratory exposure; They are not environments where patients can be isolated as much as intensive care or pandemi services. Isolation and protection are important as respiratory droplets are found within one meter of the patient when coughing or sneezing. The possibility of airborne transmission in the operating room is very high. Applications such as endotracheal intubation, bronchoscopy, open aspiration, nebulized therapy, manual ventilation before intubation, prone positioning, weaning the patient from the ventilator, non-invasive positive pressure ventilation, tracheostomy, High Flow Nasal Oxygen (HFNO) and cardiopulmonary resuscitation (CPR) are done every day in the operating room routine. If these are taken into account, it will be realized how important the protection of personnel is (14). In this period, the use of N95 filter masks has now become a routine practice in operating rooms, while applications are made to patients with suspected or determined positivity and negative ones. The use of PPEs for non-positive patients is individualized, but for positive patients, full protection of staff has been sought in all centers of the country. Although all protection methods are known and tried to be applied by health workers, unfortunately, virus contamination has also occurred among some health workers and some health workers have died because of this (15,16).

2. What precautions did we take while taking our patients into surgery?

Surgical patients have unique risks due to COVID-19. Surgery increases the risk of perioperative morbidity and mortality in patients with asymptomatic or symptomatic COVID-19 (17). In a study conducted in Italy, the 30-day mortality of Covid 19 positive patients who underwent surgical operation was found to be higher than non-surgical positive patients (18). In order to protect both patients and healthcare workers, testing all patients for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prior to operations is actually a recommended procedure all over the world . It was possible to detect covid positive patients with preoperative test screening, and the interventions of these patients were postponed for 14 days (19). Although the tests performed maximum 72 hours before are accepted, new studies are required for safer intervals. It is also among the observations that preoperative tests are important during the epidemic in elective or mandatory surgeries all over the world (20). Positive test result rates vary from region to region, depending on the prevalence of COVID-19 in the community. It is imperative to detect asymptomatic patients with SARS-CoV-2 infection so that their surgery can be safely postponed. This process protects the patient and healthcare worker by avoiding unnecessary exposure to patients infected with SARS-CoV-2 (17). In our country, PCR tests are applied to patients before they come to the operating room during the preoperative preparation stage of elective surgeries. This interval is generally limited to 48 hours (21). While the patient is taken to the operating room, ventilation and room preparation should be planned. The patient should wear a face mask during transport. PPEs of all operating room personnel involved in patient care should also be checked. Hand hygiene should be observed in contact with the patient. The protection of patients and employees should be a priority, and the number of people in the operating room should be minimized (6).

3. How did we manage and plan the operating room?

Previously identified COVID operating areas (COA) should be allocated to emergency operations of COVID patients. The operating room reserved for COVID patients should be the closest to the operating room entrance. When more than one operation is required at the same time, operating rooms should be used in order of proximity to the operating room entrance to minimize environmental contamination in the operating room block (2). Operating room staff should be at least in number to complete the procedure. If the trainees are not required in the environment, they should not be included, the planning should be done with senior and knowledgeable personnel, and the personnel who are not needed should preferably be excluded. Disposable equipment should be preferred. There is an obligation to designate a separate hall or small operating room complex for suspected or confirmed COVID-19 patients. Frequent air changes (25 per hour) should be guaranteed in the operating room rooms. Special areas should be designated for donning and removing PPEs, all doors of the operating room should be locked, and traffic entering and exiting the operating room should be strictly controlled. A contaminated area, a potentially contaminated area, and a clean area should be defined and buffer sections should be created (3,22). All surgical procedures for these patients are recommended to be performed in a negative pressure room if available. Especially aerosol-generating procedures such as intubation and tracheostomy opening require a negative pressure room, including catheter insertion, bronchoscopy, and endoscopy (21). If the air leaving the room is to be recirculated, it should definitely be passed through the HEPA filter. In order to prevent air leaks, the room must be well insulated (23). Under the conditions of our country, all the procedures performed above are tried to be applied in the world, and in this process, especially the separation of operating rooms and the practices of negative pressure operating rooms have gained continuity (5). These measures were also reported to all operating room personnel as a guide by the Turkish Ministry of Health and put into practice . In this guideline, operations should not be planned for all rooms at the same time, in order to protect teams and resources while planning surgeries during this period. While preparing the daily surgery lists, the time to be left between cases was reported as 2 hours, and it was emphasized that sufficient time should be allocated for cleaning the room after each surgery (24). This is the time required for the mechanical and chemical dirty cleaning to be done and for the disinfectant material to contact the surface. In addition, time will be allowed for the circulation of the air present inside. Especially when planning aerosol-related procedures (intubation, tracheosotomy, endoscopy, etc.), the anesthesia and surgical team should consist of the least possible number of personnel, the entrance and exit to the room should be restricted, and the passage of the team working on the infected patient to other rooms should be prevented (25). In addition, continuous supply of alcoholic disinfectants in patient contact areas and room cleaning with ultraviolet rays are among the operating room cleaning procedures applied in the world and in our country (14).

4. What were the changes and precautions in anesthetic procedures?

During the pandemic period, anesthesia practices include changes to be more careful and primarily to protect the people who apply anesthesia. All patients who will receive anesthesia should be operated after planning in accordance with the operating room conditions during the epidemic period. If general anesthesia is to be performed after all the above-mentioned precautions are taken, the patient should be masked and intubated by the senior anesthesiologist. This will minimize aerosol leaks and possible contamination (1,21). The use of videolaryngoscopy has been very important in this period and has caused a shortening of the duration of intubation and this has reduced the risk of transmission of healthcare workers (1). In our country, intubation with videoringoscopy has become a new technological application that has increased even more during the pandemic period, and it is used in most hospitals during this epidemic period for more than one year. In addition, the number of filters used in patients to prevent contamination has been increased to two, which is an accepted practice in the world (3). The American Patient Safety filter efficiency unit also stated that it is safe to use these two viral filters to be placed in the mask mouth and on the expiratory side (14). Rapid serial intubation has come to the fore again in this pandemic period, and clamping the tube after intubation has become one of the recommended practices all over the world (2). Deep muscular blockade during anesthesia and getting help from reversing agents during extubation are also among the recommendations (1). After the patient is awakened, masks should be worn on the patients, all materials used should be thrown into the medical waste box with gloves, and all surfaces should be disinfected with alcohol, in line with the warnings (24) in our country, the patient's operating room and anesthesia practices continue.

5. What types of surgeries were performed during the pandemic period? Electives / Emergencies ?

A guideline for surgical procedures was published in March 2020, immediately after the declaration of the pandemic. In terms of the safety of emergency and oncological surgery priorities and laparoscopic methods, safety and not victimization of patients have been brought to the agenda (26). During this period, elective operations were postponed in our country, especially in the hospitals declared as pandemic hospitals. mostly emergency and oncological cases were operated (27). In this process, elective procedures were suspended for a while in order to use the workforce and resource utilization effectively in most hospitals and clinics around the world. The American Surgical Society also suggested postponing elective interventions in March 2020 (28). it is emphasized to ensure that patients and team workers are protected when emergency surgery is required (28). The effects on patients with cancer or chronic debilitating disease whose surgery was canceled due to fears in the postponement of elective surgeries and strict precautions and on patients awaiting organ transplantation are still under investigation (17). Despite the additional surgical risks associated with the pandemic, determining which surgical procedures are indicated and should be continued during this period should be the main goal. Almost all published articles agreed on the suspension of elective procedures for benign pathologies, except for complicated cases requiring immediate/immediate treatment (17,26,28). The aim of these published articles is to reduce the risk of in-hospital transmission and cross-infection. In some cases that usually require emergency surgery (such as uncomplicated acute appendicitis or acute cholecystitis), conservative treatment such as antibiotics or radiological drainage should be considered if clinically possible (29). In emergency bowel resection, creating a stoma may be a better option than primary anastomosis to reduce the risk of complications and infection (30).The recommendations suggest that the multidisciplinary approach continues for surgical oncology patients. First of all, more conservative and non-invasive approaches such as neoadjuvant chemotherapy and radiotherapy should be considered, and if possible, endoscopic resection should be performed or interventions should be postponed (28). Similar practices to those in the world have been introduced in our country since March. Unfortunately, when the possibility of progression in cancer stages of many cancer patients is considered, surgical procedures, especially oncological surgeries, started to be performed on the condition that precautions are followed (27,31). It has been emphasized in many publications that the risk of transmission and the need to calculate the profit-loss ratio in the progression of cancer stage. In a study conducted in our country, especially on gynecological surgeries, the results showed that the rate of transmission was low, and it was reported that 1% of patients had Covid-related symptoms (31). Still another curiosity is the elective surgeries in the pandemic. The recommendations state to triage elective surgeries according to the capacity and condition of the hospital. This should depend on hospital resources and the current Covid patient load (26). The recommendation of the American Surgical Association also divided the pandemic conditions into 3 parts. In phase I (there are few cases of COVID-19 in the hospital), elective surgery is limited to patients who are unlikely to survive if not operated within 3 months, whereas only emergency and necessary surgeries are performed in phases II and III (28). In another study, the process in the pandemic should be divided into 4 stages in hospitals. During the alert phase (in the absence of COVID-19), elective surgery is performed as usual; As COVID-19 cases increase rapidly, a 50% reduction should be initiated and eventually suspended completely, with only urgent/urgent cases (32). Recommendations for laparoscopic surgery practices are stated in the guidelines, but priority is focused on the risk of covid transmission by staff from laparoscopic gas exposure. The guideline recommended that laparoscopic surgeries not be performed if this risk exists . During the pandemic period, laparoscopic applications should be preferred only in selected cases and for patients in whom minimally invasive surgery is more beneficial with a small number of personnel (26). Considering the conditions in our country, normalization started after a while and elective surgeries were allowed with various recommendations and precautions. Each institution should establish a roadmap for resuming elective surgery with a multidisciplinary team, taking into account local factors, patient volume and diversity, resource planning, and role in the pandemic. A reduction period in the number of patients in the last 14 days is recommended, both in the region and in the hospital, before resuming elective surgery. In the light of the protective measures mentioned above, staff and patient safety should be at the highest level. Elective surgeries can be initiated by arranging the isolation of patients with and without Covid 19. With these recommendations (33) we continue with surgical practices today.

Protection and transport of postoperative patients

The post-operative transport of Covid-positive patients during the epidemic has also been an important issue. Many studies have been carried out on this subject and have been published with recommendations in the guides. After surgery, a Covid positive patient should be taken to the Covid service or, if needed, to intensive care units with covid positive patients. The priority in this regard is the protection of the personnel who will carry out the transport of the patient (1). The number of transport teams should be minimal and patients should be transported on closed stretchers without being admitted to the post-anesthesia care unit (1, 22,34). Post-anesthesia care units are places where circulation is fast. Therefore, patients should be taken to their wards quickly in order to prevent the risk of contaminating the environment. Covid positive should not spend a long time in the operating room. In the meantime, both the patient and the personnel in charge of transportation should use N95 masks if possible (1). In our country, these applications were implemented as a result of the recommendations. If the patient with COVID-19 is stable after surgery and does not need intensive care, the warnings can be taken directly to negative pressure rooms or isolated service rooms, which are also stated in the recommendations of the Ministry of Health, and the transfer of patients is provided within this framework (35).

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CHAPTER 3

SARS-COV-2 ASSOCIATED MULTI-SYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) infection was first diagnosed in Wuhan, China in late 2019 and extended all over the world from there. The name of the disease was determined as COVID-19 in February 2020 by World Health Organization (1,2). On March 11, 2020, WHO announced that they considered COVID-19 as an pandemic (3).

There are four different genera of coronaviruses (alpha, beta, gamma, and delta). SARS-CoV-2 is a new type of beta coronavirus. These viruses contain single-stranded RNA and an enveloped capsid with a spike protein (4). All genus of coronaviruses often causes mild upper respiratory tract infections. They can produce life-threatening illnesses in infants, those with underlying diseases, and the elderly. SARS-CoV-2 is 79.6% similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and 50% similar to Middle East respiratory syndrome coronavirus (MERS-CoV) (4,5). Like SARS-CoV-2, these two viruses also commonly lead to a milder clinical course in young people. Children of all ages may be affected by COVID-19, but patients younger than 14 are less severely affected by COVID-19 than adults. As a person's age increases, the risk of disease also rises (4). Two percent of all COVID-19 cases in the world occur in children under 18 years of age (6,7).

SARS-CoV-2 was transmitted from person to person very quickly, which soon led to a worldwide pandemic. Acute infection caused by SARS-CoV-2, progressed with mild symptoms such as fever, and cough in children in the first months of the pandemic (4). Towards the end of April, fever, gastrointestinal symptoms, and myocarditis findings accompanied by coronary artery aneurysm began to be observed in some children. Initially, these symptoms were evaluated as entities like Kawasaki disease, toxic shock syndrome, and secondary hemophagocytic lymphohistiocytosis, but with increased cases identified as a new pediatric syndrome called multi-system inflammatory syndrome (MIS-C) associated with SARS-CoV-2 (4). While the COVID-19 nasopharyngeal PCR test of most of these children was negative, anti-SARS-CoV-2 antibodies were found to be positive. Therefore, MIS-C has been evaluated as a postviral inflammatory disease (8,9).

Epidemiology of MIS-C

Although the frequency of MIS-C is not known yet, it is thought to be a rare complication due to COVID-19 in children. In the literature, the incidence of MIS-C was calculated at approximately 2 in 100,000 children (10).

While acute COVID-19 was very common in children in China and other Asian countries when the pandemic began in the first few months of 2020, there were very few published MIS-C cases in these countries. Initial reports suggest that black and Hispanic children are more commonly affected than Chinese and Asian children (11).

These patients' symptoms and signs may suggest complete or incomplete Kawasaki disease (KD), but MIS-C is usually seen in older children and adolescents. In contrast, KD is often seen in infants and younger children. Acute COVID-19 progresses more seriously in patients under the age of one year and in children with underlying diseases (11). In contrast, MIS-C cases are older, and these patients typically have no underlying comorbid diseases (10).

In many studies, MIS-C was reported a few weeks after COVID-19 infection, and it was thought to be a post-infectious complication rather than a separate acute infection (10,12,13,14).

Pathophysiology of MIS-C

Like other beta coronaviruses, SARS-CoV-2 also shows tropism for epithelial cells of the lungs and gastrointestinal tract as well as for myocardial and endothelial cells. SARS-CoV-2 binds to the angiotensin converting enzyme 2 (ACE-2) receptor, which is located on the spike protein found on the cell surface. When the virus binds to the receptor, it can then enter the cell (15).

The incubation period of acute infection is approximately six days. Unlike other beta coronaviruses, most of the SARS-CoV-2 virus is isolated from the upper respiratory tract during acute infection. In addition, the viral load is highest during the initial period of symptoms and gradually decreases as the days pass (16).

Although current epidemiological findings indicate that MIS-C occurs after SARS-CoV-2 infection, no definitive information is available regarding the possible association between these two entities. In regions where COVID-19 is common, dramatic increases were seen in cases showing Kawasaki disease-like symptoms approximately one month after acute SARS-CoV-2 infections. This condition was thought to develop secondary to the inflammatory response in individuals with SARS-CoV-2 (17). While SARS-CoV-2 serology was positive in most patients with MIS-C symptoms, nasopharyngeal real-time polymerase chain reaction (RT-PCR) tests were positive in just a few limited patients. This finding suggests that MIS-C disease is a post-infectious condition rather than an acute infection (17). Of the 783 MIS-C children described in the literature thus far, 60% had positive SARS-CoV-2 antibody but negative PCR results; in 34%, both tests were positive, while 5% received negative results for both tests (11-14,18,19).

Severe respiratory failure in adults due to SARS-CoV-2 generally occurs about one week after the onset of the first symptom due to cell damage and dysregulation in the immune system that is a direct effect of the virus. Irregularity in the immune system is characterized by lymphopenia (especially a decrease in natural killer [NK] cells, CD4 T-helper cells, and B-lymphocytes) and the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (20). The milder respiratory symptoms observed in children during acute infection compared to adults are thought to be due to low gene expression of the ACE-2 receptor, which is common in pediatric patients (21,22).

SARS-CoV-2 infection can be classified into three different clinical stages. Stage 1 is the early stage of infection, where children are asymptomatic or mildly symptomatic. The second stage is the pulmonary phase, and although it is severe in adults, children report only mild symptoms or remain asymptomatic in this stage. In Stage 3, the stimulation of B-cells and plasma cells can cause a hyperimmune response that leads to MIS-C symptoms (17). It is not clear yet by what mechanisms and how SARS-CoV-2 stimulates the abnormal immune response.

The mechanism of cardiac involvement in MIS-C is also not clear. It may be due to systemic inflammation or to viral myocarditis, hypoxia, or stress cardiomyopathy (23). Since different mechanisms are responsible for cardiac involvement in each patient, the severity of the involvement may also be very different (11).

The fact that MIS-C is not seen as often in China and other Asian countries as it is in European countries emphasizes the importance of genetic infrastructure in patient presentation (17).

Clinical Findings

Although the findings of MIS-C have been defined with the published cases and case series, our knowledge is still limited and continues to develop with each new case.

Cases are generally seen between the ages of 2 and 16. Most patients have a fever for three to five days. Gastrointestinal system symptoms (nausea, vomiting, abdominal pain, and diarrhea) are most frequently observed along with fever. The symptoms of conjunctivitis and rash are reminiscent of Kawasaki disease. Central nervous system findings, such as headache, restlessness, and encephalopathy, may also be reported (17). Hypotension, which may lead to the need for intensive care, is observed in some patients. Respiratory distress secondary to cardiac failure may require invasive or noninvasive mechanical ventilation. Although decreased ventricular function is the most common echocardiographic finding, valve regurgitation and dilated coronary arteries may also be seen (17,18).

According to published cases and case series, 22–64% of MIS-C patients meet the complete Kawasaki criteria. In addition, 32–76% of all cases present with signs of shock, and 51–90% display signs of myocardial dysfunction. Serositis, acute kidney injury, and hepatitis or hepatomegaly have also been described as less-common findings. Central nervous system findings (such as encephalitis, seizures, and coma) are the least commonly reported clinical findings (11).

Laboratory Findings

A specific diagnostic laboratory test is not yet available. The diagnosis of MIS-C is therefore usually made by evaluating the clinical, laboratory, and epidemiological factors together.

Laboratory tests recommended for patients presenting with a suspicion of MIS-C are as follows: complete blood count, serum electrolytes, liver and renal function tests, cardiac markers (such as troponin and N-terminal Pro-Brain Natriuretic peptide [NT-ProBNP]), inflammatory parameters (C-reactive protein [CRP], procalcitonin [PCT], erythrocyte sedimentation rate [ESR], ferritin), blood gas analysis, coagulation parameters, fibrinogen, D-dimer, blood cultures, and SARS-CoV-2 serology and PCR (17).

In general, there is a significant increase in inflammatory markers (such as CRP, ESR, PCT, and/or ferritin) upon laboratory testing in MIS-C patients. In published cases and case series, the levels of inflammatory markers seem to be related the severity of the disease. As the severity of the disease increases, inflammatory markers also increase. (11).

Other common findings are hyponatremia, acute kidney injury, hypoalbuminemia, mildly elevated liver enzymes, elevated lactate dehydrogenase, and hypertriglyceridemia in some patients. The levels of cardiac biomarkers (such as troponin, and NT-ProBNP) also increase significantly and typically indicate cardiac failure and shock. An increase in the neutrophil count, a decrease in the lymphocyte count, a low or normal platelet count, an increase in the D-dimer level, and a low fibrinogen level may also be present (11).

Echocardiography may reveal decreased left ventricular function, coronary artery abnormalities (dilatation or aneurysm), mitral valve regurgitation, and pericardial effusion (24,25). Depending on the clinical findings of the patients, imaging methods (such as chest radiography, computed tomography [CT] of the chest, and abdominal ultrasound or CT) can be performed (12,14,19). Pleural effusion, patchy consolidation, or ground-glass opacification may be seen in the lungs (11). Free fluid, ascites, intestinal and mesenteric inflammation, and terminal ileitis may be present on abdominal imaging (26).

Evaluation of MIS-C

Laboratory studies should be performed to evaluate inflammatory markers as well as heart, kidney, and liver function in patients with suspected MIS-C. SARS-CoV-2 PCR and serology tests should also be carried out at the same time (11).

According to the guidelines of the American College of Rheumatology and the National Consensus Management Working Group of SARS-CoV-2 (PIMS-TS) in the United Kingdom, the recommended algorithms that should be applied to the patients with suspected MIS-C are as follows (27,28):

-Children presenting with moderate or severe MIS-C symptoms should have the following tests: Complete blood count, inflammatory markers, liver and kidney function tests, lactate dehydrogenase, urinalysis, coagulation parameters, cardiac markers (such as troponin and NT-ProBNP), and a cytokine panel evaluation are recommended.

-Pediatric patients who present with mild MIS-C symptoms should undergo more limited tests, such as a complete blood count, CRP, kidney function testing, and serum electrolyte analysis.

Clinicians who follow-up with moderate and severe MIS-C patients can also perform additional tests (such as blood, urine, throat, and/or stool culture as well as serology and PCR for other viruses) to fully explore differential diagnoses (29).

Definition of MIS-C

On May 13, 2020, the American Center for Disease Control (CDC) published a case definition for MIS-C based on the findings of reported patients (30) and was defined accordingly:

1- In children younger than 21 years old.
2- Clinical criteria: Documented or declared fever > 38°C for 24 hours or longer, serious illness requiring hospitalization, symptoms of 2 or more systems involvement such as cardiac, renal, respiratory, hematological, gastrointestinal, cutaneous and central nervous system involvement.
3- Laboratory evidence of inflammation: Increased levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin (PCT), D-dimer, ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6) and neutrophils, and/or decrease in lymphocyte and albumin levels. At least one of these laboratory findings must be present.
4- Laboratory or epidemiological evidence of SARS-CoV-2 infection: SARS-CoV-2 PCR positivity in the nasopharyngeal sample or antibody positivity in the plasma or a history of contact with individuals who have had COVID-19 in the past four weeks.
5- Lack of an alternative diagnosis.

Among these findings, fever + inflammation findings + multiple organ involvement + association with COVID-19 + failure to make another diagnosis, make the diagnosis of MIS-C.

Differential diagnosis

Clinical and laboratory findings of MIS-C are mostly confused with acute COVID-19, Kawasaki disease, toxic shock syndrome, and hemophagocytic lymphohistiocytosis (11,17).

Hemophagocytic lymphohistiocytosis (HLH) is a serious condition with high morbidity and mortality. The most common manifestations of HLH are fever with splenomegaly, cytopenia (anemia, thrombocytopenia, and neutropenia), hypertriglyceridemia and/or hypofibrinogenemia, ferritin ≥500 mg/L, CD25> 2400 U/ml, and low or no NK cell activity. Cardiac and gastrointestinal findings are less common in HLH (11).

The clinical and laboratory findings of MIS-C are most like Kawasaki disease and toxic shock syndrome (17). The comparison of Kawasaki disease, MIS-C, and Toxic shock syndrome in terms of clinical and laboratory findings can be seen in Table 1.

Table 1. Comparison of clinical and laboratory findings of MIS-C, Kawasaki Disease, and Toxic Shock Syndrome

	MIS-C	Kawasaki Disease	Toxic shock syndrome
Age	2-16 y	Younger	Younger
Mucous membrane involvement	±	+	±
Rash	+	+	Erythrodermia
Desquamation	+	+	+
Altered mental status	+	Rare	+
Respiratory distress	+	Rare	±
WBC count	Lymphopenia, neutrophilia	Neutrophilia	Neutrophilia
Platelets	↓	↑	↓
Fibrinogen	↓, Normal,↑	Normal	↓
D-Dimer	Normal, ↑	Normal	↑
CRP	↑↑	↑	↑
Ferritin	↑	Normal, ↑	Normal
Pro-BNP	↑↑	Normal, ↑	N/A
Coronary artery aneurysm dilatation	+	+	-
Ventricular disfunction	+	±	Rare

MIS-C: COVID-19 associated multisystem inflammatory syndrome, WBC: White blood cell, CRP: C-Reactive protein, Pro-BNP: Pro-B type natriuretic peptide

In addition, other infectious and inflammatory conditions such as sepsis, appendicitis, other viral infections, systemic lupus erythematosus, and vasculitis should be considered in the differential diagnosis of MIS-C (11).

Management of MIS-C Patients

Patients diagnosed with MIS-C can be followed-up in the ward or pediatric intensive care unit, depending on their disease severity. Critical illness and hypotension may develop rapidly in these children. Patients with hemodynamic instability, respiratory failure, and serious, life-threatening diseases should be monitored in the intensive care unit (31). Patients with normal vital signs and physical examinations can be followed closely via outpatient clinics. However, it is necessary to be sure that patients with fever has continued for 48 hours or more will come back for control (31).

The main purpose of treatment is to improve organ function by reducing systemic inflammation. At the same time, mortality and long-term sequelae may also be prevented with adequate treatment (17). Clinicians should determine the treatment course for patients with MIS-C using the patients' clinical and laboratory findings.

Shock: Treatment of patients presenting with shock symptoms should follow the standard shock protocol. Most patients with identified MIS-C present with shock that is resistant to fluid therapy. Vasoactive agents, such as adrenaline or noradrenaline, are recommended in the treatment of fluid-refractory shock. Milrinon may also be considered in the presence of signs of left ventricular dysfunction (31).

Cardiac dysfunction: Cardiac involvement usually presents as left ventricular dysfunction or arrhythmia. Monitoring of cardiac markers (such as troponin and NT-Pro BNP) and serial echocardiographic assessments provide guidance in treatment. Intravenous immunoglobulin and systemic corticosteroids are recommended for the treatment of all patients with cardiac involvement (31).

Since MIS-C can often mimic septic shock and toxic shock syndrome, it is recommended that these patients receive broad-spectrum antibiotic therapy upon admission. Clinical and laboratory findings and organ involvement should also be considered when selecting antibiotics (32).

MIS-C is seen as a post-infectious complication of COVID-19 rather than a distinct acute infection. Therefore, antiviral therapy (e.g., Remdesivir) is not recommended in these patients unless SARS-CoV-2 PCR testing is positive (31).

Immune Modulatory Therapies

Intravenous Immune Globulin (IVIG): Intravenous immunoglobulin therapy is recommended for all patients with MIS-C. As in Kawasaki disease, IVIG treatment is recommended to be administered at a rate of 2 g/kg for 8–12 hours. It may also be given over two days to patients who cannot tolerate fluid overload due to left ventricular dysfunction (27). Since the ESR level may increase after IVIG treatment, patients should also have other unaffected inflammatory markers (such as CRP and ferritin) monitored (31).

Glucocorticoids: Corticosteroids reduce the secretion of many cytokines and reduce inflammation by suppressing proinflammatory cells (33). Corticosteroids are recommended for patients with MIS-C who present with moderate and severe symptoms and also for patients whose fever and inflammatory markers do not decrease despite IVIG treatment(31).

Glucocorticoid therapy should be started with 2 mg/kg/day intravenous methylprednisolone given in two doses. If the patients demonstrate a clinical response and are to be discharged, it is recommended to continue the same dose of oral prednisolone for three to four weeks (27). Pulse methylprednisolone treatment (30 mg/kg/day, maximum 1 g) is recommended in the presence of serious life-threatening diseases or resistance to other treatment (27).

Anti-cytokine treatment: Anakinra inhibits the proinflammatory pathway associated with IL-1. It is an IL-1 receptor antagonist (34). Tocilizumab is an IL-6 antagonist and inhibits the effects of IL-6. IL-6 is the major proinflammatory cytokine (35). Infliximab is an anti-cytokine agent that blocks TNF-α and therefore plays an important role in the treatment of MIS-C (4). During MIS-C treatment, patients should consult with a pediatric infectious disease specialist and a rheumatologist. When initiating anti-cytokine treatments, the severity of the disease and the levels of inflammatory markers should both be considered.

Anti-Thrombotic treatments: Patients with MIS-C, especially those with left ventricular dysfunction or coronary aneurysm, are at risk for thrombotic complications. Therefore, it is recommended that these patients be started on a low-dose aspirin, which is also used in Kawasaki disease (31).

Anti-thrombotic therapies should also be considered in patients with a life-threatening disease or at high risk for thrombotic complications (31).

Follow-Up of MIS-C Patients

Adequate data are not yet available on the long-term follow-up protocol for patients with MIS-C. Therefore, it has been suggested that these patients can be followed-up in the same manner as Kawasaki disease patients until sufficient data are available. The recommended frequency of echocardiography and cardiac markers should be determined according to the severity of cardiac involvement. Since there is not enough information about the clinical course of MIS-C, testing should occur more frequently in the first few days, and then the intervals should gradually increase (4,31). At the same time, cardiac magnetic resonance imaging can be performed in patients up to three months after admission to identify any chronic cardiac involvement (4).

Summary

Acute infection of COVID-19 in children is usually asymptomatic or only mildly symptomatic. MIS-C has been defined as a postinfectious delayed complication due to SARS-CoV-2. The clinical and laboratory findings of the disease are similar to Kawasaki disease, toxic shock syndrome, and hemophagocytic lymphohistiocytosis. MIS-C is mostly seen in older children and adolescents. A persistent fever lasting from three to five days is present in all patients. Gastrointestinal system findings, such as abdominal pain, vomiting, and diarrhea, are also common. Cardiac involvement may present as left ventricular dysfunction, coronary artery aneurysm, or arrhythmia. The diagnosis of MIS-C is based on clinical findings, laboratory tests, and the results of SARS-CoV-2 PCR and serology testing. The first-line treatment for MIS-C is IVIG + aspirin, as in Kawasaki disease. Corticosteroids and anti-cytokine treatments may be added according to the severity of the disease and the patients' response to first-line therapy. However, more studies are needed on the conditions that predispose the disease, its pathogenesis, and treatment preferences.

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CHAPTER 4

COVID-19 AND GERIATRICS

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1. Introduction

According to the age group categories of the World Health Organization (WHO), 18-65 years old as young adults, 66-79 years old as elderly, 80 years and over as very old people[1]. Aging, which progresses with increased mortality and morbidity, is a universal process[2]. Physiological, cellular and molecular variations also affect the definition of aging[3]. Based on population growth estimates, it is thought that the number of people aged 65 and over will increase to approximately 1.5 billion in 2050, and most of this increase will occur in developing countries. The percentage of the elderly population in the world is gradually increasing, the elderly category constitutes approximately 20% of the population of Europe and the USA and approximately 28% of the population of Japan. In addition, the pharmaceutical expenditure of the elderly constitutes approximately 42% of the total load[4-6].

Polypharmacy, which is a risk factor for adverse drug reactions, especially in the elderly, may result in undesirable consequences such as hospitalization and death[7,8]. Therefore, elderly individuals are more susceptible to polypharmacy and pharmacokinetic risks compared to young adults[9]. Applying appropriate drug therapy is difficult and important in the elderly with a high risk of drug-related systemic side effects[10].

Age-related changes in the body must be known for rational drug use[11]. In the treatment of acute and chronic diseases with drugs, the physiological changes that occur due to aging in elderly patients should also be well known against the risk of drug-related adverse effects[12]. Age-dependent pharmacokinetic properties are important for evaluating drug activity. Pharmacokinetics is the changes a drug undergoes in the body, and examines the absorption, distribution, metabolism and elimination of the drug. Pharmacokinetic differences arise among elderly patients due to the decrease in organ functions, multiple organ failure and the coexistence of more than one disease with aging. Major changes in drug response occur due to differences in pharmacokinetics[13]. In addition, various factors such as dehydration and muscle atrophy seen in the elderly can lead to significant changes in drug pharmacokinetics[10]. For this purpose, the effects of aging on drug pharmacokinetics are analyzed during drug development phases[14].

1.1 Absorption

Drug absorption is thought to be the least affected parameter among pharmacokinetic changes with aging[15]. Delay of gastric emptying, decreased absorption surface and decreased gastrointestinal motility seen in the elderly, slightly reduce drug absorption[16]. In addition to drugs, there is a decrease in the absorption of iron, calcium and sugar with aging[17]. Decreased intestinal peristalsis in the elderly may occur due to existing diseases or various neuronal losses[18]. Despite the changes related to absorption, the absorption of most drugs that undergo passive diffusion remains the same in the elderly[18]. Unlike passive diffusion, there may be a decrease in the absorption of some drugs with carrier-mediated diffusion in the small intestinal epithelium[19].

In addition, it has been previously reported that gastric acid secretion decreases in the elderly[20]. However, in recent studies, it has been observed that there is no relationship between gastric acid secretion and aging[21,22]. In the elderly, the return of gastric pH value to its initial level after eating is delayed, which may change the absorption of drugs whose absorption is pH-dependent[23].

In relation to drug absorption, splanchnic blood flow and intestinal surface area decrease with aging[24]. Small intestine motility generally does not change with aging[25].

The bioavailability of an orally administered drug depends on several parameters, such as the fraction of drug absorbed from the gastrointestinal tract and the first-pass effect through the liver. Age-related changes in these parameters affect the oral bioavailability of drugs. The area under the curve

(AUC), which is one of the bioavailability indicators of drugs, changes little with aging[26].

As a result of thinning of the epidermis layer in the elderly, the absorption of transdermally administered drugs may increase, making elderly patients more susceptible to the side effects of drug[27]. However, as the tissue blood perfusion reduces in the elderly, it is possible that the absorption of transdermally administered drugs may decrease[28]. With aging, muscle mass and muscle tissue perfusion decrease, which may reduce the absorption of drugs administered intramuscularly[29]. The reduction of alveolar surface area in the elderly may reduce the absorption of drugs administered by inhalation[30].

1.2 Distribution

The decrease in the level of albumin, which plays a role in the distribution of drugs in the body, with aging may increase the free fraction of acidic drugs that are highly bound to albumin and may intensify the drug effect[16]. The decrease in albumin level due to aging increases the free fraction of drugs by approximately 10%[31]. Unlike albumin, the level of α1-acid glycoprotein, another protein that plays a role in distribution, tends to increase in the elderly. These changes in protein level are actually thought to be associated with pathological and physiological changes, not with age[32]. Changes in the binding of drugs to plasma proteins may cause significant complications and clinical interactions, especially for drugs with a narrow therapeutic range[22].

As a result of the increase in body fat ratio and decrease in body water ratio in the elderly, the distribution volume of lipophilic drugs increases and their half-life is prolonged. On the contrary, it is seen that the distribution volume of hydrophilic drugs decreases[33]. Besides, as a result of the decrease in the total water ratio of the body, an increase may be observed in the plasma concentrations of some drugs administered intravenously[34]. The main reason for the decrease in water ratio of the body is intracellular water loss, but the extracellular water ratio generally remains constant[35].

Studies have shown that the function of P-glycoprotein efflux pump, which is responsible for drug distribution in tissues such as the blood-brain barrier and liver, decreases with aging[36]. The permeability of the blood-brain barrier, which has a protective barrier role in the distribution of drugs, increases in the elderly, which may increase drug passage to the central nervous system and cause drug-related adverse effects[37].

1.3 Metabolism

The mass of the liver, which plays a major role in drug metabolism, is reduced by 25-35% and liver blood flow is reduced by 40% in the elderly[19]. In addition, the expression of some proteins synthesized by the liver changes with aging[38]. Studies have found that the synthesis of bile acids synthesized by the liver decreases with aging[39]. As a result of the decrease in epidermal growth factor concentration in the elderly, the regeneration ability of the liver decreases over time[40].

Phase-1 drug metabolism reactions through the Cytochrome P450 (CYP) system may change as a result of the decrease in liver blood flow and liver size due to aging[41]. However, phase-II drug metabolism reactions are less likely to change with age[42]. A study has shown that sulfation and glucuronidation phase-II reactions, which are responsible for the metabolism of many drugs, do not decrease in the elderly[43]. Besides, it has been observed that phase-II drug metabolism is slowed in some more sensitive elderly[44].

The activities of the oxidative enzymes CYP1A2, CYP2A, CYP2C9, CYP2C10, CYP2C18, CYP2C19 and CYP3A, which play an important role in the metabolism of many drugs, are lower in the elderly compared to adults[45]. However, the decrease in the activity of CYP enzymes and slowing down of metabolism reactions due to aging is not clinically important and generally, the dosage of drugs does not need to be adjusted[46]. It has also been observed that the activities of some hydrolytic enzymes such as acetylcholine esterase do not decrease in the elderly[47]. In vitro studies have shown that NADPH-CYP450 reductase enzyme activity, which works with the CYP450 system and is responsible for electron transfer, does not change depending on age[41].

The increase in oxidative stress due to aging is closely related to the increase in the level of lipid peroxidation products and the decrease in antioxidant enzyme activity in the liver[26].

1.4 Elimination

Studies have shown that the coexistence of syndromes such as hypertension and coronary heart diseases with aging reduces renal functions[48]. Decreased renal functions due to age and diseases are of clinical importance in the disposal of drugs that are eliminated by the renal pathway, especially drugs with a narrow therapeutic range[22].

Serum creatinine level, which is determined by various factors such as muscle mass and protein level and which is a marker of renal function and drug elimination, decreases with aging[49]. In addition, studies have shown that renal mass decreases by 20-25% with aging[50]. This reduction in renal mass is usually due to a decrease in nephrons in the renal cortex[51]. Renal proximal tubule cells, which are responsible for reabsorption by consuming energy, are highly susceptible to age-related oxidative damage[52].

Renal function decreases and elimination of drugs is altered with decreased glomerular filtration rate and creatinine clearance in the elderly[13]. Glomerular filtration, which is one of the indicators of renal functions, decreases approximately 25-50% between the ages of 20-90[19]. Tubular secretion of drugs is significantly reduced due to decreased renal blood flow in the elderly[53]. The ability of the elderly to concentrate urine is reduced due to decreased glomerular filtration and tubular secretion[34].

Decreased renal blood flow and increased angiotensin-II and endothelin levels in the elderly also lead to a decrease in renal functions[19]. The dosage of drugs should be adjusted in order to reduce the risk of drug-related adverse effects and nephrotoxicity due to decreased renal function in the elderly[12].

Since hepatic blood flow is decreased in the elderly, the plasma concentrations of some drugs exposed to first-pass elimination may increase[54]. Thus, the bioavailability of prodrugs activated by metabolism in the liver is reduced[55].

2. Physiological Changes With Aging

2.1 Cardiovascular System Changes Seen with Aging

Some changes occur in the cardiovascular system with increasing age. Activation of myofilaments in the heart brings along many molecular, biochemical and physical changes by affecting mitochondrial phosphorylation, the function of calcium and proteins, cell growth and regeneration, matrix content and apoptosis. Hypertrophy develops in the remaining cells due to the loss of myocytes.

While ventricular systolic function is preserved with aging, diastolic function deteriorates. Calcification, aortic valve degeneration and sclerosis can be seen in the elderly who do not have any health problems.

Heart works more in the elderly than in the young due to the loss of heart capacity. In stressful situations, the heart cannot return to normal beats immediately[56,57].

2.2 Respiratory System Changes Seen with Aging

With aging, some structural and functional changes are seen in the respiratory system. Capacity loss occurs in bronchioles and resistance increases. There are viscoelastic properties of alveole and thorax in the lungs. The elastic properties of the lungs depend on the surface tension of the fluid covering the surface of the alveole and the elastic fibers found throughout the lung tissue. The elastic property of the thorax depends on the elastic properties of the chest muscles, tendons and connective tissue. After the age of 40, there is a significant decrease in the number of elastic fibers, increase in Type III collagen, and senile emphysema due to enlargement of the alveoli. Thus, the number of alveoli decreases by 40%. With aging, changes occur in collagen and parenchymal tissue with a complex mechanism. The properties of the cross-links of collagen vary in a person-specific way over the years.

Changes are also observed in lung function tests. The flow in small airways decreases. Lung volume increases as a result of the closure of small airways in expiration. Closure of the terminal bronchial during normal breathing in the elderly causes a decrease in arterial oxygen pressure. Closing leads to an increase in volume, a decrease in elastic capability, and an increase in residual volume. FEV1 decreases by 30 ml/year in men and 23 ml/year in women (in healthy non-smokers older than 65 years). FVC decreases by 14-30 ml/year in men and 15-29 ml/year in women. Due to the effective alveolar surface loss that exchanges gas with age, diffusion capacity for CO2 decreases in healthy non-smoking elderly every ten years by 2.03 mL/min/mmHg in men, while in women this ratio decreases by 1.47 mL/min/mmHg (In women, this effect is 0.56 mL / min / mmHg every decade until menopause)[58-61].

2.3 Endocrine System Changes Seen with Aging

During menopause, vasomotor symptoms, depression, changes in skin and body composition (body fat increases, muscle mass decreases) are observed due to the decrease in estrogen levels. In addition, the incidence of cardiovascular diseases, osteoporosis and cognitive disorders increases in the following years. Providing estrogen support therapy with progesterone for a long time during menopause has many benefits. Hormonal signs of changes in the endocrine system of men appear in the thirties. Many studies have shown that the level of testosterone decreases with aging. It may take 60-70 years of age for testosterone levels to decrease to hypogonadism levels. Many factors are responsible for decreasing testosterone levels with aging: There is a deficiency in testosterone production from Leydig cells in the testicles. More important is the insufficiency in the hypothalamus-pituitary axis. Most older men have secondary hypogonadism[56].

2.4 Neurological Changes Seen with Aging

Atherosclerosis predisposition also occurs in the brain. Oxidative damage, vascular endothelial dysfunction, and inflammatory response cause vascular changes. Cerebral blood flow is reduced by up to 20%. These changes cause an increased risk of stroke. Besides, the decrease in brain perfusion may cause a decrease in cognitive functions. Difficulty in learning and dementia may occur depending on age[62].

2.5 Renal Changes Seen with Aging

Significant changes occur in renal physiology with aging. Glomerular Filtration Rate (GFR) has been shown to decrease by 0.8 mL/min/year every year from the age of 30. This decrease in GFR is associated with a decrease in the number of nephrons. While renal plasma flow is 600 mL/min at the age of 30, it decreases by 10% every ten years and regresses to 300 mL/min at the age of 80. This decrease is accompanied by an increase in both afferent and efferent arteriolar resistance. In functional magnetic resonance imaging performed in elderly volunteers, it was found that the ability to modulate renal medullary oxygenation was decreased. This decrease may be due to changes in the renal autocrine system (prostaglandins, dopamine, nitric oxide, natriuretic peptides or endothelin) or vascular changes. The most important changes observed in tubular functions with aging are the decrease in urine concentration and acidification ability. The decrease in concentration ability may be associated with an intrinsic defect in the tubular epithelium or an inadequate response to antidiuretic hormone (ADH).

Serum creatinine value is not a healthy indicator of GFR, which decreases with age. Because, similar to GFR, muscle mass decreases with aging. At the age of 25, muscle mass is 19% of body weight, while at the age of 70, this rate decreases to approximately 12%. Therefore, especially in elderly patients, this point should be taken into consideration during drug dosage adjustment and it should be kept in mind that there may be a significant decrease in GFR without an increase in serum creatinine concentration. For that reason, it is safer for patients to determine the drug dose according to the following formulas[63-67].

FORMULA 1.

Creatinine clearance (ml / min) = Urine creatinine (mg / dL) x Daily urine volume (mL) / Serumcreatinine (mg / dL) x 1440

FORMULA 2. (Cockcroft-Gault formula)

Creatinine clearance = (140-Age) x (Ideal weight) / Serum creatinine (mg / dL) x 72 The value found in women is multiplied by 0.85.

3. Conclusion

3.1. Special Dose Requirements of Drugs Used in the Treatment of COVID-19

The recommendations of some drugs used in the treatment of COVID-19 in cases of renal and hepatic failure are as follows[68,69].

Oseltamivir

Moderate renal impairment;

(CrCl> 30--60 mL / min): Twice daily for 5 days, 30 mg p.o.

Severe renal impairment;

(CrCl> 10--30 mL / min): Twice daily for 5 days, 30 mg p.o.

Lopinavir / Ritonavir

Contraindicated in severe hepatic impairment (Childs Pugh C).

Chloroquine Phosphate

Severe renal failure (eGFR <10 mL/min): 5Should be take half the standard dose. If treatment must be continued, the dose should be lowered to 50–100 mg/d.

Hydroxychloroquine sulphate

In case of moderate hepatic impairment (Childs Pugh B), treatment should be continued by monitoring the ALT enzyme. In severe hepatic impairment (Childs Pugh C), the dose may be reduced by 50% and a maximum of 400 mg may be given. ALT enzyme should be monitored during treatment.

Remdesivir

If the eGFR is lower than 50, its use is not recommended.

Azithromycin

If the eGFR is lower than 10, it should be used carefully.

Ribavirin

30 <eGFR <50: 200--400 mg every other day

eGFR <30: 200 mg Daily

Interferon β

It is not recommended in cases of moderate to severe hepatic impairment (Childs Pugh B and Childs Pugh C).

Atazanavir

In case of mild hepatic impairment (Childs Pugh A), 400 mg per day can be used. In cases of moderate and severe hepatic insufficiency (Childs Pugh B and Childs Pugh C), it is recommended to use 300 mg daily with meals.

Favipiravir

In case of mild hepatic impairment (Childs Pugh A), 800-1200 mg can be used twice a day for 13 days. In cases of moderate hepatic insufficiency (Childs Pugh B), it can be used 800-1200 mg twice a day for 5 days. In cases of severe liver failure (Childs Pugh C), 400-800 mg twice a day can be used for 2-3 days.

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CHAPTER 5

PAIN AND PAIN MANAGEMENT IN THE COVID-19 PANDEMIC

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INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), identified first in Wuhan, China, appeared in December 2019. Then, by the World Health Organization (WHO), COVID-19 was announced as a global pandemic in March 2020. As of May 2021, 154 million people have acquired the infection and 3.23 million people have died. In Turkey, 4.93 million people have been infected and 41.527 people have died.

This pandemic has brought many physical and psychological burdens to people and has also caused financial losses across all countries. Symptoms such as fever, chest pain, muscle pain, headache, cough, shortness of breath, sore throat, and abdominal pain have been observed in COVID-19 patients.

Because of the incidence of pain, it cannot be considered as a specific symptom defined only during COVID-19. It causes patients to suffer, their daily activities to be restricted, and negatively affects their quality of life. For this reason, the patients need to be diagnosed and treated at an early stage.

Arthralgia and Myalgia

Arthralgia has been described as pain or stiffness of joints, which causes patients to have a poor quality of life, feel negative emotions, problems with adaptation, and sometimes cessation of treatment. Myalgia, on the other hand, describes pain caused by local, systemic infections, usually as a symptom of muscle pain or disorder. It usually causes very common pain. Arthralgia and myalgia are musculoskeletal pain that negatively affects patients physically, socially, psychologically for this reason, which occurs at least once in a lifetime.

Myalgia is usually caused by interleukin-6 during viral infections. Skeletal muscle damage is determined by lactate dehydrogenase (LDH) and creatinine kinase (CK). COVID-19 patients with symptoms of musculoskeletal pain were found to have higher CK and LDH levels compared to those without symptoms. Cytokines cause pain through peripheral pain receptors when they stimulate prostaglandin E2 (PGE2) production. By binding to angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 can settle the central nervous system via peripheral nerves or directly damage the nervous system.

COVID-19 studies conducted in China investigated different types of pain and found that 1.5 - 61.0% of patients experienced arthralgia and myalgia. A study reported that 14 of the 17 SARS-CoV-2 positive patients had myalgia. In a study conducted on 155 patients with COVID-19, 82 patients reported experiencing myalgia or arthralgia. There is a positive association between the positivity of myalgia and the SARS-CoV-2 test. It is also one of the strong symptoms, as it is very common in COVID-19 patients. Although arthralgia is not a common symptom as much as myalgia, it should not be ignored when diagnosing COVID-19.

Throat ache

Pain is caused by inflammation of the tissues. Viruses (coronavirus, influenza, and rhinovirus) are responsible for 80% of cases. Patients with a sore throat may also experience coughing, ruddiness, swelling, itching, and hoarseness. The study, which examined clinical symptoms of 1.099 COVID-19 patients in China, reported that 153 patients had sore throats and the incidence was about 13.9%. In studies conducted in COVID-19 patients, the sore throat incidence was 0.7 - 47.1%. SARS-CoV-2 and the influenza virus disseminate to the respiratory passage, showing similar symptoms, and sore throat caused by influenza can also apply to SARS-CoV-2. Inflammatory agents (prostaglandins, bradykinin) released from the body in answer to SARS-CoV-2 can affect the afferent nerve in the throat tissue, inducing a sore throat.

Sore throat is prevalent in COVID-19 patients. Patients with negative COVID-19 test had 4-5 times higher sore throat incidence compared to those with positive COVID-19 test. Although the sore throat is not as prevalent as fever, these patients should be considered carriers of COVID-19, and the planning should be made according to this.

Headache

Its prevalence in the whole population in the world is 47%, and its prevalence during the lifetime of humans is 66%. Headache is a very prevalent symptom and is very important in COVID-19 infection. According to data from 1.590 COVID-19 patients in China, the incidence of headache was stated as 15.4%. In another study, 205 patients out of 1328 COVID-19 patients reported headache complaints. Five types of pain were summarized in different COVID-19 studies, accordingly, the incidence of headache is 1.7 - 33.9%. The mechanism of headache caused by COVID-19 has not been fully clarified. Some possible reasons may be mentioned, for example, in viral infections, cytokines secreted from immune cells as the body's response can cause headaches. In addition, because SARS-CoV-2 disrupts alveolar tissue, thus alveolar gas exchange is disrupted, it has been reported that it can cause a headache as a result of cerebrovascular dilation, ischemia, and embolism.

Headache in COVID-19 patients is a symptom that cannot be ignored. Patients have been reported to experience severe headaches and fatigue in the early days with no fever, cough, or breathing problems. In addition, the study found that headache in COVID-19 patients was a result of intermittent negative status at a rate of 60%. Intermittent negative status is defined as the re-detection of the virus RNA of a COVID-19-negative patient through a reverse transcription-polymerase-chain reaction (RT-PCR).

Chest pain

Chest pain affects 20 to 40% of the general population. The quality of life of patients who feel this pain can also be distorted. A study conducted on 416 COVID-19 patients in Wuhan, China, found that 13.4% experienced chest pain. In a study conducted in Australia, 5% of 2257 COVID-19 patients had chest pain. According to the studies, the incidence of chest pain was found in the range of 1.6 – 17.7%.

In chest pain, the SARS-CoV-2 virus, mediated by ACE 2, can directly invade cardiomyocytes, causing cardiac damage. Certain inflammatory structures released into the pleural cavity can cause chest pain by stimulating pain receptors located in the pleura. Chest pain and shortness of breath are more severe in COVID-19 patients. Also, chest pain can be a fatal risk factor in COVID-19 patients.

SARS-CoV-2 patients have a high risk of cardiovascular disease. In the study, it was reported that SARS-CoV-2 causes prolonged harm to the cardiovascular system of patients. Therefore, protection treatments for the cardiovascular system should continue after the treatment of COVID-19.

Abdominal pain

Pain in the abdomen is a symptom of irregular gastrointestinal activity. This symptom is often also related to comorbid complications such as fibromyalgia, depression, anxiety, and a decrease in quality of life. In a study conducted in China, symptoms of abdominal pain were investigated in COVID-19 patients and the incidence was found as 5.1%. In another study, clinical characteristics and allergy conditions of COVID-19 patients were investigated and the abdominal pain incidence was 5.8%. There are many studies showing that the abdominal pain incidence is 1.9 - 14.5%.

ACE2 is abundant in the gastrointestinal system, most commonly in the large and small intestines. Thus, SARS-CoV-2 binds to ACE2, invading the gastrointestinal tract and causing abdominal pain. A study conducted at Oslo University Hospital found that 11.8% of patients admitted to the hospital with acute abdominal pain were diagnosed with COVID-19. Based on this information, it is recommended that patients having abdominal pain must be checked in terms of SARS-CoV-2 with oropharyngeal and nasopharyngeal swabs.

PAIN MANAGEMENT

During the pandemic, there have been problems with pain management, sometimes this is related to seeing a new symptom, sometimes this is due to problems such as difficulty accessing chronic pain services. Literature and WHO reports indicate that in SARS-CoV-2, pain is seen as a widespread symptom.

Isolating the patients due to the pandemic will cause them to experience more stress and anxiety. In addition to increasing pain, this condition leads to a worse clinical picture and worsening of the patient. It has been found in studies that 50% of patients with untreated chronic pain experience depression and their pain complaints increase more. This result requires special care for patients with

COVID-19, and there are important points to consider in the pandemic process. Methods such as maintaining the continuity of care, maintaining the use of analgesic drugs, especially opioids, promoting the use of telemedicine due to the pandemic, maintaining biopsychosocial management, and being careful when using anti-inflammatory drugs and steroids are used.

Materials based on the self-assessment of patients, such as the visual analog scale (VAS) or the numerical rating scale (NRS), which provide collaboration with the patient, are commonly used in the assessment of pain. But, in the intubated patients admitted to the intensive care unit (ICU), the evaluation of the intensity of pain continues to be a constant drawback. In ICU, patients' pain is examined in four categories. These are acute pain related to the disease, constant pain caused by intermittent pain, ICU treatment, or chronic pain experienced before applying to the ICU. Some tools can be used to measure pain in the intensive care unit. In patients who are unable to express themselves in pain assessment, Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (CPOT) assessment scales are recommended in the latest clinical practice guidelines. CPOT is used in pain assessment in critical patients. The scale consists of four behavioral fields. Body movements, facial expression, muscle tension, and compliance of intubated patients with ventilation, or voice notification of patients undergone extubation are evaluated. BPS is used to measure pain in intubated patients. The scale is dependent on three behavioral criteria. The patient's facial expression is evaluated as movements of upper limbs and ventilation compatibility. These scales are helpful for pain assessment of patients with COVID-19 and other patients applying to the intensive care unit, as well as for selecting appropriate treatment.

There are no published guidelines for pain management in patients with COVID-19. Pain sourced from different organs can be the first symptom of damage to different systems. For this reason, the source of pain should be determined during the prolonged treatment procedure. The symptoms should be well judged and not ignored. Because the symptoms lead to better-planned measures, the most accurate treatment, and healing of patients.

CONCLUSION

SARS-CoV-2 does not only give symptoms of the respiratory system, contrarily many other symptoms such as fever, cough, loss of appetite, dizziness are also observed. In addition, symptoms related to the nervous system, digestive system, and cardiovascular system have also been identified. Risk factors of COVID-19 should be identified, measures should be taken to prevent further spread of the disease, and preventive measures should be taken.

For pain treatment, each patient needs an individual treatment depending on the available information and, more importantly, the patient's status and comorbidities. The presented knowledge can be representative of available information aimed at improving the clinical status of the patients. In the COVID-19 pandemic, besides the mechanism of the disease, the pain that is a consequence of the disease should be well assessed. It should be noted that social isolation is effective as a cause of worsening pain. Finally, urgent strategies and treatment methods should be developed to reduce the negative impact of pain.

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CHAPTER 6

COVID-19 AND OTORHINOLARYNGOLOGY

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1. Introduction

It was announced to the world on January 7, 2020 that a new type of coronavirus,severe acute respiratory syndrome-coronavirus-2 (SARS CoV-2), was isolated by the Chinese Government in the Wuhan region of China. Health systems of governments reacted differently in surveillance, diagnosis and treatment against the rapidly spreading and uncontrollable epidemic.The populations were not equally affected in terms of the number of cases, severe illness, and death . As a result, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak as a global pandemic on March 11, 2020 . As of 28 December 2020, 81.000.000 confirmed cases and approximately 1.770.000 total deaths have been reported for COVID-19 worldwide.

COVID-19 may progress asymptomatically or manifest itself as severe pneumonia or a disease requiring intensive care. Uncomplicated (mild) illnesses presenting with fever, dry cough, muscle pain, and upper respiratory tract symptoms are common, however progressive pneumonia and/or ARDS can be seen in severe cases.

Severe acute respiratory syndrome-coronavirus-2 has complex pathogenic mechanisms. COVID-19 is a biphasic disease, with a viral response phase in the early period and an inflammatory phase in the later period. The quick immunological response against the virus is the initial defense-line. However, an excessive immunological reaction can be evoked by the virus in the host. In some cases, the immunopathology called "Cytokine Storm" occurs, leading to dysfunctional coagulation and deep tissue damage.

Involvement of extrapulmonary organs is an important aspect of COVID-19 and makes the disease systemic. SARS-CoV-2 attaches to angiotensin-converting enzyme-2 (ACE-2) as a receptor for entry into the cells. Gastrointestinal system, liver, kidneys, vascular system (endothelial cells and smooth muscle cells) can be targets for SARS-CoV-2 with high expression of ACE-2 receptors .

It is a known fact that coronaviruses have neurotrophic and neuroinvasive features. In terms of otorhinolaryngology (ENT), SARS-CoV-2 stands out with this feature. It may cause symptoms related to otorhinolaryngology, especially smell and taste disorders, and may directly affect many organs in the head and neck. In addition, since the transmission route is the respiratory tract, otorhinolaryngologists and surrounding staff are at high risk for the disease and as in all medical departments, otorhinolaryngologists have had to work at the forefront of the disease and outside of their own fields. Therefore, the treatment of many diseases, especially malignancies, has been postponed.

2. Neuroautology

In previous studies, it has been shown that viral infections have an important place in the etiology of sudden sensorineural hearing loss (SSNHL). Therefore, it is not unreasonable to think that SARS-CoV-2 infection, a viral infection, can cause SSNHL. Three mechanisms that can cause SSNHL associated with viral infections have been described: The neuritis caused by viral involvement of the cochlear nerves, cochleitis due to viral involvement of the cochlea and peri-lymphatic tissues, and the stress response resulting in the cross-reaction of the inner-ear antigens to viral infections. It is possible that the SARS-CoV-2, with proven effects on nerve degeneration, may act through these three mechanisms.

The initial article mentioning SSNHL in COVID-19 was published by Sriwijitalai, and the patient whose clinic recovered with treatment but did not show any improvement in hearing loss is presented. Rhman et al. achieved a partial recovery with intratympanic steroid in an asymptomatic COVID-19 patient with SSNHL. In a study performed in Turkey, five patients with SSNHL have undertaken PCR tests, and one patient is diagnosed with COVID-19 . In another study, the results of pure tone audiometry and transient evoked otoacoustic emission (TEOAE) of 20 asymptomatic SARS-CoV-2-PCR positive patients were compared with the control group; higher hearing thresholds and lower TEOAE amplitudes were detected at higher frequencies. In the case presented by Degen, bilateral sensorineural hearing loss was detected and the rehabilitation of hearing loss was provided with a cochlear implant in the patient who could not recover with intratympanic steroid therapy. Koumpa et al. could not achieve a significant hearing gain in their COVID-19 patient with SSNHL, despite using oral and intratympanic steroids. As can be seen in the reports in the literature, there is a possible relationship between COVID-19 disease and SSNHL.

Similar to SSNHL, peripheral vertigo and tinnitus can also be seen due to the same mechanisms in COVID-19. Viola et al. examined 185 COVID-19 patients who were followed up in Italy. In their study, 34 patients (18.4%) reported equilibrium disorders after COVID-19 diagnosis. Of these, 32 patients reported dizziness (94.1%) and 2 (5.9%) reported acute vertigo attacks and 43 patients (23.2%) reported tinnitus; 14 (7.6%) reported both tinnitus and equilibrium disorders . Cui C. et al. presented a patient with dizziness/vertigo and reported that they added betahistine to their treatment to resolve dizziness . Vertigo is a subjective condition. Objective sign of vertigo is nystagmus. Esperanza et al. presented a patient who presented with dizziness that started one week after the onset of COVID-19 symptoms and horizontal nystagmus accompanied by intermittent rotatory component. There is no information in the literature about vertigo, which may affect daily life, becomes chronic. Chirakkal et al. presented a patient who applied with tinnitus after the COVID-19 treatment and reported that COVID-19 infection has harmful effects on the outer hair cells in the cochlea .

Remembering COVID-19 in the etiology of vertigo, tinnitus and SSNHL,is important in terms of providing isolation and preventing contagiousness during the pandemic period.

3. Rhinology

The most common symptoms of COVID-19 are non-specific symptoms which makes it difficult to distinguish COVID-19 from any other upper respiratory tract infections. The increase in the number of patients presenting with olfactory dysfunction without any other symptoms has begun to suggest that anosmia may be a potential early marker of SARS-CoV-2 infection. Anosmia as a symptom, which stands out with this feature and its difference according to other symptoms, has begun to be discussed as an early indicator of COVID-19.

3.1. SARS-CoV-2 Related Anosmia

Most common cause of anosmia in adults is post-viral anosmia with 40% incidence. The increase in COVID-19 patients who are young, healthy and have no symptoms other than sudden onset anosmia is noteworthy. It was reported that patients with isolated anosmia were positive for the COVID-19 PCR test after 72 hours. Individuals with sudden-onset anosmia without a recent history of head trauma or advanced nasal obstruction and no other symptoms of COVID-19 are recommended to be considered potential carriers.

Sudden onset anosmia is reported to be the only symptom of COVID-19. Olfactory dysfunction rate in COVID-19 has been reported between 20-85%. Different rates of anosmia is explained by the ACE2 polymorphism. COVID-19 related anosmia reported to be temporary, 76,2% of the patients recovered in eight days.

3.2. Possible Mechanism of COVID-19 Related Anosmia

Two types of olfactory dysfunction is described; conductive type and sensorineural type. Obstructive pathologies of nasal cavity result in conductive anosmia. The rate of loss of smell due to sinonasal pathologies has been reported 14-30%. Olfactory epithelium disruption or pathologies in olfactory neuronal pathway results in sensorineural olfactory disorder.

Among the findings supporting that anosmia due to SARS-CoV-2 is a conductive type, it has been shown that the olfactory dysfunction starts at the beginning of the infection (22.8%) or after the infection (26.7-65.4%). Temporary nature of olfactory dysfunction is considered as another supporting evidence of conductive dysfunction.

Nasal cavity infections can damage olfactory epithelium, are considered as a candidate of sensorineural olfactory loss. Sensorineural olfactory dysfunction could present weeks or even months after the infection, until the olfactory epithelium regenerates. Neutrophilic inflammation induced after nasal infections, which results in rhinitis and mucosal edema. This is the conductive component of olfactory loss. However histopathological examinations reported that inflammation of olfactory epithelium after nasal cavity infection results with squamous metaplasia which is the sensorineural component of olfactory dysfunction.

SARS-CoV-2 enters into host cells via ACE-2 and ACE-2 expression is higher in nasal cavity at the whole respiratory system. It has been reported that non-neural cells of olfactory epithelium (sustentacular cells, basal cells and perivascular cells) express ACE-2. Sustentacular cells of olfactory epithelium, which face the nasal cavity are hypothesized as the target cells of SARS-CoV-2. Infection of these cells with SARS-CoV-2 develops olfactory dysfunction due to local epithelial destruction.

Duration of olfactory dysfunction varies between patients. It has been suggested that SARS-CoV-2 could be transported to higher olfactory neurons located in central nervous system (CNS). It has been reported that SARS-CoV infection retrogradely transferred into CNS. SARS-CoV-2 has not been reported in CNS however it has neuroinvasive potential should be considered in prolonged olfactory dysfunction.

Another hypothesis of CNS spread of SARS-CoV-2 via hematologically. The infection of endothelial cells located in blood brain barrier, could transmit to pericytes and astrocytes which could lead into central and peripheric olfactory dysfunction. Perivascular cells of olfactory epitelium express ACE-2, which is considered as a supporting evidence of hematological spread of SARS-CoV-2.

3.3. Evaluation of Olfactory Dysfunction in COVID-19

Olfactory dysfunction related with COVID-19 characterized as sudden onset, accompanied with/without other COVID-19 symptoms, probably temporary and usually detected in younger female patients. Most of the reported cases of olfactory dysfunction are based on self-evaluation. Objective olfactory tests are not usually correlated with subjective tests. Odor samples are presented to patients in order to determine smell threshold, discrimination and identification. Some of the components of these test could be used as a self-evaluation.

Every patient who present with anosmia should be examined detailly. History of head trauma or injury, seasonal quality of anosmia, initial charactesitics, accompanying neurological symptoms should be questioned. Endoscopic evaluation of nasal cavity should be performed. If paranasal and/or intracranial pathologies suspected, imaging studies could be ordered .

3.4. Treatment of COVID-19 Related Olfactory Dysfunction

COVID-19 related olfactory dysfunction usually recovers spontaneously. If anosmia presents longer that two weeks, treatment options should be considered.

There is no treatment protocol for Covid-19 related olfactory dysfunction. Olfactory training should be suggested, for this exercise well-known odors such as lemon, rose, clove and eucalyptus, sniffed for 20 seconds, three times a day at least for three months or longer if necessary.

Respiratory symptoms of COVID-19 usually present 8-12 days after initial infection, in order to that, systemic corticosteroid treatment of COVID-19 related olfactory disorder should be delayed at least for two weeks. Oral corticosteroid treatment should be considered for patients whose anosmia present longer than two weeks. Omega-3 supplements are reported protective against olfactory dysfunction after skull base surgery and suggested as a protective agent for post-viral olfactory dysfunction. Promising results have been shown that the use of intranasal sodium citrate, intranasal vitamin A and systemic omega 3 may be beneficial in OD with its olfactory receptor, neurogenesis and anti-inflammatory properties .

4. Laryngology

SARS-COV-2 virus disperse with droplets or aerosols with upper airway passage and larynx and trachea are influenced inevitably. The identification of virus effects on related organs, management of disorders and patient follow-up are relatively challeging in considering the high infection rate of SARS-COV-2 virus.

4.1. Laryngeal complaints and examination

Laryngeal manifestations are concerned by many phycians and many studies assessed most common laryngeal complaints of COVID-19 patients. Systematic evaluation of the complaints like questioning the onset, severity, duration and presence of additional symptoms is important to reveal the underlying pathology. Most common complaints are sore throat and dysphagia, non-productive cough, globus sensation, dysphonia are the other less common laryngeal complaints for patients who did not received orotracheal intubation. The orotracheal intubation can cause the mutual complaints, but the possible organic pathologies can be differed due to the orotracheal intubation trauma. The reported laryngeal and tracheal lesions due to the orotracheal intubation were mentioned in **Table 1**.

Table 1. Reported laryngeal and tracheal lesions and management

Lesion	Author	Reason	Management	Prognosis
Vocal Cord Ulceration	Bertone et al.	Orotracheal intubation	Follow up	Total recovery
Posterior Glottis Granuloma/ Stenosis	Thong et al.	Orotracheal intubation	Granuloma excision+ Partial unilateral arytenoidectomy	Total recovery
	Naunheim et al.	Orotracheal intubation	Lesion excision+Botox injection	N/A
Paradoxical Vocal Cord Movement	Lechien et al.	Orotracheal intubation	Follow-up+Speech therapy	Total recovery
Subglottic Stenosis	Rouhani et al.	Orotracheal intubation	Follow up	N/A
	Naunheim et al.	Orotracheal intubation	Lesion excision + Baloon Dilatation	N/A
Laryngeal Eodema-Laryngitis	McGrath et al.	Orotracheal in/extubation	Follow-up/ Reintubation	N/A
Cricoid Membrane Laceration	Abou-Arab et al.	Orotracheal intubation	Tracheal repair	N/A
Tracheal Stenosis	Miwa et al.	Tracheotomy	Lesion excision	N/A
	Elarabi et al.	Tracheotomy	Lesion excision + Tracheal anatomosis	Total recovery
Tracheal Laceration	Abou-Arab et al.	Orotracheal intubation	Tracheal repair	N/A

The rigid transoral indirect laryngoscopy or flexible fiberoptic transnasal indirect laryngoscopy are the essential examination methods for laryngeal pathologies, but they are categorized as aerosol producing medical procedures (APMP). Due to this, laryngoscopy of a COVID-19 patient presents a very high risk of virus infection for otorhinolaryngologists and accompanying medical staff. Guidelines refer to perform laryngoscopy procedures if only presence of a critical impact on the diagnosis and management of the COVID-19 patient such as acute onset hemoptysis, dysphagia with malnutrition or dehydration, acute airway obstruction. If possible flexible fiberoptic transnasal laryngoscopy should be chosen for decreasing the aerosol production instead of transoral route. Computerized tomography can be considered as an alternative method to assess the airway passage for selected cases .

Laryngoscopy procedures should be performed by the experienced staff and performer should wear personal protective equipment (PPE) such as N95 or FFP2 mask with protective face shield or goggle. Additional participants for observation should not be accepted during the procedure to prevent the viral infection and reduce the PPE usage. Performers should care the proper equipment and environment disinfection conditions with personal hygiene. Besides, appropriate air circulation should be provided to reduce the virus contaminated aerosols. Similar precautions should be taken for nasogastric tube insertion, as well.

5. Head and Neck Cancer

What is more important than all these diseases and can lead to mortality is that patients with head and neck cancer cannot access diagnosis and treatment due to the COVID-19 pandemic. Among the head and neck cancers, human papilloma virus (HPV) - negative oral cavity cancers, oropharyngeal squamous cell carcinoma and advanced laryngeal cancers are cancers that are considered aggressive and do not have neoadjuvant treatment options that are deemed to cause delay in surgical treatment. In head and neck cancers, as the time between diagnosis and treatment gets longer, overall and disease-free survival decreases. For this reason, the period between application to the clinic and treatment should not exceed one month. Despite all the efforts of otorhinolaryngologists, it will be challenging to understand whether this condition is fulfilled during this pandemic process, where almost all hospitals work above their capacities, and doctors work outside their field of expertise, and patients cannot apply to the relevant complaint departments.

6. Conclusion

The COVID-19 outbreak has become a pandemic that challenges the world health system. This disease, which affects all branches of medicine, is associated with otorhinolaryngology from the first symptom period to the chronic sequelae period. It is necessary to know all aspects of this relationship, to recognize the disease and to isolate the patients, to manage the otorhinolaryngological symptoms and to follow-up and treat the conditions that may become chronic.

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CHAPTER 7

EFFECTS OF COVID-19 ON PAEDIATRIC DENTAL TREATMENT PROCEDURES: IMPLICATIONS FOR THE FUTURE OF DENTAL CLINICS

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1. Introduction

An increasing number of severe acute respiratory syndrome cases were detected in Wuhan, a major city in Republic of China, in December 2019. In the following days, several local health organizations reported that groups of patients, with pneumonia of unknown cause, may epidemiologically got infected by seafood and/or wildlife market; namely, "Huanan Seafood Wholesale Market" in Wuhan. After the rapid rise in cases, on January 9, 2020, the World Health Organization declared that a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has never been identified in humans before, causes Corona Virus Disease 2019 (COVID-19). Coronaviruses are RNA viruses belonging to the *Coronaviridae* family. Several members of the coronavirus cause mild respiratory illness in humans. However, its two subtypes, having caused serious respiratory fatal diseases, are severe acute respiratory syndrome coronavirus (SARS-CoV) discovered in 2002-2003 and Middle East respiratory syndrome (MERS-CoV) discovered in 2012.

2. Incubation Period and Symptoms of COVID-19

SARS-CoV-2 causes a respiratory syndrome that is transmitted from person to person, with an incubation period of approximately 14 days. Although the most prominent symptoms of patients infected with SARS-CoV-2 are dry cough, shortness of breath, myalgia and fever, bilateral lung imaging findings were also detected. In addition, decreased sense of smell and taste, diarrhea and nausea are also among the rare symptoms in these patients.

3. Transmission Routes of COVID-19 in Dentistry

Coughing, sneezing, saliva and droplet inhalation directly play a role in the spread of COVID-19, while contact with the mucous membranes of the mouth, eyes and nose spread indirectly. Aerosol contamination emitted during treatments in dental practice is the primary cause of disease transmission. Pre-treatment diagnosis and elimination of COVID-19 is significant in terms of cross-infection, as high-speed handpiece and ultrasonic instruments used during caries removal, crown preparation and scaling lead to aerosol generation. Infection controls need to be effective and strict to limit the spread of COVID-19. In this context, the importance of disinfection and effective hand hygiene are among the precautions to be taken in dental units.

COVID-19 symptoms in children include fever, dry cough, upper respiratory tract infection symptoms, fatigue, and gastrointestinal signs. Although fever and dry cough symptoms are most common in children, symptoms of lower respiratory tract infections are rare, unlike adults. Since the absence of specific findings in children will increase the transmission of the disease, the treatment of children with upper respiratory tract infection symptoms should be approached cautiously, and non-emergency treatments should be postponed until the symptoms subside.

It is known that one of the most effective protective methods in preventing the transmission of COVID-19 is the use of medical masks. For this reason, it should be ensured that the patients and their attendants who come to the hospital wear medical masks, and have their temperatures taken at the hospital entrances. Patients with fever should be recorded and referred to the pandemic hospitals. COVID-19 contact history should be checked at hospital entrances, and 14-day quarantine should be offered to the patient in contact with individuals with a diagnosis of COVID-19 in the previous 14 days. Additionally, non-urgent dental treatments should be postponed in these patients.

4. Waiting Room

Patients and their attendants who do not have fever or show any other symptoms of COVID-19 are required to maintain social distance and wear a mask while in the waiting room. Patients should be informed about using disinfectant for hand sanitizing.

An educational alternative in the paediatric dentistry clinic such as laying dental concept cartoons on a monitor may not only help children get bored but also can reduce anxiety during the time spent in the waiting area. Cross-infection should be prevented by removing toys, magazines, books and other objects that children in the waiting area can come into contact with frequently. On the other hand, the presence of a HEPA filter and the use of ultraviolet germicidal irradiation in clinical ventilation are procedures that will reduce infection transmission. A social distance of approximately 2 m should be maintained between the patients in the waiting room, and the waiting time should not exceed 30 minutes. If there is a reception desk in the waiting room, it should be separated with a plexiglass or glass separator to protect the personnel from droplets. The intensity of the clinic should be reduced by arranging appointments before patients come to the clinic.

5. Personal Protective Equipment (PPE)

Paying attention to hand hygiene and the proper use of personal protective equipment are necessary to prevent transmission of COVID-19 to healthcare workers. Even if there is no patient in the clinic, attention should be paid to hand hygiene and therefore personal protective equipment should be used. Disposable gowns, shoe coverings, surgical caps, N95 or FFP3-like high filter masks, face shields, goggles and gloves should be used as personal protective equipment. In particular, N95 masks reduce the filtration of particles of 0.3 µm and larger by approximately 95%. However, since looking after more than one patient with a single N95 mask will increase the risk of cross-infection, a surgical mask can be placed on the N95 mask and long-term use of the N95 mask can be achieved by changing only the surgical mask after the patient's treatment. In addition, it is recommended to use a second mask due to potential violation of the peripheral seal on the N95 mask. Since dentistry requires close contact with patients, reducing contamination is paramount of importance. Dentists and dental staff should wash their hands before examining the patient, before and after dental procedures, after touching the environment and equipment, or after touching the oral mucosa, blood and wounds.

6. Contamination Preventive Protocols

Dentists should pay attention to protection against contamination during treatment and should minimize droplet or aerosol formation processes as much as possible. The four-handed technique principle is very useful in reducing the risk of cross-infection. The use of high-volume saliva ejectors and aspirators during dental procedures can reduce droplet and aerosol.

Using mouthwash just before starting dental treatment is often used to reduce the number of microorganisms in the mouth. Thus, both the possibility of infection in the operation area and the number of microorganisms also decrease. Although there is no clinical evidence yet, it is advised that it would be beneficial to use mouthwash for about one minute before treatment.

7. Approach to the Child Patients in the COVID-19 Pandemic

The increase in social isolation during the pandemic period can affect children both physically and psychologically. During the treatments applied in the paediatric dentistry clinic, communication with the child is high of importance to approach the child, reduce anxiety and ensure cooperation. The attitudes and behaviors of a paediatric dentist towards the child may have a positive or negative effect on the dental phobia of the child in the future. In this process, it is necessary to show a compassionate approach to the child, to keep the child calm and to gain their trust. Since the intensive use of personal protective equipment is frightening for the child, it will be useful to encourage children to wear special clothes like those of dental staff.

8. Recommendations for Paediatric Dental Treatment

Imaging techniques are frequently used if they are necessary after the first examination. Intraoral x-rays are most commonly used in dental imaging. However, since intraoral x-rays increase cough and salivation, panoramic radiography and cone beam computed tomography (CBCT) should be considered as alternative options in the COVID-19 pandemic.

Restorative treatment methods that can be applied to children in primary and permanent dentition include dental amalgams, dental composites, compomers, conventional glass ionomers, resin modified glass ionomers, pit and fissure sealants, stainless steel crowns, atraumatic restorative treatment (ART), minimally invasive treatment, interim therapeutic restoration (ITR), strip crowns, preformed steel crowns, pre-veneered crowns, aesthetic restoration.

In paediatric dentistry, it has become a necessity today to evaluate the issues to be considered during and after the COVID-19 pandemic, to review the caries removal and treatment methods and to evaluate the most effective but minimal invasive treatment methods.

It is safer and more reasonable to prefer atraumatic, non-invasive or minimally invasive treatment methods that do not produce aerosols or produce minimal aerosols to remove caries in both primary and permanent dentition, during the COVID-19 pandemic and in the near future. Fluoride varnish application, ART, ITR, Hall technique and stainless-steel crown application can be preferred in the COVID-19 pandemic, since the risk of aerosol producing is at the lowest level. In order to reduce the time that the child spends in the clinic, the patient should be informed about the importance of diet, tooth brushing, dental floss, fluoride toothpaste and mouthwash after a quick examination and solving the acute problem.

The high concentration of fluoride in topical fluoride gels and varnishes is the reason why they are preferred in preventing caries in children. When fluoride is used in the treatment of initial caries, the hydroxyl ion in the hydroxyapatite crystals in the enamel is replaced by fluoride ions and turns into fluorapatite structure. Fluorapatite structure is more resistant to acids produced by cariogenic bacteria than hydroxyapatite. The use of topical fluoride allows fluoride ions to pass into enamel, dentin, dental plaque and saliva. Silver diamine fluoride is a colorless topical ammonia liquid containing silver and fluoride ions. While the silver in its content has antibacterial properties, it also increases the remineralization of dental hard tissues with the presence of fluoride. The combination of the two shows synergistic effect. It is applied on carious lesions without any preparation, occludes dentinal tubules and provides protection. The use of topical fluoride, which has an important place in caries prophylaxis on one hand, and silver diamine fluoride, which can be applied to carious teeth on the other hand, are also another two applications that can be preferred in this period, as they are short-term treatments that do not produce aerosols.

Pits and fissures on the occlusal surfaces of posterior teeth in children are areas of high caries risk since they are exposed to acids that are formed by the fermentation of nutrients by microorganisms. These areas should be covered with fissure sealants in order to protect them from caries. After the sealants penetrate the pits and fissures, they harden and act as a physical barrier against microorganisms and debris. Clouds of COVID-19 sealants are more useful materials as they have minimal aerosol generating procedures.

Interim therapeutic restorations (ITR) are generally applied in non-cooperative children, small children or children with special care needs, in cases where dental treatments need to be postponed. ITR are non-permanent restorations that are used for a temporary period of time. The purpose is to control the caries cavity. Atraumatic restorative technique (ART) has been accepted for the purpose of restoring and protecting caries in societies that cannot reach conventional dental treatments. It has been reported that the use of glass ionomers in both ITR and ART has a high caries preventive effect. Ozone therapy can also be very helpful in controlling the progression of asymptomatic caries lesions, especially in this period when there is a need to minimize the use of aerosol generating high-speed handpiece. On the other hand, Hall technique is the placement of glass ionomer cement into the stainless-steel crown with finger pressure after selecting the appropriate stainless-steel crown without requiring any cavity preparation and local anesthesia. In these treatments, it should be considered as an alternative to conventional methods, since the procedures are short, the aerosol producing is low, and the material used has anti-caries effects.

Among non-cooperative children and children who are in need of special medical care may need to be treated with general anesthesia or sedation.

Conventional treatments should be planned by taking necessary precautions in symptomatic and emergency treatment situations. During dental treatments, aerosol producing is also high, as such instruments are frequently used. One of the most practical ways to reduce contamination during treatments is rubber dam isolation. Aerosols and saliva emitted from rubber dam instruments are highly effective in reducing blood contamination. If necessary, after local anesthesia, a rubber dam is applied and the caries removal process is started. Preparation of the cavity using excavators or chemical caries removal techniques in paediatric patients for whom the use of rubber dam is not appropriate is also among the measures to be applied in the COVID-19 pandemic. The high-volume saliva ejectors used during cavity preparation reduces aerosol producing.

9. Disinfection of Contaminated Surfaces

The cleanliness of the rooms is essential, as SARS-CoV-2 can survive for approximately 72 hours. All contaminated surfaces such as dental units and door handles, chairs, tables should be cleaned and prepared for the following patient after the end of the treatment. 62-71% ethanol, 0.1% sodium hypochlorite, 50% quaternary ammonia, 1% povidone-iodine and 0.5% hydrogen peroxide can be used for disinfection. Ozone disinfection can also be considered as an alternative procedure for cleaning surfaces. Children with signs of COVID-19 and needing treatment can be treated preferably in infection isolation rooms with negative air pressure, using high-efficiency particulate (HEPA) filter.

10. Conclusion

To summarize what kind of changes the COVID-19 pandemic has led to the clinical practice in the light of the aforementioned information:

- First of all, materials such as toys, magazines, and books should be removed from the clinic since they may cause contamination and cross-infection. In the waiting areas, seats should be placed in accordance with the social distance, and the reception desk should be separated by a separator.
- Appointments of patients should be arranged by considering if any COVID-19 contact and presence of symptoms are evident during the phone calls before admissions to the hospital.
- Contact-free forehead thermometer should be used at hospital entrances, patients with high fever should be guided to pandemic hospitals. Patients without symptoms can be allowed to enter the clinic using hand sanitizer.
- When entering the hospital, patients and their attendants should wear masks and should not remove them during their stay in the clinic.
- As children may be afraid of personal protective equipment while being admitted to the clinic, personal protective equipment can be put on children to calm them down.
- While applying dental treatments, methods and applications that will minimize aerosol producing should be preferred.
- Paediatric patients and their attendants should be reminded of the importance of diet and oral hygiene.

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CHAPTER 8

INFECTION CONTROL MEASURES AND MANAGEMENT DURING COVID-19 PANDEMIC IN TURKEY

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Introduction

Coronaviruses are known to infect humans and cause respiratory diseases. It is possible to say that severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) infections, which cause serious infections, are the precursors of the corona virus disease 2019 (COVID-19) pandemic. Our world faced a new epidemic that could progress to severe respiratory failure at the end of December 2019. The presence of patients with pneumonia of unknown etiology was reported to the World Health Organization (WHO) by China on 31 December 2019. The virus was classified SARS-CoV-2 and the disease was named COVID-19 by the coronavirus working group. It took 2,5 years in MERS epidemic, about 4 months in SARS but just 48 days in SARS-CoV-2 for 1000 people to be infected. The clinical manifestations of COVID-19 infection range from asymptomatic to acute respiratory distress syndrome, septic shock, and multi-organ failure, which can lead to death. The pandemic was declared by WHO on 11 March 2020 to detect the infection, prevent its spread, highlight the seriousness of the situation and mobilize all countries by raising awareness on this issue. The rapid transmission of the COVID 19 disease has brought the health system to collapse even in the countries that have advanced health infrastructures. In addition to the disruptions in health services, the pandemic has been also caused confusion among societies in social, political and economic fields.

The novel coronavirus (COVID-19) poses a high risk for community and healthcare providers. Infected persons are the main source of the transmission of COVID 19 infection. The duration of transmission for patients with COVID 19 is unclear. It is stated that it can be transmitted just before the development and, during the course of the disease, especially in the early stages of the COVID-19. SARS-CoV-2 can also be transmitted from asymptomatic individuals and patients during the incubation period. However, it is not yet clear to what extent the disease is transmitted from the patient at which stage of the COVID-19. The virus that causes COVID-19 is transmitted from person to person through droplets and close contact. The virus, which is present in respiratory droplets produced when a person coughs, sneezes or speaks, spreads by direct contact with mucous membranes. Transmission of the virus can also occur by touching the mouth, eyes, or nose after contact with fomites, without practicing hand hygiene, and inhaling aerosols produced during general procedures. Droplets cannot move more than 2 meters, so there is no consensus about whether viruses can be transmitted through the air particles smaller than droplets that remain in the air under normal conditions. SARS-CoV-2 has also been detected in non-respiratory samples such as feces, blood, ocular secretions, semen, and their role in transmission is still unclear. Respiratory viruses are not transmitted by blood, and so transmission by transfusion has not yet been demonstrated in SARS-CoV-2, MERS-CoV and, SARS-CoV infections. There was no evidence that SARS-CoV-2 could be transmitted by contact with non-mucous membranes (non-intact skin).

Despite the advances in medicine, there is no FDA-approved drug effective against the virus that has so far been found in order to control the global COVID 19 pandemic. Other reasons that make it difficult to control the pandemic are the emergence of variant strains despite the high efficacy of the current vaccine, and the availability of the vaccine at different levels for each country. The best effective weapon against the COVID-19 influence not only the healthcare system but also economic, political and, social fields is the prevention of the spread. Consequently, the way to control the pandemic, which has spread rapidly to all countries and has become a serious threat to the community, is infection control and precautions. Infection prevention and control strategies are the most effective method implemented by many countries for optimal management of transmission risks from patients with probable or proven COVID-19.

Screening, isolation, early diagnosis and treatment are the top priority steps to break the chain of infection. Preventive strategies focus on careful infection control during diagnosis and treatment, especially in isolation of patients. The prevention and control measures in the community for COVID 19 are summarized in Table 1.

Among the measures taken by the countries at the beginning of the epidemic, the 4 main measures that they recommend to the individuals in the society and try to ensure compliance are respectively; social distance, mask, washing hands and not going out except for compulsory situations. However, considering that full compliance with the physical distance control and mask-wearing principles could not be realized, restrictions were also imposed on the corporate common areas. Extended measures, including restriction of movement, closure of schools and businesses, geographic area quarantine, and restriction of international travel, have been implemented by some countries. WHO has published recommendations covering health, transport, education, security, and all other sectors during the pandemic. According to the results obtained, with mathematical modeling made in European Union countries, including England, where the measures were evaluated, the most effective restrictions were curfews, the postponement of large meetings and congresses while the closure of the nursery and kindergarten did not have any effect on the pandemic.

Pandemic influenza preparation plans have been made in our country since the beginning of the 2000s and have been revised over the years. The central and provincial responsibilities of the Ministry of Health have been determined and the number of health workers, equipment, and drug stocks has been updated. In order to ensure coordination in the pandemic, meetings were held with all sectors at regular intervals and all stakeholders in our country were prepared. International travel was initially restricted to prevent the entry of COVID 19 cases into the country. The first case detected in our country was announced by the Ministry of Health on March 11, 2020. After the cases started to be seen in our country, regional measures were taken by imposing restrictions on the provinces with the high number of cases.The measures taken in our country with the emergence of the COVID-19 disease are shown with a timeline in Figure 1. Considering the hospital and intensive care capacities, in order not to interrupt the treatment step, firstly, the follow-up and treatment of COVID-19 cases was carried out in the predetermined hospitals. Contact follow-up studies have been initiated to prevent the spread of the disease in the community, and early diagnosis and, treatment of the cases have been provided. Domestic and regional transmissions have been reduced with isolation practices. Recommendations covering health, transportation, education, security, and other sectors have been published by the World Health Organization and the Turkish Ministry of Health during the pandemic.

Unless a large percentage of the population is vaccinated and mutations cannot be prevented from developing, cases will remain a resource. Therefore, it is very important to prevent the spread of COVID-19 in the community. The foremost practice in the fight against COVID-19 is infection control and precautions. Early recognition of cases by increasing test capacity also plays an important role in epidemic control. Educational activities, which are also included in infection control measures, play a key role in increasing social awareness and reaching the target faster. However, the main points of preventing the spread in society are hand hygiene, mask, social distance, quarantine, and cleaning.

TABLE 1. COVID-19 prevention and control methods

1. Quarantine
• Voluntary quarantine
• Mandatory quarantine (home, hospital, official and other places)
2. Other measures
• Hand hygiene
• Social Distance
• Personnel protective equipment
• Insulation
• Avoiding crowds
• Measures in schools / closure of schools
• Measures in workplaces / closure of workplaces

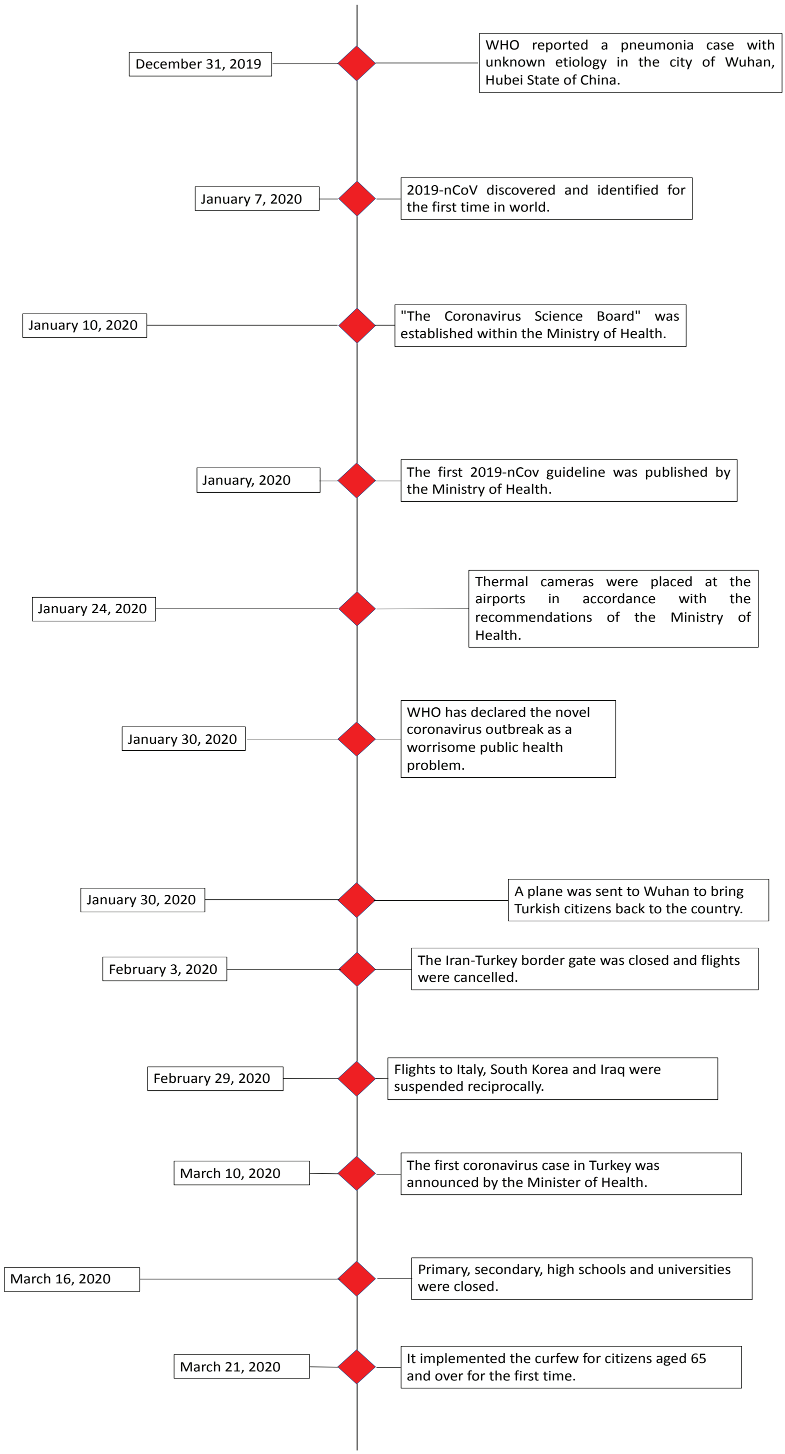

Figure 1. A schematic representation of a timeline of the measures taken by Turkey to control and prevent the spread of the coronavirus.

Hand Hygiene

Hand washing is the most effective, easy, and inexpensive way to prevent the spread of the virus during the COVID-19 pandemic. Washing hands frequently with soap and water for at least 20 seconds is the most important infection control strategy for the community. It is important to use the hand cleaner containing at least 60% alcohol in cases where soap and water are not available. To ensure hand hygiene, it is necessary to increase the widespread use of hand sanitizer in the outdoor environment by the community. Care should be taken not to touch the eyes, nose, mouth and face with unwashed hands. In addition, respiratory hygiene, which is effective in the control of respiratory tract infections, should be applied. Mouth should be covered while coughing and sneezing, then hand hygiene should be performed. Hand and respiratory hygiene posters were prepared by the Ministry of Health for informational purposes in our country (Figure 2). Videos about hand washing and respiratory hygiene were shared as public service ads through the media. Informational videos, brochures, and posters have been prepared on protection from COVID-19 all over the world, especially by WHO.

The COVID-19 pandemic has managed to draw maximum attention to hand hygiene, which ranks first among infection control and measures. During the COVID-19 pandemic, awareness of infection control measures developed more rapidly in some countries such as China, Korea, and Japan. It has been observed that the number of people carrying hand sanitizer for emergency hand hygiene application has increased and the use of masks has become widespread among the citizens of these countries. Therefore, while the pandemic was brought under control much faster in the aforementioned countries, the increase in the number of cases continued in countries where the measures were not made compulsory.

Figure 2. Poster emphasizing hand washing prepared by the Turkish Ministry of Health

Social distancing

Social distance is the measure of the distance that must be between people in order to be protected from infections that are known to spread from person to person in the community. COVID-19 mainly spreads among people who are in close contact (within about 6 feet) for extended periods of time. Droplets released when an infected person coughs, sneezes, and speaks are responsible for transmission. Studies have shown that people who are infected but not symptomatic play a role in the spread of COVID-19 disease. Social distancing of 2 meters is important, as people can spread the virus without knowing they are sick. People with high-risk diseases should pay more attention to social distancing. SARS-CoV-2 can survive on a surface for hours or days, depending on factors such as sunlight, humidity and type of surface. It may be possible for a person to contract COVID-19 by touching a surface or object with the virus on it and then touching their own mouth, nose and eyes. Maintaining social distancing helps limit the possibility of coming into contact with contaminated surfaces and infected people in areas outside the home. Schools, workplaces, public markets, and mass events have been suspended. Online applications have been introduced in many fields, especially in education. In our country, it was acted in the light of the guidelines issued by the Ministry of Health. Social distancing is critical in maintaining control over the pandemic.

Personal protective equipment

Masks are barriers that prevent your respiratory droplets from reaching others. When masks are put on, we protect ourselves and others. Masks work well when everyone wears them. The use of masks is very effective in preventing the spread of COVID-19 and other respiratory infections. Research shows that masks reduce the ejection of droplets when worn over the nose and mouth. COVID-19 often spreads among people who are in close contact with each other, it is important to wear a mask when we have to be at a distance of fewer than 6 feet. Experimental and epidemiological data support the use of masks as a community to provide source control and reduce the spread of SARS-CoV-2. Wearing the mask is not associated with clinically significant effects on respiration or gas exchange. The CDC recommends the use of community masks, particularly valveless multilayer fabric masks, to prevent transmission of SARS-CoV-2. As of April 4, 2020, the use of face masks has been made mandatory in closed and crowded areas, public transportation vehicles and workplaces where collective work is compulsory by the Ministry of Health's Coronavirus Scientific Committee. In our country, the Ministry of Health has made the following recommendations regarding the correct use of masks.

- Before putting on the mask, hands are washed for at least 20 seconds with water and normal soap.
- In the absence of soap and water, hands are rubbed for 20-30 seconds with an alcohol-containing hand antiseptic.
- The mask is worn in such a way that it completely covers the nose, mouth, and chin and does not allow air passage from the sides.
- The metal strip on the top of the mask is placed on the bridge of the nose by pressing it lightly.
- The mask cannot be touched while the mask is on the face.
- The mask should be removed without touching the front part of the nose, mouth and chin, where heavy contamination occurs.
- It is recommended to immediately remove the moistened mask to replace it with a new and dry one.
- It is recommended not to reuse disposable masks.
- The removed mask is thrown into the trash by holding its elastics or strings, and the garbage is kept closed all the time.

The CDC is currently examining the effectiveness of various cloth mask materials. The European Centre for Disease Prevention and Control (ECDC) does not recommend the use of face shields or goggles instead of a mask. However, goggles and face shields can be used after wearing the mask. Face shields and goggles are primarily used to protect the wearer's eyes. Glasses do not cover the nose and mouth, so face shields are not effective at protecting you or the people around you from respiratory droplets. The respiratory droplets can pass through the large space under the face shield and the gap between the face and the face shield. Although the necessity and effectiveness of wearing a mask has been emphasized many times, it may not be possible for some people to wear masks due to their health conditions.

Quarantine

Throughout the ages, people have taken measures to prevent the spread of the disease against the risk of a possible epidemic. Quarantine is one of the oldest and most effective methods for epidemic control. The origin of the word comes from the "quarantena" meaning 40 days in the 14th century Venetian dialect. Quarantine was applied for the first time in the Venetian-controlled city of Ragusa (today's Dubrovnik) on the Dalmatian coast, where the ship and its personnel were kept waiting before being taken to the port in case of illness. These isolation practices, which were initiated during the great plague epidemic, include keeping the personnel on the ships for 30 days before entering the port of Ragusa, so the practice was called "trentina", that is, a thirty-day period. The waiting period was increased to 40 days in control of the plague epidemic, the practice began to be called "quarantine". During the Spanish flu in 1918, the importance of quarantine was clearly understood. Quarantine is different from isolation, which means separating sick or infected persons from others to prevent the spread of infection or contamination. Persons who do not show signs of illness in quarantine but are exposed to the infectious agent are kept separate or limited in a certain area during the incubation period of the agent.

According to the CDC recommendations updated during the current pandemic process, quarantine is applied to people who have been in close contact with someone who has COVID-19, except for people who have had COVID-19 in the past 3 months or are fully vaccinated. People who have recovered from COVID-19 infection in the past 3 months do not need to be quarantined or tested unless they develop new symptoms. In studies evaluating the effectiveness of quarantine practices, it has been determined that transmission and death rates have decreased significantly. In a study performed by Nussbaumer-Streit B et al. which evaluating 29 studies in total, their research shows that quarantine practices can reduce the number of infected from 81% to 44%, and the death rate from 61% to 31%. However, with the prolongation of the pandemic, various variants have emerged as a result of the accumulation of different mutations that cause changes in some characteristics of the virus in different location of the world. Studies have shown that some variants are transmitted more rapidly and lead to a more severe clinical picture situation. It has also been determined that some variants are less affected by antibodies acquired as a result of past natural infections or vaccination.

Quarantine recommended situations are listed below.

- Being in contact with a patient diagnosed with COVID-19 at a distance of less than 6 feet for 15 minutes or more
- Providing home care to a COVID-19 patient without using appropriate personal protective equipment
- Having physical contact with a COVID-19 patient (hugging, kissing, etc.)
- Shared use of containers for food and drink

- Exposure to respiratory droplets caused by a COVID-19 patient coughing, sneezing, and other reasons

The Republic of Turkey Ministry of Health, general directorate of public health has an algorithm for the identification and follow-up of COVID-19 contacts. Based on the estimated incubation period of SARS-CoV-2, a 14-day quarantine is recommended for individuals who have been in close contact with a confirmed case. Active observations of quarantined people and their compliance with quarantine were carried out by our family physicians. In our country, planned quarantine practices are implemented according to contact status.

Cleaning and disinfection

SARS-CoV-2 is transmitted by sick individuals on surfaces contaminated by droplets scattered by sneezing, coughing, and speaking, and by bringing their hands to their mouth, eyes, and nose after contact with other people. Therefore, in addition to hand hygiene, cleaning and disinfection of frequently touched surfaces is necessary for epidemic control. The most frequently touched surfaces such as door handles and tables should be cleaned daily with disinfectants containing diluted bleach (that is, 1-part bleach to 99 parts water). Areas that are not suitable for using bleach can be cleaned with 70% ethanol. However, bleach (0.5% sodium hypochlorite) should be used for toilet and bathroom cleaning. Gloves should be used when touching surfaces, laundry, and clothing contaminated with body fluids. Clothes, bed linen and towels should be machine washed at 60-90°C with normal laundry detergent. The Republic of Turkey Epidemic Management and Working Guide contains details on environmental cleaning, ventilation and disinfection for various sectors.

Increasing testing capacity

Another very important approach to prevent the spread of the disease throughout the community is to identify, test, isolate all suspected cases and quarantine their contacts as well. For this reason, increasing the testing capacity of laboratories and developing new testing strategies make a very important contribution to the control of the pandemic by facilitating the detection of cases to be isolated. In our country, COVID-19 tests can be carried out in the reference laboratory, which is affiliated to the Ministry of Health and serves in 81 provinces.

Conclusion

In the current pandemic process, a specific drug for COVID-19 has not yet been developed, but finding effective vaccines is promising. However, with these developments, variant strains have also started to emerge. Therefore, preventing the spread of critical variants is still of critical importance. The most basic points for controlling the COVID-19 pandemic, which deeply affects the whole world, are hand hygiene, social distance, mask use and quarantine. Early identification of cases by increasing testing capacity can also limit the spread of COVID-19 disease in the community. As a result, in the process of breaking the chain of transmission, increasing awareness in all parts of the society and implementing infection control and precautions will also be the main factor in controlling future epidemics.

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CHAPTER 9

COVID-19 AND INTERNET ADDICTION DISORDER

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1. INTRODUCTION

An outbreak of the new coronavirus disease has first emerged in Wuhan, China, and World Health Organization (WHO) called it COVID-19. COVID-19 is one of today's most significant public health problems, causing the death of many people. This rapidly spreading pandemic has become a nightmare, affecting the entire world.

COVID-19 has caused many habits of individuals and societies to change, with its power. Quarantine, isolation, and social distance are among the measures taken during the pandemic. This, in turn, causes people to spend more time at home. An increase in stay-at-home time causes people to change their life habits and spend more time with electronic devices such as televisions, computers, phones, and tablets. In this case, this leads to an increase in people's internet/digital addiction.

2. COVID-19 PANDEMIC

2.1. Development of COVID-19 Pandemic

Humans have encountered three fatally pandemics in the recent two decades, namely Middle East Respiratory Syndrome (MERS), SARS, and COVID-19, which have so far been linked to new coronaviruses. In December 2019, COVID-19 was first proclaimed in Wuhan, China. Several people in Wuhan, China, were diagnosed with viral pneumonia with symptoms including weakness, a dry cough, fever, and shortness of breath. The disease was originally called Wuhan pneumonia by the press due to the symptoms of pneumonia. But it was later determined that the cause was SARS-CoV-2. SARS-CoV-2 is in the coronavirus family, which can cause severe respiratory infections in humans, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Because the new coronavirus is highly contagious, it has spread rapidly in the human population, reaching other countries around the world.

On February March 12, 2020, the World Health Organization (WHO) officially called this infection to be coronavirus-disease-2019 (COVID-19), and it declared a pandemic all over the world on March 11, 2020.

Clinical symptoms of COVID-19 vary. As there may be cases without symptoms, it is observed in cases ranging from mild disease to severe or fatal disease. The most prevalent symptoms of COVID-19 are mainly cough, fever, and myalgia. Other minor symptoms include sore throat, headache, tremble, nausea or vomiting, diarrhea, and conjunctival obstruction. Pneumonia, kidney failure, severe respiratory failure, and death may arise in severe cases.

COVID-19 can spread through both direct or indirect ways. The spread of COVID-19 from person to person occurs mainly through respiratory droplets. Droplets typically cannot move forward more than six feet (almost two meters) and droplets in the air can remain infectious for a limited period of time (up to about 3 hours). After a person touches a surface contaminated with the virus, the contact of hands with the eyes, nose, or mouth can also cause COVID-19.

This virus shows a very rapid spread. Countries apply some restrictions on social, cultural, professional, and social life areas to stop the pandemic and prevent further infections and deaths. These restrictions include bringing the business home, temporarily closing schools and universities to face-to-face education, closing shops, restaurants, and museums, canceling cultural and sporting events, short-term closures of borders and travel warnings, as well as closing mouths and noses in public places. One of the most important constraints is the “social distance” strategy, which includes the limitations of social contacts, as well as creating physical distance. Self-isolation and social distance constraints can cause individuals to experience many psychological and social problems.

Individuals expend time on the internet to maintain corporate services, to continue educational activities without interruption, to shop, to play online games, to use social media, to watch movies, and to chat. These activities can often be beneficial when reasonably used to reduce stress and apprehension or relieve depressed psychology. But uncontrolled and extreme use of the internet can turn into internet addiction.

2.2. Internet Addiction Disorder

With the development of technology, internet addiction has become a global problem. Internet addiction can be defined as the inability to prevent the desire to overuse the internet in general, spending more time on the internet, losing the concept of time when connected to the internet, and the appearance of deprivation symptoms such as irritability, tension, restlessness, and the deterioration of a person's relations with their social environment when there is no internet.

For many people, the addiction term covers the use of substances such as alcohol, marijuana, heroin, cocaine, but there are also addictive behaviors such as playing computer games, watching television. Behavioral addictions also indicate deprivation symptoms such as mood variability, deprivation, interpersonal conflict, just like alcohol-substance addictions.

The lack of consensus on the identification, nomenclature, and classification of internet addiction has led researchers to develop different assessment tools. Young considers that 5 diagnostic criteria from the 8 criteria he defines are necessary for the diagnosis of internet addiction:

1. Excessive mental activity associated with the internet (frequently thinking about the internet, dreaming about activities done online, thinking about the next activity intended to be done on the internet, etc.)
2. Increasing need to use the internet to achieve the desired enjoyment
3. Unsuccessful attempts to reduce, control, or entirely stop using the internet
4. Feeling restlessness, disgust, or resentment if internet use is decreased or completely stopped
5. Staying online longer than originally aforethought
6. Having problems with school, family, friends, and work due to extravagant internet use, jeopardizing or losing an educational or career-related opportunity
7. Lying to other people (therapist, family, friends, etc.) about spending time online
8. Using the internet to avoid problems or to get away from negative emotions (e.g. helplessness, feeling guilty, disgust, anxiety).

Internet addiction has emotional symptoms such as depression, feeling guilty, anxiety, isolation, loss of time perception, avoidance of work, and loneliness, as well as physical symptoms such as back pain, headache, insomnia, neck pain, and eye problems.

In a meta-analysis study conducted by Cheng and Li in 31 countries in different sides of the world, the global prevalence of internet addiction in the adolescent group was found to be 6%. According to this study, addiction rates were highest in Asian and Middle Eastern countries (10.9%), while the lowest places were northern and western European countries (2.6%). The prevalence of internet use ranged from 1.2% to 11.8% and was found to be higher in boys than girls in a study carried out in 12 European countries by Durke et al. In China, the prevalence results of internet addiction were determined to be 26.5% by Xin et al. In Taiwan, internet addiction was found to be %17.4 by Lin et al. Also, in our country (Turkey), the prevalence of internet addiction was reported as 14.4 % by Aktepe et al.

2.3. Internet Addiction during COVID-19

The COVID-19 infection, which appeared in Wuhan, China, quickly spread to all countries of the world in a short time and was declared a "pandemic". At the time of writing of our study (May 15, 2021), there were more than 160 million cases and more than 3 million deaths in the world. In the data of the Ministry of Health of our country (Turkey) on the same date, the total number of cases was reported as 5 million and the death rate was reported as about 44 thousand. The COVID-19 pandemic is causing great anxiety and fear, with millions of cases and thousands of deaths.

As part of the fight against the COVID-19 pandemic, countries are taking a number of precautions, such as social distance, isolation, and quarantine to avoid the dissemination of the disease. During the COVID-19 pandemic, isolation, quarantine, and social distance measures increase the time people spend at home, their daily routines disappear, and this state of restriction leads to disorders associated with fear, stress, feelings of loneliness, anxiety disorders, depression, and trauma in individuals.

Experiencing negative mental health symptoms in their social life, such as depression, anxiety, stress, and fear, may increase the internet use of individuals. Because individuals consider the internet as a savior to escape the psychological and social problems they face in everyday life. They may exhibit behaviors including watching videos, playing games, watching TV series, surfing on the internet, or using social media to reduce stress and concern due to the pandemic and/or relieve depressed psychology, and these behaviors can turn into habits in the future.

According to the results of a worldwide study conducted on people aged 16-64 in March 2020, when home media consumption was examined in the process of the COVID-19 pandemic, it was found that 45% of individuals watched more TV, 45% spent longer on messaging services (such as Whatsapp, Facebook), 44% spent longer on social media, and 36% spent more time on computer/video games. In a study conducted by Sun et al., 46.8% of participants in China reported increased addiction to internet use, and 16.6% reported having internet use for longer periods of time during the COVID-19 pandemic. A study conducted by Balhara et al. on college students found that 50.8% of participants in the COVID-19 restriction increased the behavior of playing digital games. A study conducted by Lin in Taiwan also noted that the prevalence of internet addiction among secondary school students during the COVID-19 pandemic was high.

The prevalence of COVID-19 is among the disorders that can dramatically increase internet addiction due to quarantine at home and lifestyle changes. This increase can both endanger the physical health of individuals and increase the chances of developing other mental disorders such as anxiety and depression.

3. Conclusion

Internet addiction, which has increased with the COVID-19 pandemic entering our lives since the end of 2019, is turning into psychological disorders. Especially in the pandemic process, it may be recommended to implement national programs aimed at using the internet correctly and usefully. It can also help to implement training and consulting programs to prevent internet addiction and provide solutions.

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CHAPTER 10

IS THERE A RELATIONSHIP BETWEEN ORAL HYGIENE AND SEVERITY OF COVID-19 COMPLICATIONS?

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new virus discovered in the Coronavirus family, was first diagnosed in late 2019.[1] With the outbreak of SARS-CoV-2, it caused a massive pandemic of coronavirus disease (COVID-19) and was declared emergency globally by WHO.[2] As of 3 December 2020, more than 63 million laboratory-confirmed cases in 220 countries have been reported regarding the coronavirus disease 2019 (COVID-19) outbreak caused by (SARS-CoV-2) infection. As of March 3, 2020, Covid-19 is estimated to have a mortality rate of 3.4%. The average time from the beginning of symptoms to death is 14 days.[2] Confirmed cases and a reported number of deaths of more than 1.4 million (WHO) are causing social and economic disruption globally.

SARS-CoV-2 is a member of the Coronaviridae family, which includes many virulent strains that infect humans and animals, including SARS CoV and Middle East respiratory syndrome CoV (MERS-CoV).[3] The primary entry of this virus is believed to be through droplets that lead to initial contact and colonization with cells in the oral cavity, nose or eye.[4] To date, a polymerase chain reaction test (PCR) has been used by taking nasal and sometimes oropharyngeal swabs to determine whether patients are Covid-positive or negative[5]. Oropharyngeal swabs of patients infected with SARS-CoV-2 have been identified as one of three diagnostic criteria by health authorities in China[6]. Nevertheless, numerous cases of Covid-19 have been reported with negative results with the PCR test, despite showing obvious clinical signs of the disease[7,8]. The presence of SARS-CoV-2 has also been reported in a variety of other human secretions and feces, such as sputum, feces and urine. Similar to blood, saliva is rich in numerous biological markers such as DNA, RNA, and proteins. Since saliva and blood bear many similarities in terms of molecular components, they contain easily detectable levels of microorganisms[2]. However, it has not been confirmed whether there are detectable levels of SARS CoV-2 in saliva, one of the most accessible and easily collected bodily fluids for Covid-19 patients.

The Symptoms of COVID-19

The clinical symptoms of Covid-19 appear after an incubation period of approximately 5.2 days. Varying symptoms such as fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%) and sore throat (17.4%) are developed in mild cases diagnosed as positive for this virus. It has also been shown that diarrhea is an important distinguishing symptom for Covid-19 compared to SARS-CoV and MERS-CoV[3,6].

Covid-19 has the ability to trigger an excessive immune reaction in the host, and this is called the “cytokine storm”. It causes extensive tissue damage, particularly in the connective tissue of the lungs and respiratory failure occurs in some cases. In more advanced cases it can lead to hospitalization in the intensive care unit and eventually death[2,9,10].

A number of studies are being conducted to understand the pathogenesis of SARS-COV-2 and chemokines that play an important role in its inflammation. Chemokines are a family of cytokines that are chemotactic in nature and cause inflammation-related cells to aggregate. Many pathophysiological mechanisms have been put forward to explain its physiological behavior. One of these mechanisms explained is the “cytokine storm” that causes the release of high level IL-1 beta, IL-7, IL-10, IL-17, IL-2, IL-8, IL-9, GM-CSF, G-CSF, IFN gamma, TNF alpha, MIP1A, MIP1B, MCP1 and IP10.[11] Even higher levels of IL-2, IL-7, IL-10, IP-10, G-CSF, MIP1A, MCP1 and TNF alpha are released from patients with more severe symptoms requiring admission to the ICU. High levels of Th17 pathway responses were also observed in SARS-CoV and MERS-CoV patients. Th17-type inflammatory response plays a role in the development of cytokine storm and the negative consequences of pulmonary edema and tissue damage in lung infections caused by SARS-CoV-2.[11]

Periodontal diseases are long recognized as a silent pandemic with a complex multi-factorial pathophysiology. This appears to reflect the high cytokine levels detected in locally inflamed gum tissue, in the systemic circulating cytokine levels.[12] According to the periodontal tissues of healthy patients, it was observed that IL-17-producing cells were increased in the periodontal tissues of patients with gingivitis and periodontitis, and also high levels of IL-17 were found not only in the oral tissues but also in the serum of the patients.[13] There is evidence in the literature that non-surgical periodontal therapy leads to a decrease in IL-17 levels in both GCF (local) and serum (systemic) of patients with periodontal disease.[13] This inflammatory response pathway points to an association between Periodontitis and the adverse outcomes associated with Covid-19. It also points out that periodontal disease as a predisposing factor can have negative consequences for the development of Covid-19. Understanding this relationship highlights the importance of keeping periodontal disease under control and maintaining oral hygiene during Covid-19.

Risk Groups of Covid- 19 Disease

The most confusing and still unanswered question about Covid-19 is why some individuals are more severely affected by the disease. Although the rate of complications and mortality has increased as expected in patients with defined risk factors for this disease, the proportion of young and healthy infected patients who do not have defined risk factors and who show serious side effects and complications is quite high[14].

The risk factors of this disease includes age (mean age 69), gender (males represented 70% of deaths), and 48% of cases had an underlying comorbidity (hypertension 30%, diabetes 19%, or heart disease 8%). Age in particular is one of the highest risk factors for developing severe symptoms of Covid-1915. Therefore, it has been stated that individuals over the age of 65 and those living in long-term care facilities are particularly susceptible to morbidity and mortality due to SARS-CoV-2 infection. In addition to the risk groups mentioned, people with chronic lung disease, moderate to severe asthma, severe obesity, diabetes, chronic kidney disease, and liver disease are also at high risk for severe Covid-19 symptoms, and microorganisms in the oral area aggravate the course of the disease and increase complications[16].

Microorganisms responsible for respiratory tract diseases and periodontal diseases descend from the trachea to the lungs through secretions such as saliva released from the mucosa. In individuals with poor oral hygiene, when body resistance is low and defense mechanism is weak, microorganisms living in the mouth trigger many systemic diseases. Therefore, oral hygiene is vital for individuals with chronic diseases.[17]

Importance of Oral Bacteria

In respiratory diseases, the importance of oral microflora has become more important over the past 10 years. The oral area is an important passage for the human body. The bacterial flora of the mouth area is very important for the lungs, as the air we breathe passes through the nose and mouth to the respiratory area.[18]

Microorganisms in the oral area have been shown to cause a number of oral infectious diseases such as caries, periodontitis, root canal infections, alveolar osteitis and tonsillitis.[18] The main reason for the increase of microorganisms in the oral area is the lack of oral hygiene and periodontal diseases that often develop due to this.[18-22] It has been shown that the main bacteria, which are often the causative agents of respiratory disease, colonize the oral cavity. The oral cavity hosts more than 700 bacteria, viruses and fungi that can colonize the mouth.[23] There are various microbiological habitats in the mouth; however, the primary bacterial species are P. intermedia, S. mutans, F. nucleatum and P. gingivalis24.

Periodontal disease is a very common inflammatory chronic disease that starts with bacterial infection and causes the destruction of the tissues that support teeth and thus the formation of periodontal pockets from a healthy gingival sulcus.[25,26] Periodontal pockets occur as a result of pathological migration of supracrestal connective tissues towards the apical with alveolar bone loss. Complex subgingival biofilms are formed along with the ulcerated epithelial wall as a result of these periodontal pockets.[27]

Periodontal diseases are not only limited to damage to the oral area, but also increase the incidence of systemic diseases and cause various complications. Epithelial sensitivity of proinflammatory mediators such as cytokines produced in diseased periodontal tissues and hematogenous spread may also increase the severity of previously developed systemic inflammation. Patients with periodontal disease have a 25% increased risk of cardiovascular disease, a 3 times increased risk of diabetes mellitus, and a 20% increased risk of hypertension.[28-30]

Inadequate oral hygiene and periodontal diseases increase the capacity of anaerobic bacteria in the oral area and teeth act as reservoirs for these increasing bacteria. Lower respiratory tract infection begins as a result of contamination of the lower respiratory tract epithelium by inhalation of microorganisms contained in aerosolized droplets or aspiration of oral secretions (containing microorganisms such as P. gingivalis, F. nucleatum, P. intermedia) associated with oral disease. In addition, as a result of increased bacterial load, bacterial complications continue to increase when bacteria pass between the lungs and the oral area.[31-34]

Suggested mechanisms to explain the role of oral bacteria in the pathogenesis of respiratory tract infection are:[35]

1. Aspiration of oral pathogens into the lungs
2. Enzymes associated with periodontal disease can alter mucosal surfaces to allow respiratory pathogens to adhere and colonize.
3. Enzymes associated with periodontal diseases can prevent bacterial clearance from mucosal surfaces by destroying the membranes of bacteria.
4. Respiratory epithelium can be altered by cytokines associated with periodontal diseases, inducing infection by respiratory pathogens.[36]

There are studies showing the association of oral microorganisms with many systemic diseases including cardiovascular and respiratory system diseases. The most important of these systemic diseases are sepsis, preterm labor, diabetes and pneumonia.[18]

Pneumonia and acute viral respiratory infections are the two most common airway infections in elderly patients and the largest cause of death in patients over 70 years of age.[37] Pneumonia is an inflammatory condition of the lung parenchyma tissue that develops as a result of bacteria or viruses entering the lower respiratory tract. Aspiration of infectious agents such as bacteria and viruses from the mouth and nasal cavities causes pneumonia to start.[38] When the effects of periodontopathic bacteria such as F. nucleatum, P. gingivalis and

P. intermedia on pneumonia were researched, it was found that especially P. intermedia caused severe pneumonia in subjects with higher periodontopathic bacteria levels. Severe pneumonia is the main cause of death from Covid-19.[39]

SARS-CoV-2 Virus and Its Relationship with the Oral Area

According to researches, SARS-CoV-2 is genetically less than 80% similar to SARS-CoV (about 79%) and MERS-CoV (about 50%) viruses. The important difference of SARS-CoV-2 compared to other SARS-like coronaviruses (SARS-CoV and MERS-CoV) is that it has a long spike protein.[40,41] The spike protein mediates the binding of the virus to the ACE2 receptor and its fusion with the host cell membrane. In addition, this protein is very important in determining host tropism and the spread capacity of the virus.[40,42] The SARS-CoV-2 spike protein specifically recognizes receptor angiotensin converting enzyme 2 (ACE2) in the host for its defined receptor binding domain. Basic atomic interactions between the SARS-CoV spike protein receptor binding domain and the host receptor angiotensin converting enzyme 2 (ACE2) regulate both interspecies and human-to-human transitions.[43]

Studies based on these data show that cells expressing ACE2 receptors should be considered as potential high risk for SARS-CoV-2 infection.[44] High ACE2 expression is observed in type II alveolar cells of the lungs, multilayered epithelial cells of the esophagus, colon-absorbing enterocytes, kidney proximal tubule cells and bladder urothelial cells in the body. These studies have shown that epithelial cells in the oral cavity (tongue, buccal mucosa, gingiva and salivary gland ducts) also express high levels of ACE2.[44] These findings suggest that the oral cavity mucosa may be a potential risk pathway for the spread of SARS-CoV-2 infection.[41,45]

The Effect of Oral Hygiene on the Course of Respiratory Diseases

In a large population cohort study, 49,400 chronic periodontitis patients were treated with periodontal therapy for more than 11 years. According to the Kaplan-Meier plot, it showed that the total incidence of pneumonia in the group receiving periodontal therapy decreased significantly at 12 years of follow-up ($p<0.001$). Many studies have also suggested that methods of improving oral hygiene can reduce the risk of pneumonia.[46,47]

In addition, improved oral care significantly reduced the incidence of ventilator-associated pneumonia in patients with ICU intensive care units (ICUs).[48] A randomized controlled study in Japan studied whether improved oral care could reduce pneumonia and death from pneumonia. Four hundred and seventeen patients were given oral care after each meal and compared with the control group. 19% of the control group had pneumonia compared to only 11% who received oral care. Moreover, the mortality rate after pneumonia in the control group was almost twice that of the group prescribed oral care.[37]

The link between good oral care and reduced risk of acute respiratory viral infection has been established in a number of other studies and has been prevented by improving oral hygiene.[49] Implementation of professional oral care programs to provide oral care, including tooth, tongue and prosthetic brushing, can help reduce the oropharyngeal microbial load and therefore the number of germs aspirated into the lower airway.[50] For this purpose, the effectiveness of CHX applications in reducing pneumonia has been supported by studies.[51,52]

In addition, improved oral hygiene and frequent professional oral health care have been shown to reduce the progression or occurrence of respiratory diseases, especially in the elderly population and those in intensive care units.[46] Cleaning of removable prostheses, which elderly patients often use, is also very important in terms of oral hygiene. If these prostheses are not cleaned sufficiently, they can be a source of infection. If prostheses are not left in cleaning solutions, microorganisms accumulated on them, especially during sleep, may contribute to the development of respiratory diseases by aspirating into the lung. In this elderly population, who has the potential to develop serious complications associated with Covid-19, the importance of oral hygiene is very essential.[53,54]

It is clear that bacterial superinfections are common in patients suffering from severe cases of Covid-19, and bacterial superinfections occur in over 50% of deaths. It is also common for respiratory viruses to predispose patients to bacterial superinfections, as was the case with the influenza outbreaks of 1918 and 2009.[52]

Despite the proven importance of superinfections in the severity of viral respiratory diseases, there are often insufficient studies due to the diagnostic complexity and culture-based microbiological tests that are less sensitive after antibiotics are administered.[55] More research on bacterial superinfections is needed and is urgently needed to determine the importance of oral hygiene and pre-existing oral disease in terms of the risk of death and the severity of Covid-

19, if any, the link between the oral microbiome and Covid-19 complications.[55] In order to reduce the bacterial load in the mouth and the risk of possible bacterial super infection, we recommend that oral hygiene be maintained during SARS-CoV-2 infection, even if it is not improved.

Measures to Increase Oral Hygiene during the COVID-19 Pandemic Period

Access to oral health services is becoming increasingly difficult, especially for populations at high risk for Covid-19. Patients with symptoms of Covid-19 are advised to "avoid non-emergency dental treatments". The healthcare professionals providing oral care are suggested to "postpone dental care, if possible, until the patient is healed".[56]

More than 49 million individuals residing in the US live in the Health Resources and Services Administration as Dental Health Professional Shortage Areas.[57] This limited access to healthcare has increased with the Covid-19 outbreak. Considering that schools are the only access for school-age children to protective oral and dental health in low-income communities, this access has also been restricted due to measures taken such as Covid-19 and school closures.[53]

As predicted, low-income communities are less likely to buy toothbrushes and toothpaste (39%) than high-income communities (46%).[54] With the outbreak of Covid-19, we can reasonably estimate that with the economic challenges faced by governments, access to dental needs will deteriorate.

Despite these conditions that negatively affect dental treatment, alternative ways can be sought to increase oral hygiene socially

1. **First of all, taking precautions for protection and developing non-aerosol treatment methods:**

Prevention approach is the most important parameter of public health. The Covid-19 pandemic has led the dentistry profession to turn towards prevention rather than invasive intervention. Adopting non-invasive, non-aerosolizing caries prevention methods is critical for this period.[58,59] Dental resin sealants, glass ionomers can be applied as part of atraumatic restorative treatment with the aid of hand tools and can be used without creating aerosol. In addition, silver diamine fluoride, sodium fluoride varnish and other self-applied topical fluorides can be used.[60-62] The use of these materials reduces the risk of virus contamination with the possibility of being applied without aerosol.

Informative guides have been developed based on the precautions that can be taken regarding oral and dental care, and their dissemination can also be focused.[63-66] Among the prevention strategies, there should also be information such as reducing common risk factors such as tobacco and alcohol use, a healthy diet with low sugar, fluoridation of drinking water, and oral and dental health recommendations in community areas.

2. Strengthening communication

Surveillance and monitoring is required in the dental office to check for the presence of Covid-19 transmission. For this, communication with the patient is very important. Many healthcare providers are worried about returning to their profession during the pandemic, and patients are equally hesitant about going to a dentist examination. Communication and clarity are essential, especially in societies with low literacy.[67]

3. The development of teledentistry

The Covid-19 outbreak has increased emphasis on alternative methods such as teledentistry.[75] Teledentistry provides electronic communication between healthcare providers and patients without time and space restrictions. The fact that this system is home-connected is very helpful in overcoming the lack of access during and after the pandemic.[68]

Teledentistry can be used for training, consultation and triage. It can be used to alleviate the concerns of patients about their dental complaints, to inform those in need of urgent care about advice they can temporarily alleviate their complaints at home or about treatments that can be delayed.

Conclusion

Bacterial and viral load in the mouth can further complicate systemic diseases such as cardiovascular disease, cancer, neurodegenerative disease, and autoimmune diseases.[69] Likewise, poor oral health causes the Covid-19 disease process to advance. Therefore, improving oral health in people of all ages can reduce the risk of developing systemic disease and the morbidity of Covid-19. Such an approach can also reduce the risk of other respiratory infections.[69]

We suggest that in the process of better understanding the consequences of Covid-19 disease, new studies should be conducted on the link between the oral microbiome and Covid-19 complications due to poor oral hygiene.

Kaynaklar

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CHAPTER 11

NEUROLOGICAL COMPLICATIONS RELATED TO COVID-19

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1. Introduction

Viral infection, which was first detected in the Wuhan province of China and called "Novel Coronavirus disease", emerged as a serious problem by spreading worldwide in a short time. The term "Severe Acute Respiratory Syndrome (SARS)-Coronavirus (CoV-2)" was used to describe this novel type of coronavirus and the disease caused by the virus was named COVID-19 by the World Health Organization (WHO) due to the year 2019 when the disease occurred. COVID-19 infection was declared as a pandemic by WHO on 11 March 2020 due to the spread of the disease to all countries in a short time.

Approximately 80% of cases during COVID-19 disease show no or mild to moderate symptoms, severe symptoms are observed in approximately 15% of cases, and critically severe symptoms are observed in 5% of cases. Symptoms such as dry cough, non-resistant fever, nasal congestion, headache, mild dizziness, muscle pains, and mild diarrhea are seen in the mild sign, which constitutes the majority of COVID-19 cases. Respiratory symptoms are slightly more intense, tachypnea, and resistant fever can be added to other symptoms. Severe pneumonia symptoms, acute respiratory distress syndrome (ARDS) results, sepsis, and septic shock results are observed during severe illness. More rare symptoms such as gastrointestinal symptoms, dermatological symptoms, cardiovascular events, or neurological symptoms due to COVID-19 infection have also been described. 36% reported neurological symptoms in the first retrospective study involving 214 COVID-19 patients in China. Symptoms such as headache, nausea, vomiting, myalgia, dizziness, hyposmia in patients infected with SARS-CoV-2 indicate nervous system involvement.

Table 1. Neurological manifestations in COVID-19 patients
• Dizziness, headache, nausea, impaired consciousness (non-specific neurological manifestation)
• Hypogeusia and hyposmia
• Cerebrovascular accident (infarction, intra cerebral bleeding, venous thrombosis)
• Acute necrotizing encephalopathy
• Meningo-encephalitis
• Guillain–Barre syndrome
• Myalgia, elevated creatine kinase and lactate dehydrogenase levels (non-specific muscular disease features)
• Anxiety, depression, insomnia, distress, Mental confusion (non-specific psychiatric symptoms

2. Covid-19 and Neurological System Involvement Pathogenesis

Coronaviruses (CoV) are a large and common family of viruses that can affect humans and bats, cats, rodents, birds, pigs, and other mammalian species. CoVs are 125 nanometers in diameter, enveloped, positive strand RNA viruses. The coronavirus is named after the shape of the virus, which means 'crown' in Latin. The virus can be transmitted from animals to humans and today's spread is thought to be in this way. However, the source remains unclear. It is assumed that the first case seen in Wuhan province passed from bat to human. However, it was determined in later cases that the spread was not only through this way, but also through human-to-human droplets or direct contact with infected surfaces. 6 types of coronavirus known as 229E, OC43, NL63, HKU, SARS-CoV, and MERS-CoV were known to cause disease in humans until December 2019.

Not every virus can make neural invasion even though viruses can cause nervous system damage with various mechanisms in the infectious signs they create. A virus must be neurotropic to make a neural invasion. SARS-CoV-2 consists of three structural proteins: the peplomers (spikes) that make up the viral envelope, the membrane, and the nucleocapsid comprising the RNA genome. The virus recognizes the human angiotensin-converting enzyme 2 (ACE2) receptor via its peplomer, which is an important factor in the virulence of SARS-CoV-2.

Several mechanisms are emphasized for CoV-2 to affect the nervous system. Among these, the most emphasized theory is the mechanism through the ACE2 receptor. It has been found that the human ACE2 receptor is also the SARS-CoV-2 receptor and SARS-CoV-2 can quickly reach the brain through the olfactory bulb. Virus antigen was found in the olfactory bulb in excess 2-3 days after the infection. Virus antigen has also been shown in the cortex, basal cartilages, and middle brain in autopsy studies. All of these areas have connections with the olfactory bulb. SARS-CoV-2 is thought to have a significant relationship between neural invasion potential and respiratory failure. A study has shown that ACE2 receptors, which are extensively found in lung alveolar cells, are also commonly found in cardiorespiratory neurons, motor cortex, and reflex nuclei in the brain stem, and it has been concluded that the virus enters the brain through these pathways. Another theory is hematogenous spread advocating the participation of the virus in the direct systemic circulation through the cribriform plate of the ethmoid bone (Figure 1). However, the fact that the virus could not be shown in other structures other than the neuronal structures of the brain weakens this possibility. COVID-19 has the ability to invade peripheral nerve terminals and progresses slowly through the synapse-linked pathway to reach CNS according to another hypothesis. There are also hypotheses that neuronal damage due to COVID-19 can occur through the immune system triggered by a direct viral infection, and that the virus creates neuronal invasion and transport through the enteric nervous system and sympathetic afferent neurons, and thus reaches CNS.

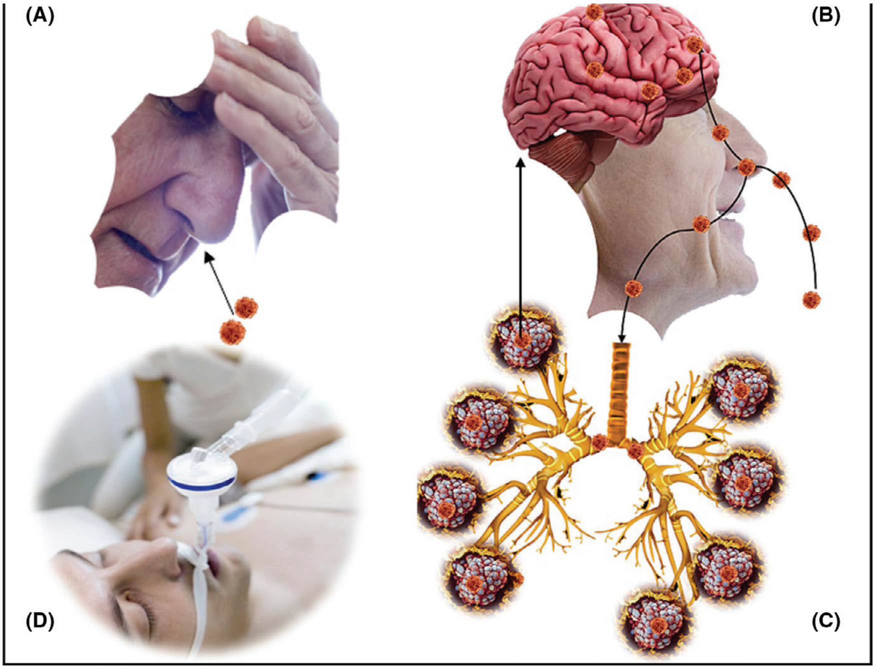

Figure 1: Neurological manifestations in COVİD-19. Fever with headaches (A) may occur early in Covid -19 patients. Specific manifestations related to neurological deficits like loss of smell and taste, ataxia and convulsions have been reported in Covid-19. The possible entry of SARS-CoV-2 to reach the brain via cribriform plate (B) or after systemic circulatory dissemination following infection of the lung (C), in early or late phases of Covid-19 may result in loss of involuntary control of breathing resulting in acute respiratory insufficiency requiring assisted ventilation (D).

3. Neurological Signs Related to Covid-19

3.1. Headache:

Headache is the most common neurological result caused by COVID-19. It is assumed that it occurs when the virus enters the brain with a cribriform plate in the first 60-68 hours of infection and/or causes headache in patients by causing increased proinflammatory cytokines to circulate and hypoxia. It has been reported that 6-40% and 1/3 of patients hospitalized due to COVID-19 have a headache, that headache can vary from moderate to very severe, that it can continue suddenly or increasingly, and that its response to analgesics is low in the literature.

Headache should be questioned in patients with COVID-19 and this condition should be prevented from becoming chronic by regularly treating attacks, arranging appropriate medical treatment, and follow-up. As social isolation, stress, diet and sleep changes can trigger attacks, patients should be informed about this. Excessive drug use should be avoided, simple analgesics such as paracetamol should be used during attacks, the use of anti-inflammatory drugs that inhibit ACE-2 enzymes should be avoided as there is insufficient evidence of its safety, and antidepressants and antiepileptic drugs should be taken if necessary, even though there are controversial situations regarding medical treatment.

3.2. Taste and Smell Disorders:

Loss of smell and taste during COVID-19 disease are the most commonly reported symptoms of peripheral nerve involvement. Sudden loss of taste and smell occurs in the vast majority of cases (76.24%). Other viral infections have also been reported to have a loss of smell due to nasal mucosal inflammation, but unlike COVID-19-related inflammation, nasal congestion, and nasal discharge do not occur. It has also been reported that it may rarely be permanent even though it has been reported that it usually resolves with the disappearance of viral symptoms. The sense of taste and smell returns within 1 week to 10 days, but can continue for up to 1 month. This condition due to COVID-19 is thought to occur due to the virus invading the olfactory nerve and bulb or alternatively the sensory fibers of the vagus nerve, which innervates different organs such as the larynx, trachea, and lungs in the respiratory tract from the brainstem since the sense of smell due to congestion caused by viral inflammation usually passes within 1-3 days. SARS-CoV-2 is recommended to be further investigated in terms of CNS involvement in patients with loss of smell, ataxia, and convulsion in the early period.

3.3. The Altered States of Consciousness:

Loss of consciousness is one of the most common neurological symptoms in cohort studies and has been reported in 1.8% to 21.3% of hospitalized COVID-19 patients. COVID-19-related altered states of consciousness are common, especially in elderly and chronically ill individuals. Intense cytokine storm caused by CoV-2 infection and related metabolic and hypoxic changes, central nervous system involvement, side effects of the drugs used, respiratory failure caused by the infection, and multiple organ failure are considered as the causes of these altered states of consciousness in the elderly population, which can be seen delirium even with a simple viral infection. These patients are usually severe patients and are followed up in the intensive care unit and in need of mechanical ventilation. Systemic diseases, laboratory results, and drugs used by patients with altered states of consciousness should be carefully examined, these patients should be evaluated by cranial imaging, electroencephalography, and lumbar puncture if necessary. There are 19 identified suspected cases of encephalitis associated with COVID-19 in a published review. The diagnosis was made with signs of meningeal involvement, altered states of consciousness and focal neurological findings, unexplained epileptic seizures, and supportive cranial magnetic resonance imaging (MRI) findings in these cases. 13 of these cases were diagnosed with meningoencephalitis, and the SARS-CoV-2 virus was detected in cerebrospinal fluid (CSF) examination in only four of these cases. In addition, cases of thromboencephalitis, acute necrotizing hemorrhagic encephalopathy, encephalopathy, and CNS infection presented with focal demyelinating results have been reported. The fact that the direct virus could not be shown in CNS but inflammation results such as protein increase and cell detection in CSF suggested that it may cause encephalitis clinic with immune-mediated mechanisms other than the direct effect of the virus in some cases. Detailed CSF imaging and, if possible, postmortem pathological examination studies are required to understand the mechanisms of CNS spread in these cases. Von Weyhern et al. highlighted the presence of lymphocytic panencephalitis and meningitis in an autopsy study performed on 6 Covid-19 patients. Another study documented the presence of Covid -19 in postmortem CSF of a patient with negative covid-19 PCR. Again, in a recent study, it was indicated that 20% of patients with encephalitis had microvascular lesions on cranial MRI images.

3.4. Stroke:

Stroke is one of the important emergency complications of COVID-19 and has been reported in 2% of patients hospitalized for COVID-19 infection. Hypertension, which is a risk factor for the development of cerebrovascular disease, coronary artery diseases, atherosclerosis, advanced age, and male gender are also risk factors for the severe course of COVID-19 infection. Li et al. retrospectively examined 221 patients diagnosed with COVID-19 and reported that 11 patients had an ischemic stroke, 1 patient had a stroke due to sinus vein thrombosis, and 1 patient had a stroke due to hemorrhage. High fibrinogen and D-dimer detected during the clinical course of COVID-19 infection may be associated with low platelet coagulopathy and stroke. It was reported in case series with neurological symptoms that serum C-reactive protein (CRP) and D-dimer levels were significantly elevated in patients with stroke, that most of the cases had severe lung involvement, that 3 patients with concomitant venous thrombosis had antiphospholipid antibody positivity, 3 patients had multiple cerebral infarctions, and 1 patient had the major vascular disease. Meppiel et al. examined 259 patients with neurological involvement retrospectively and reported that 189 patients (85%) had cental nervous system involvement (CNS) and 63 (28.4%) of these patients were diagnosed with stroke. Of the patients diagnosed with stroke, 57 were reported as ischemic, 5 hemorrhagic, and 1 stroke due to central venous thrombosis. It has been reported that stroke may develop within an average of 12 days after the onset of Covid-19 symptoms, and it may be the reason for first arrival to the hospital.

Zao et al. recently summarized the cerebrovascular complications associated with Covid 19 in a review (Table 2).

Table 2. Summary of the cerebrovascular complications of COVID-19

Authors	Total Cases	Type of CVD in patients with Covid-19	
		IS - n(%)	CH - n(%)
Mao et al.	214	5(2.3)	1(0.5)
Helms et al.	64	3 (4.7)	
Klok et al.	184	5 (2.7)	
Li et al.	219	10 (4.6)	1 (0.5)
Annie et al.	9358	64 (0.7)	
Rothstein et al.	844	20 (2.4)	8 (0.9)
Stéphane et al.	64	17 (27)	
Merkle et al.	1916	31 (1.6)	
Francisco et al.	1683	17 (1.0)	5 (0.3)

CVD: cerebrovascular disease, **IS:** ischemic stroke, **CH:** cerebral hemorrhage.

The risk of stroke increases secondary to the fact that being infected with COVID-19 alone causes damage to the heart and vascular endothelium due to increased inflammation and prothrombotic factors without accompanying risk factors. Standard stroke assessment steps should be applied in cases of stroke infected with COVID-19. In addition, follow-up of coagulation markers such as D-dimer, fibrinogen, CRP, and IL-6 has been recommended in these patients. However, it is still unclear whether sepsis-induced coagulopathy or antiphospholipid antibodies cause stroke or thrombotic events. The use of a "tissue plasminogen activator" seems appropriate in the treatment of COVID-19 and ischemic stroke. There is not yet complete clarity regarding the use of low-molecular-weight heparin (LMWH) or full-dose heparin. However, LMWH is thought to be useful in sepsis-induced coagulopathy. Studies on human recombinant ACE-2 are also promising.

The patient should be discharged by teaching home exercises to the person who will take care of the patient as soon as possible, the importance of home exercises should be explained to the patient and their relatives, and the concerns that home treatment will delay neurological recovery should be eliminated when the general condition of the patient is stable during the acute stroke period. Common rehabilitation areas should not be used as much as possible; rehabilitation should be performed in the patient room by providing appropriate isolation conditions and providing the necessary protective equipment to the physiotherapist who will perform the exercise in in-hospital rehabilitation in the post-acute period. The patient's temperature should be measured regularly, treatment of those with a temperature above 37.5°C should be postponed until the necessary tests are performed, and the diagnosis is clarified before starting the exercise. Patients with mild respiratory distress without diagnosis should be given the necessary oxygen support and oxygen saturation monitoring should be performed. Patients and physiotherapists should use FFP2 or FFP3 type masks, oxygen saturation monitoring should be performed, and tests should be performed as soon as possible in patients who do not have respiratory leakage and fever and who are suspected of COVID-19. Active rehabilitation of patients with positive test results should be terminated and transportation to isolated infection clinics should be provided urgently. Rehabilitation may be postponed by outpatient clinics in some patients with chronic stroke during strict quarantine periods. The importance of home neurorehabilitation should be explained to the patient, and their relatives, and the patient and their relatives should be motivated, otherwise, this may delay recovery and worsen the current situation in patients.

3.5. Polyneuropathy:

Acute polyneuropathy (PNP) is one of the neurological emergencies. Many studies have shown that coronaviruses cause acute polyneuropathy, neuroinflammatory, and autoimmune disorders. Mao et al. reported peripheral nervous system results in 8.9% of 214 COVID-19 positive cases. Even though increasing numbers of cases with Guillain Barre Syndrome (GBS) secondary to SARS-CoV 2 have been reported in the literature, it has not been clearly determined whether this association is coincidental or whether the virus directly invades the peripheral nerves. In a recent study in France, 7% of patients with nervous system involvement were diagnosed with GBS, 57.1% of these patients had increased protein in the cerebrospinal fluid (CSF), 92.9% had demyelination on electromyographic examination, the majority of patients was reported to be treated with immunoglobulin. It was reported that GBS was diagnosed an average of 18 days after the onset of Covid 19 symptoms. In addition, there are cases of COVID-19 presented with peripheral facial paralysis in the literature. Furthermore, cases of multiple cranial neuropathies developing at different times during COVID-19 have been reported in New York. Miller Fisher Syndrome and multiple cranial nerve involvement have been observed in two COVID-19 positive cases in Spain. Ophthalmoparesis was detected in two cases in the USA.

3.6. Muscular Involvement:

Skeletal muscle involvement also occurs in COVID-19 patients and clinically occurs in the form of fatigue, muscle aches, and an increase in muscle destruction enzymes. This is associated with muscle damage due to neuroinflammation. There are not enough studies on the development of myopathy in COVID-19 patients. 6 cases with clinical and electrophysiological results indicating critical disease myopathy developed acute tetraplegia after intensive care treatment in a study conducted in China. It was reported in a study conducted in China that 50% of all cases had muscle pain and 10.7% of severe patients had an increase in creatine kinase enzymes. However, no further studies on myopathy such as EMG, muscle pathology, or MRI were performed. One case showed an increase in rhabdomyolysis-induced muscle enzymes and associated renal failure as a delayed complication. It is important to closely monitor kidney functions and muscle enzymes in these cases. Studies involving electromyography, muscle imaging, and muscle biopsy are recommended to determine whether these symptoms are related to viral myositis. It was reported that 34.8% of cases had myalgia in another study involving 138 cases. Symptoms and results may worsen with COVID-19 infection added to neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) and various myopathies, which may cause the involvement of respiratory muscles since one of the primary symptoms of the virus is respiratory results. Rhabdomyolysis may occur in metabolic myopathies. In addition, some autoimmune neurological diseases such as myasthenia gravis are thought to occur with infection caused by the virus.

3.7. Neurological Signs Associated with Intensive Care:

New or worsening disorders in physical, cognitive, and mental health status that occur during or after intensive care hospitalization due to critical illness and continue after discharge from intensive care or hospital are defined as "Post-intensive care syndrome" (PICS). Physical complications may occur in approximately 70% of patients after a critical disease and skeletal muscle strength, pulmonary function, pain, ability to walk, and disorders in daily life activities develop. These complications may last for months or years after the critical disease. Intensive care-associated muscle weakness is defined as diffuse, symmetrical, acute muscle weakness in the extremities due to critical disease. Muscle weakness associated with intensive care is divided into subgroups as critical disease polyneuropathy accompanied by electrophysiological and histopathological results, critical disease myopathy, critical disease neuromyopathy, and muscle deconditioning where diagnostic tests are normal.

Female gender, sepsis, multi-organ failure, systemic inflammatory response syndrome, long mechanical ventilation time, immobility, hyperglycemia, glucocorticoids, and neuromuscular blocking agents are risk factors for intensive care-related muscle weakness. The distal and proximal parts of the extremities are symmetrically affected, and the facial muscles and cranial nerves are normal in this sign. In addition, other causes that may cause weakness for diagnosis should be excluded.

3.8. Other Neurological Conditions:

No cases of COVID-19-related multiple sclerosis (MS) and extrapyramidal system results have been reported so far. However, it should not be forgotten that MS patients are more prone to infectious diseases because they use disease-modifying drugs. However, it is thought that the drugs used in the treatment of these diseases can be used in treatment by suppressing the excessive immune response and preventing cytokine storm. There is not yet sufficient data on seizure development secondary to COVID-19 infection. Seizures were not reported in any of the patients in a multicenter retrospective study involving 304 patients in China. Non-specific EEG changes were observed in eight cases in a case series. One case showed evidence of encephalopathy in EEG. Generalized seizures in addition to these were added to COVID-19 infection results in a young patient on the 9th day, virus antigen was detected in the cerebrospinal fluid and right ventriculitis and encephalitis results were observed on cranial MRI. It was emphasized that a patient with no previous history of seizures had seizures five times and no pathological results were detected in the patient's CSF results and cranial MRI, which may be secondary seizures caused by encephalitis caused by the direct effect of the virus or cytokines.

4. The place of rehabilitation in the acute and chronic period of COVID-19

Mild to moderate COVID-19 patients and most severe cases usually recover without long-term adverse outcomes. However, serious or critical COVID-19 can cause long-term disability, especially by affecting the central or peripheral nervous system. Sequelae and disability associated with both intensive care and acute care period complications and COVID-19 fall within the field of Physical Medicine and Rehabilitation (PM&R). The planning of the treatments of patients with COVID-19 in need of rehabilitation, the reorganization of the services, the use of new treatment models and technology have entered our agenda since PM&R specialists will be faced with the treatment of a new disabled patient population.

4.1. Early Rehabilitation:

Rehabilitation practices applied while the necessary medical treatments are in progress from the time of hospitalization of the patients are defined as early rehabilitation. Before starting rehabilitation, the patient should be evaluated in detail and an appropriate rehabilitation program should be determined according to the cooperation, functional status, and comorbidity status of the patient-specific to each patient. However, the risk of excessive transmission in these patients is the greatest obstacle to rehabilitation. The almost instantaneous change in hemodynamic stability in these patients, accompanying comorbid conditions, multiple organ involvement, and even the abundance of unknowns about the disease makes the situation even more difficult. Severe complications such as contracture, pressure sore, deep vein thrombosis can be prevented in patients with appropriate positioning, joint range of motion exercises, early mobilization in patients with the stable general condition, and electrical stimulation in patients with simple applications such as intensive care. Early mobilization in the intensive care unit is regulated according to the functional status of the patient. Sitting balance exercises, ROM exercises, and muscle-strengthening exercises should be performed if the patient is at bed level. Standing up, load transfer and balance exercises should be given, and walking training should be provided with auxiliary device support when necessary if the patient's sitting balance is present and muscle strength is sufficient. In addition, both muscle strength increases with neuromuscular electrical nerve stimulation during intensive care, and mechanical ventilation time, intensive care, and hospital stay are shortened. Aerobic exercises and strengthening exercises can also be included in early rehabilitation practices. These exercises should be planned to increase endurance in a way that they are low-resistance, frequent, and repetitive. This frequency and resistance can be gradually increased depending on the patient's cardiorespiratory tolerance. Progressive-resistant upper extremity exercise practices and aerobic exercises performed with an arm ergometer increase cardiorespiratory condition and decrease dyspnea, increasing the quality of life of the patient for this purpose. Rehabilitation practices have been shown to be safe in critical patients. However, there are also publications that there are no positive results on long-term functional benefit and mortality.

4.2. Rehabilitation in the Chronic Period:

The recommended criteria for admission of patients to post-acute rehabilitation are the absence of high fever in the last 72 hours, the absence of medical treatment for high fever, stable oxygen saturation, and respiratory rate, and the absence of radiological progression of the disease. Rehabilitation can be applied if the patient does not have fever and dyspnea, the patient is hemodynamically stable, respiratory rate <30/min, and O_2 saturation >93% in the COVID-19 patient hospitalized in the system. The rehabilitation program should be shaped according to the patient, if possible, the patient should be discharged as soon as possible, and an exercise program should be given to be performed at home.

The patient should be re-evaluated at regular intervals and the exercise program should be shown to the patient and the caregiver. However, rehabilitation should be performed by the physiotherapist by providing appropriate protective equipment to patients with severe disability by standing or lying down. The rehabilitation program to be applied in the chronic period should also be planned according to the functional status of the patient and cardiorespiratory capacity. Appropriate beds should be provided to patients at bed level first, changing the lying position at least at 2-hour intervals to prevent the formation of pressure sores and contractures, and the importance of passive ROM exercises should be explained and shown to the relatives of the patients. The focus should be on bed rotation and straightening exercises and transfer exercises during this period. Patients who have passed this period should also be studied on sitting balance and the patient should be tried to gain independent sitting balance. Verticalization should be created with Tilt Table at a rate that they can tolerate every day and the patient should be kept upright for 30 minutes at 90° to prevent the development of orthostatic hypotension in patients who gain sitting balance. The patient should be provided with balance, load transfer, and walking training at the parallel bar and then walking training and climbing stairs outside the parallel bar after providing vertical posture ability. It should be evaluated for the need for auxiliary devices and support and appropriate devices should be provided if the patient cannot be ambulated independently.

5. Conclusion

The outbreak has spread rapidly around the world, killing millions of people since the first data on COVID-19 emerged in China in late 2019. Long-term sequelae of COVID-19 began to be recognized as time passed and the situation caused worries to increase while global healthcare services were given priority to acutely ill people to reduce the rate of spread of infection and reduce mortality. The virus continues to confuse science by causing new clinical symptoms every passing day. It is vital that clinicians act quickly and carefully considering the possibility of COVID-19 infection in every patient in the current pandemic situation. Moreover, long-term rehabilitation programs are needed for the treatment of existing sequelae in acute patients. This will increase the economic burden on healthcare systems and social security institutions. Recently, efforts to develop vaccines around the world have been intensified and their applications have begun. We hope that humanity can cope with this infection as soon as possible and prevent mortality and morbidity.

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CHAPTER 12

GASTROENTEROLOGICAL AND HEPATOLOGICAL EFFECTS OF COVID 19

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1. Introduction:

Coronaviruses (CoV) are a large virus family with single-stranded RNA, enveloped, with protein protrusions on the surface. In addition to mild and moderate respiratory diseases, it is also responsible for severe diseases such as MERS (Middle East Respiratory Syndrome), SARS (severe acute respiratory syndrome). Sars-Cov-2 infection, a clinical condition that emerged in December 2019 and is rapidly affecting all over the world, caused the death of approximately 3 million people at the time these lines were written. The new epidemic disease caused by Sars-Cov-2 was named as COVID-19 by the WHO. Although it was thought as a pneumonia-ARDS (acute respiratory distress syndrome) picture at the first stage, it was understood that it was a systemic disease that affected much more structures in the human body.

In this part of the book, we will talk about the gastroenterological and hepatological effects of COVID-19, not the respiratory tract and systemic effects. We will also talk about the applications in endoscopy units during the pandemic process.

2. COVID-19 and its gastroenterological effects;

Sars-Cov-2-RNA has been detected in many parts of the gastrointestinal tract. Virus RNA has been proven to be present in faecal samples of patients hospitalized for COVID-19, with or without gastrointestinal symptoms. Sars-

Cov-2-RNA has also shown in the endoscopic biopsies from esophagus, stomach, duodenum, colon, and rectum. In addition, there are studies showing that even after the virus is cleared in the respiratory tract, it is in stool for up to thirty days. In addition, viral RNA was also isolated in gallbladder, pancreatic cyst fluid.

ACE-2 (angiotensin converting enzyme 2) mRNA and its protein, one of the most important cell entry receptors of Sars-CoV-2, are abundant in the small intestine and colon, and are also present in the gallbladder and pancreatic epithelium. ACE-2 receptors are responsible for the gastroenterological effects of the virus.

Inpatients with severe COVID are at high risk for gastrointestinal complications during their stay. During prolonged hospitalization, approximately 74-86% of patients with severe COVID may experience complications such as transaminitis, mesenteric ischemia, poor oral intake, and gastrointestinal bleeding.

2.1. Liver and Sars-CoV-2;

Approximately two-thirds of patients with severe COVID-19 have elevated transaminases. In some cases, this can lead to liver ischemia. Although the mechanism of liver damage in COVID-19 is still unclear, it is multifactorial and other factors causing liver damage should be reviewed and excluded when evaluating the patient. Many studies have shown that transaminase elevation is an independent indicator of the severity of the disease and is a risk factor for mortality. There are many different mechanisms of liver damage in patients with COVID. In a liver biopsy performed in a case of COVID-19, moderate microvesicular steatosis, moderate lobular and protal activity was detected, and viral inclusion was not shown. Since hepatocytes do not have ACE-2 receptors, they are not direct targets for the virus. In this respect, the virus is not expected to cause direct hepatocyte damage. Another reason that raises transaminases is drug side effects. In particular paracetamol and the other drugs used as antipyretics, favipiravir and other antivirals can cause transaminitis. Cytokine storm that develops due to systemic inflammatory response can also cause liver damage. In addition, hypoxic ischemic injury due to viral pneumonia is another possible cause of liver injury.

It is obvious that in cases with chronic liver disease, COVID-19 is much more severe. The risk of death is 60% higher in those with chronic liver disease than in the normal population. This risk may increase depending on the Child-Turcotte-Pugh classification of the disease or the MELD score. In addition, Sars-Cov-2 is also associated with decompensation in patients with chronic liver disease. Some guidelines recommend screening for Sars-CoV-2 in patients with decompensated chronic liver disease, even without respiratory symptoms. The effects of the pandemic which is current ongoing and significantly changing our clinical habits on esophageal – stomach cancer screenings, hepatocellular cancer screenings, immunosuppressive treatment regimens, esophageal varices follow-up and viral hepatitis care are not clear. Ongoing studies will show this to us in the near future. For instance, in autoimmune diseases, the use of budesonide rather than prednisone appears to be increased in the practice of most clinicians. The decrease in organ supply and the decreased number of intensive care beds also negatively affected the liver transplantation process in patients with chronic liver disease. In addition, increased alcohol consumption during shutdown periods and increased obesity rates are likely to lead to an increase in the frequency of chronic liver disease in the post-pandemic period.

It should be kept in mind that reactivation with steroids used in the treatment of COVID-19 may occur in patients with chronic viral hepatitis or a history of hepatitis B or C, and precautions should be taken. Doses of immunosuppressive drugs should be kept at the lowest level to prevent rejection in patients with liver transplant who have been diagnosed with COVID-19. In one series, no significant increase in mortality was observed in transplant patients.

Acute cholecystitis has been over-reported, especially in critically ill patients with COVID-19. Cholecystitis mostly acalculosis and its etiology is still unclear. While hypomotility in the gallbladder is to be blamed, direct viral damage to the gallbladder cannot be excluded, since there are ACE-2 receptors in cholangiocytes. Antibiotics and drainage should be considered in the treatment of severe patients. Surgery may be considered in cases where drainage does not respond.

As a result, although COVID-19 is not directly toxic to the liver, it has negative effects on the liver with possible biliary tract damage, indirect negative effects in the care and follow-up of chronic liver patients, and decompensation.

2.2. Pancreas and Sars-CoV-2;

The development of acute pancreatitis is quite common, especially in patients with severe COVID-19. 27 per thousand of hospitalized patients present as acute pancreatitis. The majority of these are in the form of acute idiopathic pancreatitis. Since pancreatic cells contain ACE2 receptors, the probable cause of pancreatitis is direct viral cellular damage. Treatment of pancreatitis in patients with COVID is the same as in patients without COVID. Endoscopic percutaneous or surgical debridement may be required in the event of progression to necrotizing pancreatitis.

2.3. Upper gastrointestinal tractus and Sars-CoV-2;

Upper GI symptoms may include loss of appetite, vomiting, nausea, and abdominal pain. Although viral esophageal symptoms are not directly reported, heatburn is common and its treatment is the standard approach. Although loss of appetite is non-specific, it is the most commonly reported symptom. Its possible mechanism may be systemic inflammation caused by Sar-CoV-2. In addition, the side effects of drugs used in the treatment and anosmia may also contribute.

2.4. Ileus and COVID:

Up to half of critical COVID-19 patients in intensive care units may have ileus. Its etiology is multifactorial and probably contributed by opioids and sedatives used in ventilator compliance.

2.5. Gastrointestinal system emergencies in patients with COVID-19

In COVID-19 patients, as in every emergency, GI emergencies are clinically difficult situations. Making the decision to perform an interventional procedure on the infected patient, protective measures during the interventional procedure, etc. are compelling issues.

Diarrhea is the most common gastrointestinal emergency associated with COVID-19, but fortunately it is often mild. However, diarrhoea leading to electrolytic disturbances and acute kidney injury has also been reported. Rarely, inflammatory, bloody diarrhea may precede pneumonia.

The most common gastrointestinal symptom in patients with COVID-19 is abdominal pain, as we mentioned above, abdominal pain can have many causes like pancreatitis, acalculous cholecystitis. Sars-Cov-2 has been shown to be present in the biliary epithelium, as previously written, this may be related to ACE receptors in the biliary epithelium.

It has not been shown that the frequency of GI bleeding is increased in patients with COVID-19. Nevertheless, gastrointestinal bleeding is the main reason why a gastroenterologist sees a patient with covid.

The cause of bleeding cannot always be determined, as patients are generally followed conservatively with high-dose ppi (proton pump inhibitors. Mucosal herpetic lesions are frequently seen when endoscopy is performed on bleeding patients with COVID, and sars-cov2 has been isolated in endoscopic biopsies.

Lower GI bleeding is also one of the most common causes of GI emergencies in patients with COVID. In a study conducted in Italy, the most common causes of lower GI bleeding were segmental colitis associated with diverticulosis, ischemic colitis, and hemorrhagic ulcerative colitis. The etiology of hemorrhage due to ischemic colitis includes direct damage by the virus, hypoperfusion and a predisposition to thrombosis. This intestinal hypercoagulable situation leading to ischemic colitis can also increase d-dimer and fibrinogen. Stress ulcers can also be seen in critically ill mechanically ventilated COVID cases, ppi is superior to H2 receptor blockers in preventing stress ulcers.

In addition, it is known that the number of procedures performed in endoscopy units has decreased significantly in order to prevent the spread of virus during the pandemic process. According to a study from New York, cases of GI bleeding during the pandemic were more negative than before the pandemic. Interestingly, when COVID-negative cases were examined in the same study, it was shown that the prognosis was worse than before the pandemic.

2.6. Gastrointestinal endoscopy during the COVID-19 pandemic

Endoscopy unit staff have a high risk of COVID-19 transmission. Inhalation of droplets, conjunctival contact, and potential fecal-oral transmission play a role in this transmission.

It has been shown that human feces contains live virus and infection occurs by periendoscopic inhalation. Therefore, GI endoscopy is a high-risk procedure. Endoscopy unit employees can get it from patients as well as infect other hospital staff and patients. For this reason, hospital epidemics have been seen in Europe.

Infection prevention and control measures are effective in preventing transmission. This effectiveness cannot be achieved with the use of protective equipment alone. Complex processes including transparent process management, risk classification of patients, correct use of protective equipment, identification, testing and, if necessary, separation of high-risk patients for COVID-19 can be achieved.

2.7. How should GIS endoscopy be applied during the COVID-19 pandemic?

Endoscopy unit staff should be informed and trained in terms of infection prevention and control strategies. This includes measures such as identifying potential sources of contamination, separating risky patients, and using protective equipment correctly.

Unit personnel should check themselves daily for possible signs of COVID.

Sars-Cov-2 can be destroyed with common disinfectants. Disinfecting endoscopy devices according to previous guidelines is sufficient in this respect.

Each endoscopy unit should have its own cleaning and disinfection plan. Endoscopy units should be disinfected with virucidal agents after every highly suspected or positive case.

Where possible, online medical support should be sought (telemedicine).

Hands should be washed with warm water and soap for at least 20 seconds after each contact with sick or possibly contaminated surfaces. Mobile phones, pens, keyboards, medical equipment should not be shared. Personal items such as watches, rings, etc. should not be used in the endoscopy unit.

2.8. Pre-Endoscopy Risk Management

Before endoscopy, patients should be classified as high or low risk for transmission;

Low risk patient; -No symptoms such as cough, fever, shortness of breath, diarrhea -No history of contact -Negative test result for COVID-19	**High risk patient;** - Symptoms such as cough, fever, shortness of breath, diarrhea -With contact story -Having a positive COVID 19 test
What precautions should be taken? -Surgical mask -Glove - Goggles - Waterproof apron - Bonnet must be worn	**What precautions should be taken?** -FFP2-FFP3 mask - Double layer gloves - Goggles - Waterproof apron - Bonnet must be worn

Relatives of the patient should not be taken to the endoscopy unit unless necessary. Everyone entering the unit must wear a surgical mask. High-risk or positive cases should be followed in separate areas after the procedure. If possible, negative pressure chambers can be used for the process. When an indication for endoscopy occurs in intensive care patients, the procedure should be performed at the bedside.

All elective endoscopic procedures should be postponed during pandemic or wave periods.

Endoscopy should be applied in the following cases;

- Hemodynamically unstable lower-upper GI bleeding
- Capsule enteroscopy in patients with emergency bleeding
- Hemodynamically unstable anemia
- Foreign body in the esophagus or risky foreign body in the stomach
- Obstructive pathologies
- Acute severe cholangitis.

During the active period of the pandemic, endoscopic procedures should be postponed in the following cases;

- Barrett’s esophagus, low grade dysplasia, intestinal metaplasia screening inf. bowel disease screening
- Screening after endoscopic resection – screening after polypectomy
- Dyspepsia without alarm symptoms - irritable bowel syndrome-like symptoms
- Cancer screenings and bariatric endoscopic procedures.

3. Conclusion

It will take some time to understand the effects of the pandemic, a relatively new clinical situation that the world has experienced again after many years. In this section, we have organized COVID-19 and its effects in the gastrointestinal system by considering the existing literature. It is clear that more comprehensive studies are needed to clearly reveal the effects of the pandemic for both clinical and endoscopic procedures.

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CHAPTER 13

COVID-19: DIAGNOSIS, TREATMENT, MONITORING, HOME CARE AND PUBLIC HEALTH NURSING PRACTICES IN TURKEY

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INTRODUCTION

The COVID-19 pandemic starting at the end of 2019 has affected the life negatively all over the world, and its effects still linger. Considering that the rate of spread, incidence, prevalence and herd immunity rate of COVID-19 have not reached the desired level, it is obvious that hospitals have difficulties in bearing the heavy burden of the pandemic. Therefore, home care services have come to the foreground as an alternative solution to effectively alleviate and mitigate the phenomenon.

Home health services involve provision of examination, sampling and analysis, treatment and rehabilitation services including psychosocial counselling services, to those individuals who have become dependent on others for their daily living activities due to various diseases, by a professional health team in their own home. Research shows that home health services can help relieve the pressure on hospitals and emergency rooms, and thus prevent the spread of infection.

The COVID-19 pandemic has accelerated the delivery of health care services at home, as it helps in reducing contact with the infected people and limiting the capacity of health care facilities. The role and importance of a qualified implementation of home care, which is always updated and shaped according to the requirements, has become more prominent during the pandemic process. During the COVID-19 pandemic, those people who are in need of care and cannot leave their home may demand more home health services than normal times, and the need for protection of vulnerable, disadvantaged people and patients is increased. Therefore, the care of elderly people during the pandemic, home care services for people with chronic diseases and bedridden people must be organized and planned to cover the general population.

HOME CARE SERVICES IN TURKEY DURING THE COVID-19 PANDEMIC

After the first case was spotted in the Republic of Turkey and the outbreak was declared as a pandemic by the World Health Organization, the measures taken to keep the spread of the epidemic under control were tightened considerably. According to the announcements made by the Ministry of Health in Turkey, there has been an upsurge of 500% in applications made to the Home Health Services Communication Center to receive these services during the COVID-19 pandemic. This situation provides a sound proof that patients hesitant to go to the hospital due to the fear of contracting the virus consider home health services as an alternative solution in order to maintain their diagnosis, treatment, care and follow-up procedures.

Home healthcare services have been categorized into four roles including diagnosis, follow-up, treatment and care at home during the pandemic period. In Turkey, home health services are provided by three types of units within community health centers, hospitals affiliated to the Ministry of Health, and oral and dental care health facilities. In addition, family physicians are responsible for identifying those who need home health services from registered individuals and making regular home visits. In order to combat against the pandemic in Turkey, a single type of mobile filiation/field investigation teams has been formed from three types of home health service units. Filiation teams are of pivotal importance in preventing the disease, detecting cases at an early stage, making the necessary intervention and keeping them under control.

DIAGNOSIS AND MONITORING AT HOME DURING THE COVID-19 PANDEMIC

The COVID-19 Rapid Diagnosis Kit and the COVID-19 PCR Test Kit are mostly used by family physicians to detect the SARS-CoV-2 virus. While using the COVID-19 Rapid Diagnosis Kit, one drop of blood is taken from the fingertip and the presence of IgG and IgM antibodies in the blood is detected within 10-15 minutes. The COVID-19 PCR Test Kit provides a definitive diagnosis by directly detecting the virus present in samples such as throat and nose swab or sputum sample taken from the patient in 3 hours. This test is also known as the molecular diagnostic test.

PCR testing of samples taken from screened people and suspects in Turkey is carried out in a total of 129 laboratories accredited by the Ministry of Health in 73 provinces. A rapid diagnosis kit has been developed to detect the coronavirus in Turkey. This developed kit has been used routinely in the National Virology Laboratory.

Monitoring Patients at Home

The probable/definite cases COVID-19 cases aged under 50 years showing mild symptoms ut not having any of the risk factors such as diabetes, chronic cardiac disease, hypertension, chronic renal failure, chronic pulmonary disease or immune deficiency that may aggravate COVID-19 and no poor prognostic factors are followed at home by starting appropriate treatment until the symptoms resolve. The home care process continues until the patient's symptoms improve. Healthcare professionals or public health workers are continuously contacted.

Patients who are treated at the hospital and meet the discharge criteria can complete their recovery period at home. The discharge procedures of the patients who have negative COVID-19 post-tests and whose general condition is suitable for home monitoring are planned by the healthcare team. When the patient is discharged, the hospital provides the drugs to be used for the treatment of COVID-19 and a sufficient number of masks. During discharge, the case status of the patient in PHMS is indicated as "Discharged for Home Monitoring" by the Public Health Management System (PHMS) user. Later, the family health center with which the patient is affiliated is informed and the patient is kept in quarantine at home for a while. The patients monitored at home are followed up by the family physician until they fully recover.

If the patient is an elderly individual living alone, the demands of the elderly are met by volunteers from the headman's office, municipalities, or non-governmental organizations in order to provide their medicines and meet their other needs. If the elderly person does not live alone, both the patient and their relatives are informed about testing other members of the family, maintaining the necessary distance even if the patient is not contagious, and avoiding close contact for at least 14 days.

HOME TELE-HEALTH PRACTICES AND APPLICATIONS DURING PANDEMIC

With the help of tele-health applications, home health services have been easily adapted to the epidemic period. During this period, tele-health systems started to be used in the campaign against coronavirus, screening and patient follow-up besides continuation of routine controls and healthcare counselling. Since the follow-up of the patient discharged from the hospital after COVID-19 treatment is carried out by his/her family physician, family physicians call these people for 10 days and inquire about COVID-19 symptoms such as coughing, fever, and shortness of breath. According to the information given by the patient, the follow-up information is recorded in the daily follow-up form in Family Medicine Information System. If symptoms develop in these individuals during the follow-up process, family physicians contact the Provincial Health Directorate Infectious Diseases Unit, immediately reporting the case and sharing the patient's information.

The infected or suspected individuals are controlled and monitored in their homes through mobile applications such as "Hayat Eve Sığar", "Pandemic Isolation Tracking Project" or "Corona Precaution" developed by the Ministry of Health in Turkey. In "Hayat Eve Sığar" mobile application, individuals are warned when approaching risky areas. Since people can register their family members to the system, they can also follow them if they allow it. This application is also used in transition to social life, as it has been proven that individuals do not pose risks in their travels, are not sick or in contact. According to the answers given to the questions asked via "Corona Precaution" mobile application, the probability of the individual contracting the corona virus can be evaluated. The system warns the individual to go to the nearest health facility by wearing a mask in a risky situation. Using the "Pandemic Isolation Tracking Project" application, those who have positive COVID-19 test result/contact with those diagnosed are followed up at home. When these individuals in isolation at home leave their homes, they are cautioned by sending a warning message to their phones, and even these people are immediately contacted with an automatic call and asked to return to their homes. Those people who do not care about the warnings and continue to violate the rules are reported to security units.

TREATMENT AND CARE AT HOME DURING COVID-19

The suspected or confirmed COVID-19 patients who indicate mild clinical symptoms and have no other disease do not require hospitalization and can be treated safely at home. In addition, home care can be applied in the follow-up of those people discharged from the hospital after the treatment of COVID-19.

Things to do before deciding on home care

The patient's condition, housing status, the presence of elderly or chronic patients at risk, and appropriate caregivers at home are evaluated for the patient to receive home care. If family members are to take care of the patient, they are followed up at home by a healthcare professional. It is questioned whether there is a separate bedroom where the patient can stay, get food, access to other services as well as availability of these resources, and accessibility of protective equipment such as masks and gloves by the patient and family members.

What to do after deciding on home care

After the patient is informed about what he/she has to do during home care and his/her penal responsibilities, the consent form containing this information is signed by the patient and health professionals. Sufficient number of drugs and masks are provided to the patient who is sent home.

What to do during home care

Communication with the home care provider (family doctor, nurse) is maintained until the patient fully recovers. Adequate information is given to the patient and the family about transmission routes, prevention, treatment and care of COVID-19. Visitors are not allowed in the house. The patient's contact with family members, caregivers and pets is limited as much as possible. The patient wears a face mask in the house in presence with others or in shared areas. It is ensured that the patient regularly takes the drugs recommended by the physician, has adequate and balanced nutrition, consumes plenty of fluids, sleeps enough, rests and stays away from stress. When the general condition of the patient deteriorates, emergency service is called immediately.

The patient's room is isolated. A separate toilet is used if possible. If the toilet is shared, it is constantly ventilated and cleaned with disinfectants. The house is constantly ventilated and the patient's door is closed while the windows are kept open. The patient's clothes, towels, and bedding sheets are washed at 60-90°C. The patient is asked to eat in his/her own room, use disposable spoons and cutlery, and if not possible, the dishes are asked to be washed in the dishwasher or using hot water and soap with gloves. Surfaces contaminated with respiratory secretions/body exudates and frequently touched surfaces should be disinfected. It is necessary to use a separate dustbin to dispose of used gloves/masks and other contaminated items, to close the garbage bag tightly after being transferred to a second bag and throw it away, to use gloves when handling and disposing of the bag.

The caregiver of the patient must wear a mask and gloves during close contact, avoid direct contact with the patient's body fluids. The caregivers and family members are expected to observe their own health status in terms of COVID-19 symptoms and apply to a health institution in the event of a symptom.

Terminating Home Care and Isolation

In order for the person isolated at home to end the isolation, the individual must not have symptoms that require hospitalization and must have completed the 10th day of home quarantine.

If no tests have been performed, but there are symptoms of COVID-19, there should be no fever for at least three consecutive days, symptoms such as cough, difficulty in breathing, and at least seven days must have passed since the onset of symptoms. For definitive results, having two consecutive negative test results 24 hours apart is sufficient to terminate the isolation.

Public Health Nursing Practices in Using the Intervention Wheel in the Management of COVID-19

It is also known as the Community Based Intervention Wheel Public Health Model. It was developed in 1998 by the Minnesota Department of Health's Department of Public Health Nursing. The first stage of the Intervention Wheel practices involves political interventions to improve public health. The second stage aims to improve health for the individual and family. The third stage aims to increase the awareness of the society by changing the behavior and attitudes. The main purpose of all three applications is to improve the health of the public,. Apart form these pactices, there are seventeen public health interventions, which can be used in the management of COVID-19;

Using Follow-up (1), Public health nurses have closely monitored up the individuals with chronic diseases, those who go and return from abroad, COVID-19 patients monitored at home, and their contacts by phone until their signs and symptoms disappeared. In the follow-ups, it has been recognized that there is an urgent and growing need for well-structured remote access information technologies, improving the technological skills of public health nurses, educating the society, and making efficient use of technological tools widespread in order to reduce the risk of contamination. Researching about disease and other health events monitors family members in terms of signs and symptoms by training them on COVID-19 Management at Home (2). Finding the first hosting source during the epidemic (filiation) facilitates controlling. Due to the COVID-19 pandemic, disadvantaged groups are at more risk than other groups in terms of social, physical, economic and psychological aspects. It is important for public health nurses to manage and protect especially the risky groups. While referring to the Social Assistance (3) intervention, the nurse finds the risky populations under her care, and can guide the individuals and families by providing information and access to support about what can be done about this situation and how to reach necessary services. Using Screening(4), the public health nurse identifies the symptoms and findings of those who are suspected of COVID-19 infection who apply to the Family Health Center, takes a respiratory tract swab sample, and ensures that the screening is performed. The nurse also takes the patient's health history and manages the Case Finding(5) area by identifying the contacts and directing them to the filiation team. By following the Referral and Tracking (6) transactions, the nurse performs Case Management(7).

Epidemiological studies have shown that 80% of those with COVID-19 infection have a course with mild or moderate symptoms and do not require hospital care. These people are more likely to apply to primary health care institutions. Therefore, alleviating the symptoms of people who apply to the public health center is possible with strict monitoring and isolation at home. The use of the Delegation of Tasks(8) in cases where the public health nurse cannot follow-up the patient reduces the emergency health risks.

In the COVID-19 management, public health nurses have actively used their Intervention Wheels in order to raise awareness of individuals and improve their health by performing Health Education(9), Counselling(10), Consultation(11), Cooperation(12), establishing cooperation with local administrations, scientific and professional groups (13), holding Community organizations(14),maintaining sustainable conditions in favour of promoting their health and the public health, playing Protective role(15) focused on influencing/changing behaviors such as using the right mask, hand hygiene, social distancing, managing chronic diseases at home, getting health counseling via phone, Social marketing(16) and Policy development and execution(17).

Conclusion

Before COVID-19, home care services in Turkey were generally offered to people with disabilities, elderly, hospice or chronic diseases by physical contact, but after COVID-19, this has dramatically changed with remote management to cover infectious diseases and the whole society. The value of health and nursing practices outside the hospital such as home care and family health centers began to be recognized. In order to prevent confusion during the pandemic process, filiation teams consisting of healthcare professionals were formed to follow up COVID-19 cases, contacts and provide home care services, thus maintaining the sustainability of the services of the patients receiving routine home care. The awareness level of the nurses working in the filiation team on specialization in these fields has increased since they actually took on the duties of public health and home care nursing. During the COVID-19 period, the practices of home diagnosis, care, being monitored have provided many advantages such as easy course of disease for infected people, reduction of infection, prevention of crowding in hospitals, and cost-effectiveness. Therefore, the demand for home care services in Turkey has increased and their value has been well understood. In addition to these practices, telehealth applications have multiplied rapidly. The home care model has been strengthened with algorithms that measure the speed and spread of the pandemic. As a result of the pandemic, a new home care service model has emerged in which many sectors such as basic food aid, social support groups, security/safety, health care team, municipalities cooperate with each other. Despite the global effects of COVID-19, home care services have been determined to be an integrative approach to protect and maintain the health of both the individual and the community.

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CHAPTER 14

COVID-19 IN INTENSIVE CARE UNIT

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1. Introduction

After series of pneuomina cases with unknown ethiology, a novel coronavirus type was detected in Wuhan, China on December 2019. The virus was titled severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The infection spread rapidly all over the world starting from China. The World Health Organization (WHO) named the spectrum of disease caused by SARS-CoV-2 as "coronavirus disease-19" (COVID-19) and pandemia was declared. The total of people infected with COVID-19 has exceeded 100 million worldwide since December 2019. COVID-19 caused deaths are 2.907.944 people by April 10, 2021. Turkey confirmed 4.025.557 COVID-19 people and 34.734 COVID-19 related mortality so far. The daily number of cases reached 49.584 on April 6, 2021 which made Turkey second country in the most reported cases to WHO.

COVID-19 has been one of the most devastating epidemics encountered in recent years which has forced healthcare provision because of the quick spread of the disease, high case numbers, high hospital and intensive care admission rate. Intensive care units (ICU) were on high demand in this epidemic due to increased critically ill patients. Therefore, ICU bed capacity and staff number had to be increased rapidly in many countries. We have been facing the COVID-19 pandemic for more than a year. While the pandemic continues with an increase in cases globally, and unfortunately, there are still many unknowns in diagnosis, treatment and follow-up. It's crucial that COVID-19 patient follow-up units, especially ICU's need to be managed thoroughly in order to prevent mortality and morbidity. In this chapter, essentials of managing COVID-19 patients in the ICU's were summarized.

2. Clinical features of critically ill patients

The symptoms of COVID-19 are non-spesific symptoms that are shared by most viral diseases and the clinical spectrum has very wide range between asymptomatic to critical illness and death. The most seen symptoms are; dry cough, fever, difficulty breathing, weakness and myalgia along with sore throat, nasal congestion and nasal discharge. Although ageusia and anosmia are not specific to COVID-19, they are thought to be characteristic to COVID-19 and has an incidence of 64-80%. Furthermore; COVID-19 may present without respiratory symptoms and with gastrointestinal, neurologic symptoms only. Symptoms of the disease emerge in an average 4-5 days, and it may vary due to seriousness of the disease. In addition, SARS-CoV-2 mutation has been reported and it has multiple variants which may change frequency of symptoms and severity of illness. For instance, B.1.1.7 variant which was held responsible for increased cases in the UK has sore throat, weakness and myalgia as predominant symptoms. However; recently discovered variants are worried for it's more contagious and mortal nature, the data lack evidence.

The WHO classified COVID-19 patients according to its level such as; critical illness, severe, moderate, and mild,. According to this classification; mild illness includes COVID-19 patients with pneumonia and without hypoxia emergence, moderate illness includes patients with symptoms of pneumonia as fever, cough, dyspnea and yet excludes severe pneumonia symptoms, severe illness includes patients with at least one pneumonia symptom as breath rate over 30/mins, severe respiratory distress with oxygen saturation (SpO_2) in room air below 90%, critical illness includes patients with severe viral pneumonia who has life threating conditions like sepsis, septic shock, acute respiratory distress syndrome (ARDS), acute thrombosis. In a large study from China, it was reported 81% of the patients developed mild to moderate disease, 14% severe and 5% critical disease that required ICU. Patients with severe disease consisted of elderly patients with comorbidities which are hypertension and diabetes predominantly. In addition; male gender, chronic obstructive lung disease, cardiac, hepatic, cerebrovascular disease, kidney disease, malignancy, immune deficiency, pregnancy cigarette smoking and obesity have also been defined as other risk factors for extreme disease development. In a metaanalysis of 32849 patients in which examined effect of COVID-19 on disease severity, 25.6% of the patients had a history of smoking who found to have an increased risk for mortality, disease progression and mechanical ventilation for both current smokers and ex-smokers. Fresan et al. reported that 433995 COVID-19 patients with a body mass index of 40 and above were founded to have an increased risk of hospitalization with severe disease development. The risk was prevalent especiallly in the group under 50 years of age and it was defined as risk factor for mortality in this group. Moreover; some COVID-19 patients with mild clinical course may progress to more severe form of disease approximately 7-14 days after the start of symptoms. Clinicians should recognize that some of the patients may have potential to deteriorate seven day after the beginning of the disease

The follow-up rate of COVID-19 patients in the ICU varies for each country depending on the severity of the disease and the intesive care bed capacity. However; efficient use of intensive care capacity is pivotal for the COVID-19. Because, improper use of ICU beds conduce to unnecessary use of country resources and hampering of treatment for critical patients who may benefit from intensive care services. Therefore, guidelines for management of COVID-19 patients are published as in our country by Directorate General of Public Health, Turkish Ministry of Health. In this guideline, patients with respiratory rate more than 30/min, progressive dispnea, increased oxygen demand, SpO2 below 90% or partial pressure of arteral oxygen below 70 mmHg with 5 l/min oxygen flow, blood lactate level above 2 mmol, increased troponin level, arrythmia, hypotension, symptoms of acute organ failure needs to be evaluated regarding intensive care admission.

3. Respiratory support

ARDS is a syndrome characterized by inflamatory pulmonary edema resulting decreased lung compliance and hypoxemia and associated with high mortality and morbidity. The Berlin definition was made for ARDS in 2012, and according to this definition; ARDS is an acute hypoxemic respiratory failure presented with progressive pulmonary symptoms within a week, and bilateral pulmonary infiltrates on radiographic examination which cannot be explained by cardiological reasons. One of the most common serious clinical conditions and the main cause of mortality in patients with COVID-19 is ARDS requiring invasive mechanical ventilation and acute hypoxemic respiratory failure. Although rate of progression of COVID-19 from pneumonia to ARDS varies from country to country, it has been reported in the literature that this rate is between 3% and 63%. In a systematic review of 69093 criticaly ill COVID-19 patients, ARDS incidence was found 85% and 58% of whom needed invasive mechanical ventilation. Risk factors for developing ARDS and respiratory failure are; male gender, age over 65, high levels of c-reactive protein, lactate dehydrogenase, ferritin, and d-dimer, high viral content and lymphopenia.

The Pathophysiology of COVID-19 related ARDS has distinctive features unlike other ARDS types. For instance, COVID-19 causes intensive endothelial dysfunction with thromboinflammation and this leads to thrombosis in pulmonary bed, inhibition of hypoxic pulmonary vasoconstriction and eventually irregularity in pulmonary perfusion. In addition; autopsy examinations from patients with severe COVID-19 pneumonia showed similar to ARDS.

Early identification and treatment of respiratory failure is essential in preventing mortality and morbidity. Hypoxemia and increased respiratory workload in a variable extent may be present in COVID-19 patients during admission to ICU. Interestingly enough, hypoxemia may develop in some patients with COVID-19 without respiratory symptoms and may result in increased mortality by causing delayed diagnosis of respiratory failure. Although, the optimal SpO_2 value for adult COVID-19 patients is not known, it's plausible to keep SpO_2 in the range of 90%-96%. For this purpose, conventional oxygen support can be provided to patients with nasal cannula, venturi mask and non-rebreather mask. Oxygen titration is recommended in patients with hypoxemic respiratory failure in order to hamper the potential harms of hypoxia and hyperoxia. In a recent study of 2928 critically ill patients, 90-day mortality was found equivalent between groups with target partial pressure of arterial oxygen of 60 mmHg and 90 mmHg. However, further studies are needed in order to change medical practice. In some patients, non-invasive mechanical ventilation (NIV) support and high-flow nasal cannula oxygen (HFNC) support can be given to prevent respiratory failure from turning into serious forms that require invasive ventilation support. It's recommended that, HFNC is preferred to NIV in COVID-19 patients with hypoxemic respiratory disease. NIV can be applied if HFNC is not available and the patient does not need intubation. Recent data showed, although HFNC and NIV can decrease the need for invasive mechanical support, possible delay in endotracheal intubation may result in increased mortality. For that reason, patients recieving oxygen treatment by HFNC and NIV should be closely monitorized in terms of the need for endotracheal intubation. Roca et al. defined rate-oxygenation index in order to assess intubation requirement in hypoxemic and respiratory insufficient HFNC applied patients. Rate-oxygenation index is basicly the ratio of SpO_2/fraction of inspired oxygen (FiO_2) to breathing amount. It has been found that patients with this index of 4.88 and above have a low risk of intubation and that HFNC will likely fail in patients below 3.85. Studies have shown that, rate-oxygenation index is a good indicator for predicting intubation requirement in HFNC applied COVID-19 patients. However, the most suitable time for intubation in COVID-19 patients with hypoxemic respiratory failure is not clearly known yet. At the begining of pandemic, it was recommended that these patients should be intubated early in order to prevent virus spread. Although some of the authors supported this approach with the idea that it may prevent patient self-inflicted lung injury, some did not support. While the debate has been ongoing since the beginning of the pandemic, there is no clear evidence in the literature that one strategy is superior to another. However, in a recent systematic review and metaanalysis examining the intubation timing on clinical outcomes in ICU patients with COVID-19, it showed that intubation timing had no effect on death and morbidity in ICU patients. Since endotracheal intubation is a high-risk and aerosol forming procedure in terms of virus transmission, it should be undergone with video-laryngoscopy in a single-person negative pressure room using personal protective equipments such as N95 mask, goggles, watertight overalls or long-sleeve gowns, double gloves. Moreover; other aerosol forming procedures such as extubation, NIV, tracheotomy, cardiopulmonary resuscitation, bronchoscopy, bag-mask ventilation, drug nebulization should be performed using personal protective equipment in order to prevent nosocomial transmission as in endotracheal intubation.

Lung protective ventilation strategies should be applied in mechanically ventilated ARDS patients such as low tidal volume (4-6 mL/kg predicted body weight), targeting plateu pressure $\leq$ 30 cmH_2O and driving pressure $\leq$ 15 cmH_2O. In Berlin Definition, ARDS was divided into 3 groups according to the severity of hypoxemia while a minimum PEEP of 5 mmHg applied as mild (PaO2/FiO2 200 to 300 mmHg), moderate (PaO2/FiO2 100 to 200 mmHg) and severe (PaO_2/FiO_2 less than 100 mmHg). High positive end-expiratory pressure (PEEP) should be preferred to low PEEP in especially patients with moderate and severe ARDS. Although, high PEEP levels can provide improvement in oxygenation and decreased atelectotrauma by preventing alveolar collapse, it may cause barotrauma and certain levels of hemodynamic problems. The patients should be monitored in terms of possible side-effects of PEEP and PEEP should be titrated considering it's possible beneficial and harmful effects. Neuromuscular blocking agents can be administered by avoiding long-term infusions in patients with mechanical ventilator dissynchrony at constant high platau pressure and patients undergoing prone ventilation, but their routine use should be avoided. Prone position application for 12-16 hours in mechanically ventilated patients with moderate and severe ARDS improves oxygenation by reducing ventilation perfusion mismatch. Prone position should be applied for 12-16 hours in ARDS patients with COVID-19 and PaO_2/FiO_2 lower than 150 mmHg. Prone position application may still improve oxygenation in patients who do not recieve mechanical ventilation treatment, but there is not enough evidince for effectiveness of this application. In a metaanalysis comparing standard care with non-ventilated prone position in COVID-19 patients in terms of intubation and mortality, it was found that non-ventilated or awake prone position application improved oxygenation, however it showed no difference in mortality and rates of intubation. Some experts stated that, some patients with COVID-19 associated ARDS have differences from other ARDS patients, thus COVID-19 associated ARDS may have 2 phenotypes. Some patients with COVID-19 have preserved compliance, low response to applied PEEP, respiratory workload even with severe hypoxemia, and this group is named phenotype L (low elastance).

Some of the patients with COVID-19 are characterized by stable compliance, low response to applied PEEP, preserved respiratory workload even with severe hypoxemia, and this group is named phenotype L (low elastance). The patient group with typical ARDS findings is named phenotype H (high elastance). It was also stated by the authors that, unlike lung protective mechanical ventilation strategies, higher tidal volumes can be safely applied to patients with Phenotype L. However, later studies showed mechanically ventilated patients with COVID-19 associated ARDS have similar ventilatory mechanics with other ARDS patients.

4. Weaning and tracheotomy

Extubation and tracheotomy are risky procedures in terms of COVID-19 transmission and should be performed by using personal protective equipments. The decision of weaning from mechanical ventilator and extubation is very important in COVID-19 patients. Failed extubation and reintubation is a high risk situation for both healthcare professionals and patients. Therefore, COVID-19 patients should be examined thoroughly in the process of extubation decisionmaking as in other patients, yet it should not be postponed due to concerns about virus transmission. When making the decision for weaning from mechanical ventilation patients should have a good consciousness, adequate coughing effort, stable hemodynamic values and Rapid Shallow Breathing Index below 100 for 2 minutes during a daily spontaneous breathing trial as in non-COVID-19 patients and it should be ensured that patients can maintain adequate airway opening with minimal respiratory stress. Before starting spontaneous breathing trials, the patient should be evaluated by bedside radiographic examination in order to determine remission of lung disease. Another factor associated with the success of extubation is the oxygenation and ventilation status of the patient, that is when PEEP is 5-8 cmH_2O and FiO2 is 0.4-0.5, being PaO_2/FiO_2 above 200 and pH above 7.3 is a good indicator for sufficient oxygenation and ventilation. There are concerns about aerosol forming due to T-piece usage during spontaneous breathing trials. Therefore, the spontaneous breathing trial can be applied using closed systems with pressure support ventilation between 30 minutes and 2 hours. However, if T-piece is applied a humidifier with virus filtering feature should be used. In order to reduce the possibility of extubation failure, planned NIV can be applied after extubation in COVID-19 patients, but it should be noted that NIV is an aerosol forming procedure and it should be applied with necessary precautions.

COVID-19 patients with respiratory failure frequently need prolonged mechanical ventilation support that lasts 2-3 weeks and sometimes more. Long-term endotracheal intubation has many complications such as tracheal stenosis, difficult weaning. Furthermore, these patients may have sticky and increased secretions, which may cause obstruction in endotracheal tubes leading airway obstruction. Although there is no clear evidence yet for optimal timing for tracheotomy in these patients, early tracheostomy may decrease invasive mechanical ventilation time and support weaning. Although, tracheotomy has not yet been shown to provide survival benefit in COVID-19 patients, the complications of long-time intubation are well-known. Therefore, it is a cornerstone in the therapy of these patients. In patients with COVID-19, open or percutaneous technique can be preferred according to the experience of the practitioner. However, it should be kept in mind that tracheotomy is an aeresol-forming procedure, and it should be applied by taking necessary precautions.

5. Sepsis, septic shock and cytokine storm

Sepsis is a systemic disease with high mortality secondary to infection with pathogens such as bacteria, viruses and fungi. The clinical features of sepsis include uncontrolled systemic inflammation associated with the release of pro-inflammatory and anti-inflammatory biomarkers such as inerleukin-6, interleukin-1, tumor necrosis factor-α, procalcitonin, and c-reactive protein. Many patients with severe COVID-19 develop multiple organ failure, which includes hypotension and shock, acute respiratory failure, acute kidney damage, and coagulation abnormalities and most of these patients meet the sepsis and septic shock criteria specified in the Sepsis-3 International Consensus. In a analysis of 104 studies in which the presence of sepsis was examined in patients with COVID-19 according to Sepsis-3 criteria, it was shown that 83% of the patients in the ICU had sepsis and ARDS was reported as the first common organ dysfunction in both ICU and out of ICU patients.

Hypercytokinemia, cytokine release syndrome, cytokine storm or cytokine storm syndrome is an uncontrolled systemic hyperinflammation, which is characterized by hyperactivation of the immune system triggered by various conditions such as infections, autoimmune diseases and increased release of proinflammatory mediators, which may result in multiple organ failure or even death. Cytokine storm syndrome is also called hemophagocytic lymphohistiocytosis or macrophage activation syndrome depending on the underlying medical condition. Hemophagocytic lymphohistiocytosis is characterized by high fever, organomegaly, cytopenia, high ferritin, high LDH, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis in bone marrow aspirate. Cytokine storm is one of the mechanisms responsible for the impairment and death of multiple organ systems in patients with COVID-19. In patients with cytokine storm associated with COVID-19, interleukin-1β, interleukin-6, tumor necrosis factor, macrophage inflammatory protein 1α and

1β are cytokines with detected high levels. Interleukin-6 is a cytokine that can be produced by various cell types, including lymphocytes, monocytes and fibroblasts and high levels of interleukin-6 have been found to be associated with disease severity and mortality in patients with COVID-19. Furthermore, other indicators associated with mortality in these patients are high levels of c-reactive protein, ferritin, d-dimer and lymphopenia.

Although it is well defined that many patients with COVID-19 develop cytokine storm, elevated cytokine levels and hyperinflammatory status, which are held responsible for organ failure, may differ from those seen in patients with sepsis and ARDS due to other causes. The study examining the levels of tumor necrosis factor α, interleukin-6 and interleukin-8 in COVID-19-associated ARDS patients showed that critically ill COVID-19 patients had lower concentrations of cytokines than ARDS patients due to bacterial septic shock. Likewise, in a meta-analysis examining all studies that compare interleukin-6 concentrations between severe or critical COVID-19 patients and cytokine storm, sepsis, non-COVID-19 related ARDS patients; although interleukin-6 values are frequently detected at high levels in patients with COVID-19, it has been reported that this level is 100 times lower than patients with cytokine release syndrome, 27 times lower than patients with sepsis, and 12 times lower than patients with COVID-19 unrelated ARDS. In addition, the same study showed that non-cytokine biomarkers such as D-dimer, C-reactive protein and ferritin were found to be increased at the extent similar to or greater than other diseases compared in the study. Therefore, COVID-19-related complications are now largely associated with immunosuppression, especially lymphopenia, rather than cytokine storm. However; further research is needed to confirm whether COVID-19-associated organ damage and organ failure is caused by cytokine storm or immunosuppression. Because the inflammatory response commonly seen in patients with severe or critical COVID-19 may differ from other hyperinflammatory conditions, the hyperinflammatory syndrome (cHIS) score for COVID19 was created by Webb et al. to identify the patients who has the risk for mechanical ventilation and death. cHIS score has six parameters. In the 299 patients with COVID-19, a cHIS score of 2 and above was reported to have 96% sensitivity, 49% specificity 81% accuracy, for predicting mortality, and 92% accuracy, 95% sensitivity, and 59% specificity for predicting progression to mechanical ventilation. In another study, hyperinflammation was defined as C-reactive protein over 150 mg/L at admission or doubling within 24 hours or ferritin above 1500 µg/L, and patients meeting this definition was associated with clinical deterioration or mortality.

6. Steroid treatment and tocilizumab

Corticosteroid therapy is currently the most effective treatment for severe COVID-19. Numerous large studies showed that corticosteroid therapy can reduce death in severe COVID-19. In RECOVERY study, one of these large studies, COVID-19 patients were randomized into 2 groups as dexamethasone (n = 2104) and usual care (n = 4321), and dexamethasone (6 mg/day for 10 days) considerably reduced 28-day mortality in patients who received mechanical ventilatory support and needed oxygen support compared to usual care. In the CoDex study, patients with moderate to severe COVID-19 were given dexamethasone at a dose of twenty mg for the first five days and ten mg for the next five days or until discharge from the ICU. The study resulted in significant increase in the number of ventilator-free days at 28-day follow-up in the treatment group. Likewise, a meta-analysis of seven randomized controlled trials examining the efficacy of corticosteroids (dexamethasone, hydrocortisone or methylprednisolone) in patients with COVID-19 confirmed the benefit of corticosteroids in patients with severe COVID-19. The use of systemic corticosteroids in COVID-19 patients was also recommended by WHO as a strong recommendation for severe and critical COVID-19 patients. Other guidelines recommend the use of dexamethasone or alternative glucocorticoids in the absence of dexamethasone.

The REMAP-CAP and RECOVERY studies on tocilizumab showed that tocilizumab has beneficial effects in terms of mortality when administered with corticosteroids in patients with COVID-19, who have an increased need for oxygen, a rapidly deteriorating condition and an inflammatory response. Tocilizumab was administered to critically ill patients first 24 hours of respiratory support (HFNC, NIV or mechanical ventilation) in the REMAP-CAP trial, whereas in the RECOVERY trial, it was administered to participants who had SpO2 below 92% at room air or receiving oxygen therapy and Crp above 75 mg/L. The recently updated guideline also recommends the use of tocilizumab as a single dose of 8 mg/kg (maximum 800 mg) of actual body weight in combination with dexamethasone in the hospitalized patients with rapid respiratory decompensation due to COVID-19. In the guideline, the groups recommended for tocilizumab were specified as patients who were recently hospitalized (3 days after admission), admitted to the ICU within the last twenty four hours and received ventilation support, NIV or HFNC (> 0.4 FiO2 > 30 L/min of oxygen flow) and patients who were not being followed in the ICU but with rapidly increasing oxygen, NIV or HFNC needs and increased inflammation markers (C-reactive protein ≥ 75 mg/L). Tocilizumab is not recommended to be used in patients who are significantly immunosuppressed, especially those who have recently used other biological immunomodulators, patients with alanine aminotransferase > 5 times the upper limit of normal, high risk for gastrointestinal perforation, severe uncontrolled infection other than Covid, neutrophil count < 500 cells/µL, platelet count < 50.000 cells/µL and known hypersensitivity to drug.

7. Coagulapathy and anticoagulant treatment

COVID-19 is known to be associated with microvascular and macrovascular thrombotic complications. In a study by Zhang et al, the frequency of venous thrombombolism in COVID patients was reported as 13% among hospitalized ones, 7% in non-ICU patients and 31% in ICU patients which was found to be higher than non-ICU patients. Moreover; disseminated intravascular coagulation, which is a less common coagulapathy disorder, is also found in the COVID-19 patients. Its incidence rate was reported as 3% in a meta-analysis and it was linked with a bad prognosis.

Timing, duration and dosing of anticoagulation therapy and selecting a proper agent remain uncertain in the critically ill COVID-19 patient population,. Current guidelines for managing coagulopathy in COVID-19 patients recommend prophylactic dose of low molecular weight heparin for all hospitalized COVID-19 patients except patients with active bleeding or platelet count is $< 25 \times 10^9$ L or fibrinogen levels < 0.5 g/L. Mechanical thromboprophylaxis was recommended in patients for whom pharmacological thromboprophylaxis is contraindicated. However, the International Society on Thrombosis and Hemostasis recommends medium dose low molecular weight heparin for high risk patients. Since there is no enough evidence about anticoagulant treatment strategies in patients with COVID-19 yet, the treatment of patients can be individualized for the risk of bleeding and thrombosis.

8. Hemodynamics and fluid management

Since aggressive fluid management and hypervolemia may worsen oxygenation and are related with a extended duration of mechanical ventilation, 0.5-1.0 liters of negative fluid balance per day is recommended for patients with ARDS plus COVID-19 in the absence of shock. However, COVID-19 patients may have hypovolemia especially in the early stages of the disease due to reasons such as fever, decreased oral intake, diarrhea and in the late stages due to sepsis. Uncorrected hypovolemia can lead to peripheral organ hypoperfusion and especially renal damage. In addition; it may facilitate thrombus formation in patients with severe COVID-19 where coagulopathy is relatively common. Hence, fluid status of patients with COVID-19 should be cautiously evaluated, and fluid resuscitation must be applied targeting euvolemia. Fluid status and fluid responsiveness of the patients can be evaluated by fluid challenge test and interpreting dynamic parameters. Passive leg raise test can be used to evaluate fluid status and fluid responsiveness in patients, given its easy applicability. Tidal volume challenge test, in which changes in pulse pressure variation are evaluated with a temporary increase in tidal volume, may also be a good option to evaluate fluid responsiveness in ARDS patients with deep sedation and low tidal volumes. According to current guidelines, fluid resuscitation should be performed with balanced crystalloids and dynamic parameters including skin temperature, capillary filling time and serum lactate level measurement should be used in order to evaluatie fluid responsiveness in COVID-19 patients with shock. Furthermore; perfusion goals should include mean arterial pressure > 65 mmHg, urine output > 0.5 mL/kg/hour and improvement of extremity perfusion. Norepinephrine should be the first choice of vasoactive agent in patients with septic shock where the target mean arterial pressure cannot be achieved. Vasopressin and adrenaline can be used respectively in patients whose target values cannot be achieved with norepinephrine. Another reason for hemodynamic instability in COVID-19 patients may be disease related cardiovascular complications such as myocarditis, heart failure, arrhythmias, acute coronary syndrome and thromboembolic complications such as pulmonary embolism. ECG monitoring should be applied in suspected patients. In patients with COVID-19 who have cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, dobutamine should be administered besides norepinephrine.

9. Acute renal injury and renal replacement therapy

Acute kidney injury (AKI) is common in both hospitalized and critically ill COVID-19 patients. In a multi-center report of 3099 COVID-19 ICU patients in the United States, 20.9% of patients developed AKI requiring renal replacement therapy, and chronic renal disease, high body mass index and severe hypoxemia during ICU admission were found to be independent risk factors for the development of AKI requiring renal replacement therapy. In a paper by Yang et al., 39% of the COVID-19 ICU patients developed AKI and approximately 16% of them had undergone renal replacement therapy. The pathophysiology of AKI in COVID-19 is not fully known, Hemodynamic changes due to invasive mechanical suport, the use of nephtoroxic drugs such as antibiotics and hypovolemia may also cause AKI development in patients with COVID-19. AKI guideline of the Kidney Disease Improving Global Outcomes recommends renal replacement therapy to be initiated when metabolic and fluid requirements exceed the capacity of the kidney. It is recommended that the choice of renal replacement therapy for COVID-19 AKI patients should be continuous renal replacement therapy, and if it is not available, prolonged intermittent renal replacement therapy is recommended instead of intermittent hemodialysis. However, intermittent hemodialysis can be applied if it is not possible to apply continuous renal replacement therapy and prolonged intermittent renal replacement therapy.

10. Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is often used as a last therapy in patients with pulmonary or cardiovascular problems who do not respond to conventional care. Veno-venous (VV), veno-arterial (VA) or veno-arteriovenous (V-AV) ECMO may be preferred depending on the underlying etiology and the condition of the patient. VV ECMO is the method preferred mainly in severe ARDS patients, and VA ECMO is the method preferred in relatively few patients with circulatory disorders such as myocarditis, massive pulmonary embolism and acute coronary syndrome. The use of VV ECMO among adults have been increasing rapidly especially after the COVID-19 pandemic. However, it is a costly procedure that should not be performed in every COVID-19 patient with severe ARDS. ECMO requires especially patient management and can have devastating complications. Current guidelines recommend ECMO therapy in patients with refractory hypoxemia and hypercarbia despite advanced ventilation strategies including neuromuscular blockade, high PEEP and prone position. ECMO is suggested for patients with $PaO_2/FiO_2 < 80$ mmHg over six hours, $PaO_2/FiO_2 < 50$ mmHg over three hours, or with partial carbon dioxide pressure > 60 mmHg and pH < 7.25 over six hours despite conventional ARDS treatments. VV ECMO is not recommended for patients who have central nervous system damage, systemic bleeding or contraindications for anticoagulation, who especially ventilated with $FiO_2 > 0.9$, plateau pressure > 30 cmH_2O for more than 7 days.

11. Antiviral treatment

Management of COVID-19 is mostly supportive, and antiviral treatments are still being studied currently. One of the recommended drugs for the treatment patients is favipiravir. Favipiravir is an RNA-dependent polymerase inhibitor which was the first drug approved for the treatment of influenza in Japan and SARS-CoV-2 in China. In the recently updated guideline of COVID-19 patients in Turkey, it is stated that Favipiravir may be used as a maintenance dose of 600 mg twice a day for 5-10 days after a 1600 mg loading dose twice a day. In addition, the Favipiravir dose can be administered at a loading dose of 1800 mg twice a day, followed by 800 mg twice a day for a total of 10 days in patients >50 years of age and with comorbidities. However, Favipiravir is contraindicated in pregnant and breastfeeding women. The efficacy of Favipiravir in the treatment of COVID-19 patients is currently being studied, and one of the ongoing large-scale studies is the "PRINCIPLE" study. Another drug recommended for the treatment of COVID-19 is Remdesivir. It is the only drug approved by the Food and Drug Administration for the treatment of COVID-19 in hospitalized adult and pediatric patients (12 years and 40 kg). However, WHO does not recommend routine administration of Remdesivir in addition to standard care. The National Institutes of Health guideline suggests remdesivir for hospitalized adults requiring supplemental oxygen, while combination of dexamethasone and remdesivir is recommended for patients requiring an increased amount of oxygen and those in need of HFNC or NIV. The use of Remdesivir is not recommended in patients requiring invasive mechanical ventilation or ECMO. Likewise, The National Institute for Health and Care Excellence recommends Remdesivir for adults who need oxygen without invasive mechanical ventilation, children aged 12 years and over 40 kg. The Infectious Diseases Society of America recommends Remdesivir in severe COVID-19 patients with a SpO_2 of 94% or less in room air and requiring supplemental oxygen, mechanical ventilation or ECMO in the treatment and management guideline. The recommended dose and duration of treatment for Remdesivir is 5 days after the first dose of 200 mg, 5 days in patients using 100 mg oxygen, and 10 days in patients with mechanical ventilation or ECMO. The recommended dose and duration of treatment for Remdesivir is 100 mg for 5 days in patients using oxygen and 10 days for patients with mechanical ventilation or ECMO after the first dose administered as 200 mg.

12. Conclusion

COVID-19 has been one of the most difficult diseases we have encountered in this century. The importance of intensive care units has been understood once again with the COVID-19 pandemic. Despite promising developments such as the vaccines over the year with COVID-19 pandemic, there is still a long way to go. Updating the strategies and guidelines for the management of the disease according to new evidence and improving the care standards of COVID-19 patients are important in terms of decreasing the disease-related mortality rates.

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CHAPTER 15

PERIOPERATIVE PLANNING FOR CARDIOVASCULAR OPERATIONS IN THE COVID-19 PANDEMIC IN TURKEY;

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1. Introduction

A novel coronavirus, originally reported in Wuhan, China, has resulted in an ongoing epidemic as of late December 2019. The causative microorganism was defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).The World Health Organization (WHO) has now announced that the situation has become a pandemic.It should be noted that coronavirus disease-2019 (COVID-19) caused more than 42,000 deaths in 857,641 confirmed patients worldwide, while the first case of COVID-19 in Turkey was reported on March 11, 2020.

COVID-19 prevention measures and treatment algorithms are updated by the authorities every day.Although there are ongoing discussions about the pandemic treatment algorithm, anesthesia and airway management guidelines are thought to be well documented.However, the structure of the operating room (OR) and the necessity of surgical steps has not been clarified until now. Likewise, there is no existing algorithm for emergency heart surgeries in COVID-19 patients.

It is clear that a suspected/confirmed COVID-19 patient should be evaluated with a specific procedure for any medical or surgical intervention. This report aims to provide an overview of optimal prevention conditions for a COVID-19 patient and cardiovascular healthcare workers requiring cardiovascular surgery.

All recommendations for COVID-19 patients in this article have been developed with expert opinions. The current treatment algorithm should be followed strictly through the publications and websites of WHO, Centers for Disease Control and Prevention (CDC) and Turkish Ministry of Health.

2. General measures taken by government and hospital management

After the declaration of the pandemic, general measures were taken by both the administration of health institutions and the government in TURKEY. The main concern of these measures is to be able to respond to the estimated increasing number of COVID-19 patients with the capacity of the existing health system. There are two important issues addressed in the health system during the pandemic.

2.1 Postponing elective procedures to reduce the burden of the health system, taking into account the rate of spread of the pandemic. For this purpose, determining the priority level in cardiovascular surgery diseases.

2.2. In emergency and priority patients who need surgery, infection protection measures should be taken in the intensive care unit before, during and after surgery.

In this direction, as a first step, all elective surgeries were postponed to a suitable time period.Subsequently, the definition of “pandemic hospital” was made, consisting of an intensive care unit (ICU) and all tertiary care centers (state, university or private hospital) with health personnel (Infectious Diseases Specialist, Internal Medicine Specialist or Pulmonology Specialist) by the TR Ministry of Health. Shift work rule has been introduced in workplaces to cope with the reductions in the number of health personnel due to the possibility of exposure to SARS-CoV-2 and to prepare for the increase in these cases. The number of visitors and their duration are also limited. Social distancing rule has been applied. Outpatient appointments are restricted. Daily changing protocols and guidelines were shared with medical staff.

3. Timing of cardiovascular surgery procedures

It is not possible to define surgical urgency based on the patient’s specific diagnosis. For general surgical procedures, some surgical situations may be delayed for a long time; however, cardiovascular surgery patients may be associated with progressive disease. The need for surgery for a particular disease state should be recognized by an experienced surgeon to identify risks that may develop in case of delay. The risk to both the patient and the healthcare provider must also be fully considered. The decision to perform or delay a cardiovascular surgical procedure should be based on the patient's haemodynamics and the health system's suitability. That is, decision-making strategies should not depend solely on the risks associated with COVID. Regarding the capacities of the health system, the final decision depends on medical staff (i.e. surgeon, ICU or perfusion), ICU beds, anesthesia staff and isolation beds, surgical/anesthesia equipment (e.g. ventilators, pumps, intraaortic balloon pump [IABP] or extracorporeal membrane oxygenation), blood and blood product availability, and consumables (i.e. sutures, drapes, grafts, or valves).

Surgical decision-making in emergency triage for cardiovascular surgery has been defined in our routine practices by our international guidelines. However, we need to discuss the current emergency situation in the light of limited data and expert opinions and in the light of our published guidelines.

A classification of the cases may be helpful for us in that stage. The definitions of the widely seen cardiovascular interventions are shown in Table 1.Following the definitions of elective cases should be postponed as much as possible, whereas urgent and emergent cases should be operated withprotective measures

All patients should be discussed by the Heart Team as to whether to postpone surgery and the timing of the surgical procedure. There are some considerations for both non-COVID-19 and suspected/confirmed COVID-19 patients who definitely need cardiovascular interventions. If the patient is classified as an elective case, it is recommended to postpone the intervention in the current health institution defined as a pandemic hospital.

If the patient is classified as an emergency, it is recommended that the response be planned within the existing healthcare facility according to infection prevention measures. Thus, the risk of contamination that may occur during patient transport can be eliminated.

Table 1. Surgical Timing

A. **Elective Surgery** (routine admission for operation)
Coronary artery disease (CAD) • Patients with asymptomatic or stable angina
Valvular heart disease (VHD) • Chronic and hemodynamically stable patients
Aneurysmal vascular disease (AVD) • Unruptured and hemodynamically stable patients
Peripheral arterial disease (PAD) • Chronic limb ischemia with rest pain or tissue loss • Patients with intermittent claudication • Asymptomatic bypass graft/stent restenosis
AV Access for hemodialysis • Fistulas revision for malfunction/steal • AV fistula and graft placement for dialysis
B: **Urgent Surgery** (patients who have not been electively admitted for operation but who require intervention or surgery on the current admission for medical reasons. These patients cannot be discharged without a definitive procedure)
CAD • Acute Coronary Syndromes (NSTEMI, STEMI, USAP) (timing of the procedure should be decided on an individual basis, according to symptoms, hemodynamic stability, coronary anatomy, and signs of ischemia and failed/unsuitable for percutaneous intervention) such as;severe left main (LM) or three-vessel CAD involving the proximal left anterior descending artery (LAD).
VHD • Acute mitral regurgitation • Acute aortic regurgitation • Obstructive prosthetic valve thrombosis in critically ill patients without serious comorbidity • Active endocarditis
AVD • Thoraco-abdominal aortic aneurysm (TAAA)/abdominal aortic aneurysm (AAA) with acute contained rupture with hemodynamically stable patients • Rapid progression of the aneurysmal diameter and large diameter (TAAA/AAA >6-6.5 cm) • Symptomatic peripheral artery aneurysm • Pseudoaneurysm (not suitable for thrombin injection and ultrasonography (US)-guided compression)

PAD • In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case-by-case decision • Infected arterial prosthesis without overt sepsis hemorrhagic shock, or impending rupture • Symptomatic acute mesenteric ischemia • Amputations for infection/necrosis and non-salvageable limb
AV access for hemodialysis • Thrombosed or non-functional dialysis access • AV fistulas revision for ulceration • Infected access • Tunneled catheter
Pericardial tamponade or postcardiotomy syndrome with hemodynamically stable patients
C. Emergency (operation before the beginning of the next working day after decision to operate)
CAD • Patients with a patent ischemia-related artery (IRA) but with unsuitable anatomy for percutaneous coronary intervention (PCI), and either a large myocardial area at jeopardy or with cardiogenic shock. • Continuing or recurrent ischemia, ventricular arrhythmias, or hemodynamic instability • Patients with myocardial infarction (MI)-related mechanical complications who require coronary revascularization
VHD • Valve disorder (regurgitation/stenosis/endocarditis) with acute cardiac heart failure
AVD • TAAA/AAA and peripheral aneurysm with rupture with hemodynamically unstable patients
PAD • Acute limb ischemia (in the case of neurological deficit)
Dissection of aorta • Complicated type B aortic dissection • Type A aortic dissection
Pericardial tamponade or postcardiotomy syndrome with hemodynamically unstable patients

NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; USAP: Unstable angina pectori

4. Preparing the cardiovascular surgery room

Considering the intra-hospital spread of the virus, precautions should be taken for both patients and healthcare workers to prevent hospital-acquired transmission. A separate OR(COVID-19 OR) for suspected/ confirmed COVID-19 patients should be isolated with pre-allocated access routes for the patient. It should be marked with the warning signs of COVID-19. The feasibility of OR setup and workflow is an important consideration for all surgical procedures. The distribution of surgical instruments and anesthetic equipment must be unique to the previously identified COVID-19 OR. Patient-specific equipment should be prepared. All equipment that will not be used should be removed from the OR. The coordination of the personnel assigned in the COVID-19 OR and the workflow of the COVID-19 OR should be planned daily. Personal protective equipment should be introduced and used in the isolated OR. There should be limited and necessary health personnel in the OR. Workflow of COVID-19 OR includes routine universal infection prevention practices, donning and removal of personal protective equipment (PPE) and decontamination after procedures. Intubation items, peripheral artery/central venous cannulation, syringes, gauze, surgery .All necessary items such as drapes, surgical instruments, sutures, cannulas for cardiopulmonary bypass (CPB), oxygenator and CPB circuit, prosthetic grafts, and valves should be set up before the patient enters the OR. Congestion in the OR should be minimized. The procedure should be performed by a limited number of healthcare professionals (ie, surgeon, anesthesiologist, perfusionist and pouch nurse). All equipment to be used should be prepared in the OR before the procedure begins. Contact and entry and exit to the isolated OR should be minimal. High-contact equipment (infusion pumps, CPB machine, cell protection device, IABP, heat exchangers and computer for documentation) should be wrapped in plastic wraps to facilitate decontamination as well as possible contamination during patient transport prior to surgery. Strict anesthesia management and infection control procedures should be applied to patients with suspected/confirmed COVID-19.

5. Cardiopulmonary bypass(CPB)

Similar to changes in anesthesia management of patients with the COVID-19 virus, some aspects of CPB behavior may be affected. Currently, there are no guidelines on how to best manage these patients. The well-known pro-inflammatory nature of CPB and associated interventions may exacerbate virus-induced hypercytocinemia. Few data are available on any adverse effects of coronavirus on membrane oxygenator function during CPB. When managing gas transfer during CPB, higher ventilation (scavenge rates) and FiO 2 levels should be used. The US Food and Drug Administration (FDA) has recently relaxed standards for the use of polypropylene oxygenators for long-term support (more than 6 hours). The known failure rate of these devices can result in further compromise of gas exchange as well as plasma leakage and aerosolization of droplets. Replacing a polypropylene oxygenator on failure may also result in increased non-endothelial surface exposure, which exacerbates inflammation. Strategies for CPB-associated COVID-19 infections are summarized in Table 2.

Table2. Cardiopulmonary bypass-related strategies for COVID-19 infection.

CPB-related strategies	Underlying factors-targets
Heparinization	Higher patient loading dose of heparin: 400-500 IU/kg Higher prime loading dose of heparin: 10-15K IU CPB-related strategies Underlying factors-targets
Coagulation	monitoring More frequent coagulation assessment: Q 20min Monitor AT III activity
Blood management	Techniques to optimize hemoglobin levels: Retrograde autologous priming, prime volume reduction, ultrafiltration
Equipment Oxygenator	Larger surface areas to increase gas exchange Increased ventilation flow and FiO2
Ultrafiltration	CUF to reduce hemodilution ZBUF to reduce cytokine load
Centrifugal cell salvage	Source of gas aerosolization
Myocardial protection	Sanguineous cardioplegic solutions More frequent dosing to limit ischemic time
Avoid antifibrinolytics and prothrombotics	Contraindicated in DIC Prothrombotic nature of PCC and rFVIIa
Simulation practice	PPE donning, oxygenator/circuit change-outs

CUF: continuous ultrafiltration; ZBUF: zero-balance ultrafiltration; DIC: disseminated intravascular coagulation; PCC: prothrombin complexconcentrate; PPE: personal protection equipment

6. Extracorporeal equipment

The heart-lung machine can be the primary source of fluid hydraulics and aerosol production. Therefore, all perfusion personnel should be experts in appropriate enhanced droplet and contact precautions (EDCP). EDCP should be applied throughout the entire procedure, including the postoperative disposable and disinfection period. Higher levels of protection (eg AAMI level 3 or equivalent gown) should be considered alongside the use of PAPR. Because of potential hypercoagulability, all extracorporeal devices and tubing must include surface modification to reduce thrombogenicity. Vacuum-assisted venous drainage should be used with caution, as it may increase the disturbance in the blood-gas interaction, leading to more gaseous microemboli, leading to more viral contamination.

Although the use of centrifugal red cell separators has been shown to reduce hemoglobin loss and acquired anemia, applying vacuum through the aspiration circuit causes the liquid to become aerosolized. When properly connected to the hospital's filtered vacuum system, aerosolized substances should be removed from the clinician. However, when the negative pressure is removed, the aerosolized particles are no longer aerated and can pose an increased risk.

7. Intraoperatıve measures

Infection prevention measures for both surgery and anesthesia

Patients without COVID-19 should undergo standard procedures (i.e. standard anesthesia, standard method, and standard OR procedure).

Personnel performing tracheal intubation and surgery should be in Level III protection for COVID-19 patients, including disposable N95 mask, surgical headgear, work uniform, latex gloves, medical protective uniform, and full-face respiratory protective devices or electrical air-purifying respirator, if available. A minimum number of surgical teams should be assigned, including anesthesiologist, anesthesia technician, surgical nurse, surgeons, perfusionist, circulatory nurse and technician before a COVID-19 patient enters the OR. In order to minimize the intensity in the OR, unemployed personnel should not enter the room. All personnel must be protected with appropriate PPE.

COVID-19 patient with N95/surgical mask should be transferred to COVID-19 OR by predetermined route. Only necessary equipment should be in the room during anesthesia induction and intubation. Aerosol-generating procedures (such as airway manipulation, face mask ventilation and open airway aspiration) should be performed very carefully. Since general anesthesia is applied in open heart surgeries, the patient must wear a surgical mask during the procedure. Nasal oxygen support can be administered under a surgical mask.

There should be a minimum number of healthcare providers in the OR during anesthesia induction. All intubation equipment and drugs used for anesthesia should be ready in the OR before the patient is transferred. In order to minimize mask ventilation time, anesthesia induction and preoxygenation should be performed quickly with a well-fitting face mask.A video laryngoscope, if available, is preferred for intubation, and it is recommended that the patient be intubated by the most experienced person to avoid re-attempts by personnel. After the cuff is inflated, the ventilator is connected to the patient before positive pressure ventilation is initiated. Closed tracheal aspiration systems can be used to avoid interruption of the circuit. Anesthesia and intubation protocols have been recently reported by experts.

The surgical team consisting of surgeons, nurse and perfusionist should follow PPE instruction (Table 3). In addition, surgeons and the pouch nurse should wear a surgical cap and surgical mask over the PPE and then put on a double glove surgical gown. Gloves should be long sleeved and fixed to the sterile coating with adhesive drapes. All surgical gowns and gloves must be removed in the COVID-19 OR. First, remove the second layer of gloves and perform hand hygiene. Then the surgical gown and surgical mask should be removed. The steps to remove the PPE must be followed separately for doffing.

Transport of a COVID-19 patient should be performed by personnel with PPE. If the patient is intubated during the transport, ventilation is performed with a disposable ambu bag. Positive pressure ventilation should be stopped before leaving the ventilator while the patient is placed in the ambu bag. If the patient is extubated, N95/surgical mask should be worn on the patient. The intensive care bed for the COVID-19 patient should be isolated.

All equipment used in the OR, the floor and wall of the OR, and object surfaces should be disinfected and decontaminated with appropriate procedures. Reusable surgical instruments should be transferred to the nearest sink (with the COVID-19 warning sign) and decontaminated by personnel wearing PPE. Wetting disinfection of reusable instruments should be done for at least 30 minutes with 5,000 mg/L chlorine-containing disinfectant for visible contamination, and 1,000 mg/L chlorine-containing disinfectant for invisible contamination. Disposable equipment used in the operation should be discarded. All plastic wrap around the equipment should be removed and discarded after the operation. Visible contamination from floor, wall and object surfaces must be thoroughly cleaned before disinfection. While disinfection of floors and walls is done by mopping, spraying or wiping with 1,000 mg/L chlorine disinfection solution, object surfaces are wiped with a similar solution. Untouched object surfaces are wiped first; then frequently touched surfaces are deleted. A period of 30 minutes is required for effective disinfection. Disinfection should be done three times a day and when the room is contaminated. All plastic wraps around the equipment should be renewed after decontamination. Plasma air cleaners can be used for air sterilization; otherwise, ultraviolet lamps can be used for one hour.

Table 3. Sequence for donning and doffing personal protective equipment

Donning procedure	**Doffing procedure**
Perform proper hand hygiene	Remove shoe covers (if applicable)
Put on shoe cover (if applicable)	Remove gown and gloves together
Put on gown	Perform proper hand hygiene
Put on mask/respirator (if applicable)	Remove eye protection
Put on goggles	Remove mask/respirator (if applicable)
Put on gloves	Perform hand hygiene

8. Inflammation during covıd -19 and effects of cardiac surgery

In COVID-19, current treatments are mostly supportive. There is an urgent need for the development of new treatments and effective prevention, particularly for life-threatening severe acute respiratory distress syndrome (ARDS) and hyperinflammatory syndrome (characterized by fulminant and fatal hypercytokineemia with multiple organ failure). Many cytokines play a role in the pathogenesis of the disease.Likewise, some of these cytokines cause vascular permeability and leakage, pulmonary edema, ARDS, acute heart damage and multi-organ failure.New therapies such as interleukin (IL) antagonists (dupilumab), interferon blockers (eg, entecavir, penciclovir, sorafenib), JAK2 inhibitor (fetratinib), and stem cell and mesenchymal cell therapies have been applied to neutralize the cytokine storm and have produced some improvement.

Cardiac surgery sustained exposure of blood to non-endothelial surfaces (perfusion circuit) produces a systemic inflammatory response (ie activation of coagulation pathways, complement system and tissue factor, and production of several cytokines). The cause of ARDS may be inflammatory response and may cause acute lung injury (TRALI) due to blood transfusion during cardiac surgery.ARDS and TRALI are dangerous complications that complicate the postoperative period in COVID-19 patients.

During cardiac surgery, the inflammatory response occurs not only to CPB but also to anesthesia, surgical trauma, cardiac manipulation, cardioplegia and myocardial ischemia, heparin and protamine. Control of the inflammatory response to CPB includes off-pump cardiac surgery, temperature regulation (32 to 34°C for operations requiring up to 2 hours of CPB), heparin-coated perfusion circuits, complement inhibitors, and glucocorticoids. Other equipment for immune response in cardiac surgery (minimally invasive extracorporeal circulation and cell protection) may also have positive effects on immune response and reduce systemic cytokine load.

All these measures affecting immune response and inflammation may be reasonable and should be kept in mind for COVID-19 patients during cardiac surgery.

9. Post-surgery measures in COVID -19 (suspected/ confirmed) patients

In the post-operative follow-up of COVID-19 patients, a cardiac COVID-19 team with special expertise should be formed in the cardiac intensive care unit consisting of a cardiovascular surgeon, anesthesiologist, infectious disease specialist and pulmonologist decisions should be made jointly. Multidisciplinary decision-making among the COVID-19 Team can minimize expertise bias and prevent self-direction from interfering with optimal patient care.

In patients undergoing cardiovascular surgery, extubation should be planned for suitable patients in the OR. Patients to be hospitalized in the intensive care unit should be transferred in accordance with COVID-19 infection prevention measures.

In addition, there are many diagnosed cases of COVID-19 among healthcare workers. Therefore, healthcare professionals should follow the infection control procedures currently in place in healthcare facilities. For healthcare workers performing aerosol generating procedures on COVID-19 patients in the ICU, it is recommended to use fitted respirators (eg N95 respirators, FFP2 or equivalent) in addition to other PPE (eg gloves, gown) and eye protection such as safety glasses) as described in infection prevention measures for COVID-19.If possible, the working hours of health workers should be reduced to four hours. Additionally, it is preferable to perform aerosol-generating, non-aerosol-generating procedures in ICU patients with COVID-19 in a negative-pressure room and use a portable high-efficiency particulate air filter in the room, if available. To minimize the risk of contamination and the number of intubation attempts in patients requiring endotracheal reintubation, it should be performed by the healthcare professional with the most experience in airway management, using video-guided laryngoscopy instead of direct laryngoscopy, if available.

During the follow-up of COVID-19 patients in the intensive care unit, patients should be closely monitored in terms of systemic inflammatory response syndrome, ARDS and cytokine release syndrome.

Treatment options (including the antiviral treatment strategy, which is subject to change) for the diseases themselves and subsequent serious clinical conditions (ARDS or shock) should be taken according to the guidelines recommendations.

10. Conclusion

Cardiovascular surgery procedures that can be delayed (Elective Surgery) should be determined by the Heart Team and the patient's consent should be obtained. Other procedures (Emergency Surgery, Emergency) should be done very carefully. Strict precautions and extreme attention to healthcare providers should be exercised for the management of coronavirus patients and infection prevention. Hospitals should create and operationalize sustainable plans to ensure proper care for patients with COVID19 infections while concurrently addressing all the other healthcare needs of their nonnfected local populations. Since there is not specific or definitive treatment and solution, for an increasing number of COVID-19 patients in our clinical practice, there will be a need to be properly prepared to handle this rapidly evolving and changing clinical scenario. In the anticipation of new drugs and vaccines, emphasis should be focused on prevention and symptomatic management as well as mindful following of constantly updated evidence-based guidelines and research. To date, these remain the onlyways to contain the spread and mitigate the impact ofthe COVID-19 pandemic.

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CHAPTER 16

PULMONARY EMBOLISM IN PATIENTS WITH COVID-19 PNEUMONIA

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Introduction

COVID-19 was first reported as a viral disease that could result in pneumonia, acute respiratory distress syndrome (ARDS: Acute Respiratory Distress Syndrome) and even death, which was first seen in Wuhan, China, in late 2019. The World Health Organization has determined the disease caused by the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) as coronavirus disease 2019 (COVID-19).

Although SARS-CoV2 seems to target the respiratory epithelium preferentially, it can infect many cells by binding to the ACE2 (angiotensin converting enzyme-2) receptor . It can progress from symptoms such as new-onset fever, shortness of breath, cough, diarrhea, taste disorder to serious clinical pictures such as systemic inflammatory response syndrome (SIRS), ARDS, multi-organ failure, diffuse intravascular coagulation (DIC) and shock. . In addition to its tropism to the lungs, hypercoagulability is highly present in patients with COVID-19, thrombotic complications such as venous or arterial thromboembolism have been associated with an increased incidence of death in infected patients.

The predominant coagulation disorder in COVID-19 disease is hypercoagulability, that is, predisposition to thrombosis, bleeding is rare. This condition has been called thromboinflammation or COVID-19-associated coagulopathy (CAC: COVID-19-associated coagulopathy) by some experts. The pathophysiological mechanisms underlying CAC are still unclear.

However, endothelial damage, stasis and hypercoagulability, which are the three components of the Wirchow triad, have been held responsible.

Endothelial damage – There is evidence of direct invasion of endothelial cells by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in cell damage. Some experts have suggested that endothelial damage, microvascular inflammation, endothelial exocytosis and/or endothelitis play a majör role the pathogenesis of acute respiratory distress syndrome and organ failure in severe COVİD-19 patients.

The contribution of complement-mediated endothelial damage has also been suggested, and an in vitro study also found that the SARS-CoV-2 spike protein can activate the alternative complement pathway. Studies have shown that complement activation markers, such as C5b-9, are increased in the circulation of individuals hospitalized with COVID-19, relative to the control group (healthy people, people with flu, or people with non-COVID-19 respiratory failure in the intensive care unit). Complement levels were found to be higher in severely ill patients than in those with moderate disease, and those requiring mechanical ventilation compared to those without. Signs of complement activation have also been reported in tissue biopsies.

Stasis – Immobility can cause a slowdown in blood fluidity in all hospitalized and critically ill patients, regardless of whether they have COVID-19.

Hypercoagulable state – A number of changes in circulating prothrombotic factors have been reported or suggested in severe COVID-19 patients :

Very high D-dimer levels have been observed, correlating with disease severity; D-dimer is a degradation product of cross-linked fibrin, which shows enhanced thrombin formation and fibrin dissolution by plasmin. In addition, high D-dimer levels are common in individuals with a number of infectious and inflammatory diseases. Similarly, antiphospholipid antibodies capable of prolonging the activated partial thromboplastin time (aPTT) are common in viral infections, but these are usually transient and do not always imply an increased risk of thrombosis.

VTE: It was very common in patients with COVID-19 in the early stages of the pandemic, including venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE), and patients in the intensive care unit (ICU) were in a third of patients, even when prophylactic anticoagulation was used. was seen in one.

Several autopsy studies have highlighted the contributions of hypercoagulation and associated inflammation in patients who have died from COVID-19:

A study presenting autopsies of 21 people with COVID-19 found microthrombi in the alveolar capillaries in 5 (45 percent) of 11 people and significant PE in four. Three of the patients had findings suggestive of thrombotic microangiopathy with fibrin thrombus in the glomerular capillaries. Information on the use of anticoagulation in these patients was available for 11 people, and all 11 people were receiving some form of anticoagulation. Underlying cardiovascular disease, hypertension and diabetes mellitus were commonly detected.

In another autopsy study of 12 people with COVID-19 (8 men; 10 hospitalized), DVT was detected in 7 (58 percent) of 12 people . Bilateral leg involvement was found in all DVT cases. Evidence of thrombosis was found in 5 (42 percent) of 12 people with pulmonary histology. The cause of death in four of these patients was PE. Extremely high values were found in some of those with D-dimer testing (two >20,000 ng/mL and one >100,000 ng/mL; normal value <500 ng/mL [<500 mcg/L]). He had underlying cancer, ulcerative colitis and/or chronic kidney disease.

In a large study of more than 3,000 hospital admissions and most of them using prophylactic doses of anticoagulation, multivariate analysis found that risk factors for VTE were higher age, male gender, Hispanic ethnicity, previous myocardial infarction, coronary artery disease.

A large database review of 637 patients documented VTE in 45 patients (7.2 percent) requiring mechanical ventilation . Another series of 829 ICU patients with severe COVID-19 reported VTE in 13.6 percent (PE in 6.2 percent and DVT in 9.4 percent). Another series of 102 ICU patients reported a cumulative 14-day incidence of VTE as 9.3 percent

Another series of 184 consecutive patients with severe COVID-19 in the intensive care unit reported DVT in 1, PE in 25 (14 percent), and catheter-related thrombosis in 2. The cumulative incidence of VTE (based on different follow-up periods) was calculated as 27 percent. All were receiving at least standard dose thromboprophylaxis.

Previous series of ICU inpatients have reported VTE in 22 to 39 percent of individuals despite using prophylactic anticoagulation. A series published in spring 2020 reported VTE in 64 of 150 ICU patients (43 percent, mostly PE), coagulation of the extracorporeal circuit in 2 of 12 patients undergoing extracorporeal membrane oxygenation (ECMO), and 28 of 29 patients receiving continuous renal replacement therapy. All patients were receiving thromboprophylaxis (mostly low molecular weight [LMW] heparin), and of these, 70 percent were receiving anticoagulation with a prophylactic dose and 30 percent with a therapeutic dose.

A retrospective study of 1240 patients documented PE using computed tomographic pulmonary angiography (CTPA) in 103 (8.3 percent) non-ICU inpatients. In the multivariate analysis, risk factors for PE included male gender, elevated C-reactive protein, and longer delays between symptom onset and hospitalization. Anticoagulation was associated with a lower risk of PE.

In another study involving 2505 hospitalized patients not in the intensive care unit, VTE was 3.6 percent (DVT 2.0 percent and PE 2.2 percent). Patients were evaluated only if symptomatic.

Studies evaluating symptomatic patients have reported slightly higher rates of VTE (about 3 to 6%). Some developed clots despite receiving prophylactic anticoagulation. In one study, half of VTE events were detected within the first 24 hours after admission, suggesting that thromboprophylaxis may be ineffective because VTE has already occurred.

Studies that screen all patients for VTE, regardless of symptoms, show higher rates of VTE. A study evaluating 71 non-ICU patients hospitalized with Covid-19 for more than 48 hours, systematically assessed by performing bilateral lower extremity duplex ultrasounds at discharge, found a higher rate of DVT (21 percent). Only 2 of 15 patients with DVT were symptomatic; Bilateral involvement was detected in five of them. PE was found in 10 percent, one of which was fatal.

Outpatients — Thrombotic events have also been observed in non-hospitalized COVID-19 patients, but data on incidence are limited. In one study, 72 outpatients with COVID-19 pneumonia admitted to the emergency room and referred for CTPA were evaluated; Pulmonary embolism (PE) was detected in 13 (18 percent).

Diagnosis of DVT or PE- Evaluation of deep vein thrombosis (DVT) or pulmonary embolism (PE) can be difficult because the symptoms of PE are similar to COVID-19 and imaging studies may not be possible in all cases. Given the high frequency of these events and the presence of additional venous thromboembolism (VTE) risk factors in many individuals, the threshold for evaluation or diagnosis of DVT or PE should be low.

PE **–** We believe that the American Society of Hematology (ASH) guidance regarding the diagnosis of PE should be considered:

A normal D-dimer is sufficient to exclude a diagnosis of PE if the pretest probability for PE is low or moderate, but is less helpful in those with a high pretest probability. The increase in D-dimer is not specific for VTE and is not sufficient to make a diagnosis.

In patients with suspected PE due to unexplained tachycardia, hypotension, worsening pulmonary function, or other risk factors for thrombosis, computed tomography with pulmonary angiography (CTPA) is the test of choice to confirm or exclude the diagnosis. Ventilation/perfusion (V/Q) scanning is an alternative if CTPA cannot be performed or is inconclusive, but V/Q scanning may be useless in people with significant pulmonary involvement from COVID-19. Consultation with the pulmonary embolism response team (PERT) is recommended for decision making, if possible.

Coagulopathy Monitoring and Treatment in Adult Patients with COVID-19 in Turkey

In our country, T.C., which was last updated on November 3, 2020.
Ministry of Health, General Directorate of Public Health, COVID-19 (SARS-CoV-2 Infection) Guidelines for adult patients
Coagulopathy follow-up and treatment recommendations are as follows:

1. Coagulopathy should be investigated with the diagnosis of patients. Given the diagnosis, 100 mg/day aspirin was recommended because there are studies reporting a reduction in lung damage progression. Platelet, PT, aPTZ, D-dimer and fibrinogen levels should be observed in the follow-up. If the following values are detected, the patient should be hospitalized and treated;
   a. Platelets <100,000/μL
   b. 5 sec prolongation in aPTZ.
   c. 3 sec prolongation in PZ
   D. 2-3 fold increase in D-Dimer (threshold not clear).
   to. Fibrinogen <200 mg/dL
2. All patients with COVID-19 should receive thrombosis prophylaxis with heparin unless contraindicated. For prophylaxis, LMWH is rarely recommended because it causes thrombocytopenia and requires infrequent injections.

3. Thrombosis prophylaxis in patients with non-severe COVID-19 diagnosis:
   a. Creatine clearance (KKr) >30 mL/min and
      BMI <40/kg/m2: Enoxaparin 40 mg/day,
      BMI >40/kg/m2: Enoxaparin 40 mg should be administered subcutaneously twice a day.
   b. LMWH is not recommended if KKr is < 30 mL/min. AFH 5000 Ü should be applied 2 x 1 or 3 x 1 subcutaneously.
4. Thrombosis prophylaxis in patients with severe COVID-19:
   a. If creatinine clearance (CR) is >30 mL/min, enoxaparin: 40 mg should be administered subcutaneously every 12 hours or AFH 7500 U every 8 hours.
5. If monitoring is possible, it is recommended to do it with anti-Xa.
6. High D-Dimer (>2 fold) is high risk for venous thromboembolism and anticoagulant prophylaxis should be applied for >45 days.
2. LMWH should be preferred for anticoagulation at the therapeutic dose (AFH is recommended if acute renal failure or CKr <15-30 mL/min) and is recommended only in the following cases:
   a. Detection of thromboembolic complications
   b. Although imaging cannot be performed when a high probability thromboembolic complication is considered (considering pulmonary embolism in case of sudden severe respiratory distress),
   c. In case of recurrent catheter or thrombosis of extracorporeal circulation routes (eg dialysis and ECMO circuits) despite standard anticoagulation, moderate or therapeutic dose anticoagulation is recommended.
3. Dipyridamole is recommended as 2 x 75 mg in the early stages of the disease, since it reduces viral replication in in vitro studies and has anti-inflammatory/antiaggregant effects.
4. Thrombolytic therapy; It is not recommended except for ischemic stroke, ST-elevation myocardial infarction, and massive pulmonary embolism leading to hemodynamic compromise.
5. Anticoagulant prophylaxis should be performed with fondoparinux in patients with a previous history of heparin-associated thrombocytopenia (HIT) and HIT-related thrombosis.
6. Anticoagulant prophylaxis should be stopped if platelet <25 x 109/L or fibrinogen <0.5 g/L. Therapeutic anticoagulation should be stopped if platelet <30-50 x 109°/L or fibrinogen <1 g/L.

Thrombotic events are also observed in outpatient COVID-19 patients. In a study evaluating 72 outpatients with COVID-19 pneumonia who presented to the emergency department and referred for pulmonary CT-Angiography, pulmonary embolism (PE) was detected in 13 (18 percent) patients.

Routine examination of coagulation parameters is not recommended in outpatients. However, the Ministry of Health has developed the following algorithm for home anticoagulant use in discharged patients.

Duration of anticoagulation prophylaxis at discharge from hospital

Low risk of thromboembolism
- -Rivaroxaban 31-39 days
- -Betrixaban 35-42 days
- -Enoxaparin 14-30 days
- -Aspirin* (*not recommended in some groups)

High risk of thromboembolism (D-dimer> 2x, inmobilization, active cancer)
- -Rivaroxaban 45 days
- -Betrixaban 45 days
- -Enoxaparin 45 days

The pattern of coagulopathy that occurs in COVID-19 is different from sepsis, where the platelet count is usually reduced, and from DIC, where there is a prolongation of PT and aPTZ and a tendency to bleeding due to consumption of coagulation factors. As a result of overactivation of the immune system, a procoagulant environment is formed. In case of thrombosis in more than one organ system, multiorgan failure picture may develop and especially the development of thrombosis in pulmonary small vessels may cause ARDS development in the patient and result in death. Unless contraindicated, patients should be evaluated for anticoagulation with higher doses of AFH or LMWH than prophylactic doses, taking into account early anticoagulation and high fibrinogen levels.

Conclusion :

In conclusion, COVID-19 may lead to arterial and venous thromboembolic events by inducing excessive systemic inflammatory response, procoagulant activity, immobilization and hypoxia or by causing disseminated intravascular coagulation. Cases of acute PE associated with COVID-19 infection have been reported in a number of series.

This suggests that sudden, unexpected deaths outside the hospital during the pandemic period mentioned in these series may also be associated with COVID-19 infection. Viral infections can induce coagulopathy by affecting the coagulation cascade, primary hemostasis, and fibrinolysis. It is known that especially respiratory tract viral infections increase the risk of deep vein thrombosis and PE. Between 2003 and 2004, severe acute respiratory syndrome caused by coronaviruses was reported in studies of pulmonary infarction due to damage to small and medium-sized pulmonary vessels, deep vein thrombosis, disseminated intravascular coagulation, and pulmonary thromboembolism.

COVID-19 infection appears to trigger venous thromboembolism, particularly PE, even if it is not a risk factor. It should be kept in mind that patients admitted to the hospital with the clinical picture of PE without signs and symptoms of infection during the pandemic may also have COVID-19 infection. In addition, acute PE should be considered in the case of sudden clinical deterioration, hypoxia, hemodynamic deterioration or cardiac arrest in a COVID-19 patient during follow-up, even if the patient is receiving anticoagulant therapy.

In autopsy studies in patients with COVID-19, the incidence of macro and microthrombus has been shown to be high, up to 58%. The incidence of VTE in inpatient COVID-19 patients is similar to that of SARS and MERS-CoV viral pneumonias. In patients with COVID-19, D-Dimer, fibrinogen and factor VIII levels, which are markers of hypercoagulability, are increased, and aPTT is shortened. In a study using standard thromboprophylaxis, the incidence of VTE was found to be 27% in COVID-19 patients followed in the intensive care unit due to severe pneumonia, and 25% in another study without prophylaxis. Pathogenesis Studies have shown that coagulation activation is frequent and intense in patients with severe COVID-19. The presence of diffuse microthrombi throughout the pulmonary vascular bed in autopsy studies suggests that vasculopathy is important in the pathogenesis of COVID19. These post-mortem studies also highlight the existence of severe endothelial cell damage. Apoptosis and loss of zonula occludens (tight junction) have been shown as evidence for this. These findings suggest that endothelial cells play a conductor role in abnormal pulmonary intravascular coagulopathy associated with SARS-CoV-2 infection.

Follow-up of Patients for Pulmonary Embolism It is thought that after the acute phase of the disease, patients may remain in the hypercoagulation phase for a while. Therefore, prolonged thromboprophylaxis may be considered in patients at such a risk. There is no consensus among the guides on this issue either. Those who advocate continuation of prophylaxis at home after discharge refer to the positive results of previous prophylaxis studies in medical patients. In addition, it has been shown that the risk of fatal PE in the early period after discharge is high in similar medical patients who are not given prophylaxis. Therefore, guidelines are especially recommended for COVID-19 patients with high risk for VTE (previous history of VTE, cancer, continued immobilization, patient discharge from intensive care unit, advanced age, D-dimer level > 2 times normal, Modified IMPROVE-VTE score ≥ 4). If the risk of VTE is higher than the risk of bleeding due to anticoagulant, they recommend that prophylaxis be continued at home with LMWH or NOAC (enoxaparin 6-14 days, rivaroxaban 31-39 days; betriksaban 35-42 days) considering the benefit/loss ratio. Those who do not recommend continuation of thromboprophylaxis after discharge indicate the lack of definitive data on the high risk of thrombosis after discharge in particular for COVID-19 patients, and the bleeding risk of the anticoagulant to be given. Thromboprophylaxis is not recommended for patients who do not have pneumonia and have mild COVID-19. Again, initiation of antiaggregant and antiplatelet agents for thromboprophylaxis in COVID-19 patients is not recommended for thromboprophylaxis in hospitalized patients or after discharge. In patients who received these treatments for other reasons before, the treatment should not be discontinued.

In the prevention of venous thromboembolism in COVID-19 patients, a study that plans to compare standard heparin, inhaled standard heparin, enoxaparin and acetyl salicylic acid (NCT04466670) and studies comparing Copidogrel with LMWH and standard heparin (NCT04409834) are ongoing. Treatment and follow-up of patients diagnosed with pulmonary thromboembolism (PE) while having acute COVID-19 should be performed according to the protocols in the PE guidelines. Patients who are thought to develop pulmonary hypertension (PH), the only complication of PE, during their follow-up should be referred to PH centers. There is no data yet on how often chronic thromboembolic PH (CTEPH) develops during follow-up in patients who have had PE during COVID-19 infection. Anticoagulant therapy should be discontinued at the end of 3 months if there is no significant residual thrombus and CTEPH is not suspected. Patients diagnosed with PE and whose symptoms persist should be evaluated for CTEPH with ECO cardiography, ventilation-perfusion (V/Q) scintigraphy, and CT angiography. However, the use of V/Q scintigraphy in patients who develop sequela lesions/fibrosis in the parenchyma due to COVID-19 is not recommended as it may lead to incorrect evaluations. D-Dimer should not be used to diagnose or exclude possible chronic thromboembolic disease and CTEPH.

There is no data to support the approach to make decisions based on D-Dimer levels in discontinuing anticoagulant therapy after COVID-19 disease. Because D-Dimer is usually elevated as a non-specific acute phase reactant in COVID-19, and its elevation is associated with a poor prognosis (58). In a COVID-19 series including 1099 patients, D-Dimer was found to be high in 46% of patients. In another series that included 198 patients, it was shown that the D-Dimer levels of surviving patients were lower than those of deceased patients. Although very high levels are more associated with VTE than moderate elevations, it is not possible to determine a threshold value to distinguish between VTE and COVID-19-related elevation. However, the presence of acute thrombus can be excluded in COVID-19 patients who have normal D-Dimer levels and are not considered clinically likely to have PE.

Considering the risk of bleeding in COVID19 patients at high risk for VTE at discharge, they recommend continuing prophylaxis at home with LMWH or DOAC (enoxaparin 6-14 days, rivaroxaban 31-39 days; betriksaban 35-42 days).

In our country, the measures taken since January 2020 have been taken and the work has started rapidly. In this process, first of all, international flight restrictions, quarantine practices for those coming from abroad, closure of schools after the cessation of artistic activities, closure of public living spaces, working from home for suitable sectors, administrative leave for employees with chronic diseases and curfew for certain age groups were applied.

Activation of Provincial Pandemic Boards and surveillance studies have started. Surveillance studies are of great importance in terms of combating the epidemic. In addition to the fact that the current cases are included in the notification system, the filiation teams go to the homes of the patients who have positive tests and have not been hospitalized, and take necessary approaches through the provincial/district health directorates. For filiation, it is ensured that the patient is examined retrospectively and in this way, the source is sought as well as the identification of his contacts. The rules to be followed by determining the patients and their contacts who will receive treatment by staying at home are followed by signing consent forms. In addition, follow-ups are carried out by family physicians via telephone. Samples are taken for testing from those who are in contact or who develop symptoms. In this way, in addition to testing and treatment services in the hospital, studies are also carried out in the field.

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CHAPTER 17

SARS-COV-2: GENERAL PROPERTIES, GENOME STRUCTURE AND MICROBIOLOGICAL DIAGNOSIS

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1. Introduction

Coronaviruses are ribonucleic acid (RNA) viruses that can infect a wide variety of animal species and humans. Human coronaviruses had been known responsible for 15-30% of all common cold cases until severe acute respiratory syndrome (SARS) has occurred.1 common cold was generally mild infections and constrained itself. New generations of coronaviruses has been seen from 2002. Disease has shown with more severe symptoms than usual cold cases. First of these, in Guangdong China, was a severe acute respiratory syndrome (SARS) which would have been thought to infect cats by bats then bats trough humans at February 2003. The agent has been named as SARS-CoV. The Second new coronavirus infection is Middle East Respiratory Syndrome (MERS) that would have been thought to infect human via camel Saudi Arabia at 2012. Agent is defined as MERS-CoV. MERS-CoV contagion has been caused 791 dead in 2229 case. The viral infection which is named as 2019-nCoV that had been thought to be originated from Huanan Seafood wholesale market, and is the new coronavirus infection affected people whole over the world. Agent has been defined as a coronavirus that has never been detected in human at 7th January 2020. Agent is named as SARS-CoV-2 because of similarities to SARS-CoV. It has been thought that SARS-CoV-2 is a zoonotic infection as in SARS-CoV and MERS-CoV. There is no available medically approved antiviral medicine against to COVID-19. However, a few broad spectrum antivirals against to COVID-

19 had been evaluated in clinical studies. World Health Organization (WHO) is affiliated to United Nations has named this coronavirus disease as COVID-19 at 11th February 2020. WHO declared COVID-19 to be a pandemic.

2. Characteristics of CoV

Coronavirus are named because of crown-like spikes on its surface. Family Coronaviridae places in order Nidovirales, and are monopartite, positive-sense, enveloped RNA viruses that has been consisted sub-families Coronavirinae and Torovirinae. Sub-family Coronavirinae has been divided to four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. HCoV-229E, HCoV-OC43 and HCoV-NL63 which cause common cold in human are in Alphacoronavirus; one of other common cold agent that is HKU1-CoV, SARS-CoV that is defined in 2003 and responsible for severe acute respiratory syndrome (SARS) and MERS-CoV that is defined in 2012 and responsible for Middle East Respiratory Syndrome (MERS) classified under genus Betacoronavirus. Coronaviruses can cause respiratory, enteric, neurological and hepatic infections by means of having infect mammals and birds. There have been severe and occasionally even fatal respiratory disease contagions in last 20 years. These CoV strains are determined that phylogenetically different from common human CoV had been originated from bats and have infected human via an intermediate host.

SARS-CoV-2 are close to SARS-coronavirus group evolutionally. These new strains have higher virulence and can cause deadly infections in some people. Respiratory insufficiency resulting from alveoli damage causes dead in severe cases.

3. SARS-CoV-2 and Genomic Structure

The new coronavirus that is named as SARS-CoV-2 and causes COVID-19 have been reported a member of β-coronavirus group like as SARS-CoV and MERS-CoV. Coronaviruses are single-stranded RNA viruses in 30 kbs length and with a diameter of 65–125 nm approximately. Genome consist of 29903 nucleotides and have 11 open reading frame (ORF) region. Genome 4 have region of gene that coding main protein: S (Spike), E (Envelope), M (Membrane), N (nucleocapsid). Additionally it also codes non-structural proteins (nsps) and accessory proteins (ORF3a, ORF6, ORF7a and b, ORF8, ORF10).

Non structural proteins are assigned in replication-transcription of genome and vesicle formation and accessory proteins counteract host's defense mechanisms. Changes in S glycoprotein is considerably responsible for coronavirus host diversity and diversity of tissue tropism. S glycoprotein is a type-1 membrane protein which has different functional regions on close to amino (S1) and carboxyl (S2) edges. S1 subunit places in periphery and is related to receptor-binding functions, S2 subunit is a transmembrane protein mediates viral fusion. N protein is only one protein that produces nucleocapsid and function to bind to RNA genome of coronavirus. N protein takes part in processes related to viral genome, viral replication of RNA and plays role in host's cellular response to viral infection. Furthermore, it is shown that N protein expression increases virus like particles production considerably. M protein stimulates virus by forming a transmembrane protein (M-M) net which can exclude host membrane proteins out of viral envelope or getting interaction S glycoproteins and viral ribonucleoprotein (RNP) which is located in replication region. E protein is the smallest one of structural proteins and also mysterious one. While this protein is expressed abundantly to the infected cell, only a small part of it is included in virion envelope. Envelope protein may place in Endoplasmic reticulum or in golgi and as well as between the region of these two organelles. E protein takes role in gathering and spreading of virus and also viral pathogenesis. It is reported that SARS-CoV-2 genome is identical to SARS-CoV genome at a rate of 80%. Orf1ab gene is the largest scaled gene that codes pp1ab protein and 15 nsp. Recent studies showed that 8a protein doesn't exist in SARS-CoV and SARS-CoV-2 and the numbers of amino acids in 8b and 3c proteins for SARS-CoV-2 considerably different. (figure 1)

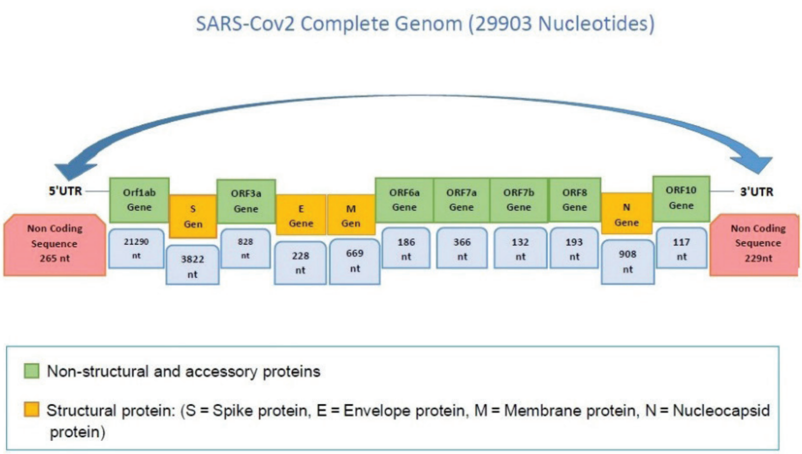

Figure 1: SARS-COV-2 genom structure.

4. Life Cycle of Virus

Life cycle of SARS-CoV-2 virus consists of four main steps (Figure 2). Spike Protein which is located on outer surface of SARS-CoV-2 mediates enter cell and infects the host by means of its binding to angiotensin converting enzyme angiotensin-converting enzyme (ACE-2). SARS-CoV-2 utilizes TMPRSS2 protease to complete to enter cell. (Figure 3). Changing the structure of S protein after binding to receptor facilitates fusion to cell and remove its envelope then RNA of SARS-CoV-2 is released inside to cell. Then translation of RNA to viral replicase poliproteins occurs and divided into small parts by viral proteinase. As a result of perpetual transcription via polymerase chain reaction, a mRNA sequence is produced and takes place a translation to viral proteins. Viral proteins and RNA genome combines in endoplasmic reticulum and in virions which is in golgi apparatus then excreted to out of cell. SARS-CoV-2 is a combination of SARS-CoV of bat and an unknown β-CoV. S protein of SARS-CoV-2 includes 3-dimonsional receptor binding domain (RDB) which is enable to protect Van der walls bonds. 394 glutamine in RBD region are recognized by lysine 31 on ACE2 receptor. Then it enters cell by using similar mechanisms. The SARS-CoV-2 RBD-ACE-2 interaction is 10 times stronger than the SARS-CoV-ACE-2 interaction. It is thought that this situation may be effective in having a higher rate of transmission of SARS-CoV-2 than SARS-CoV.

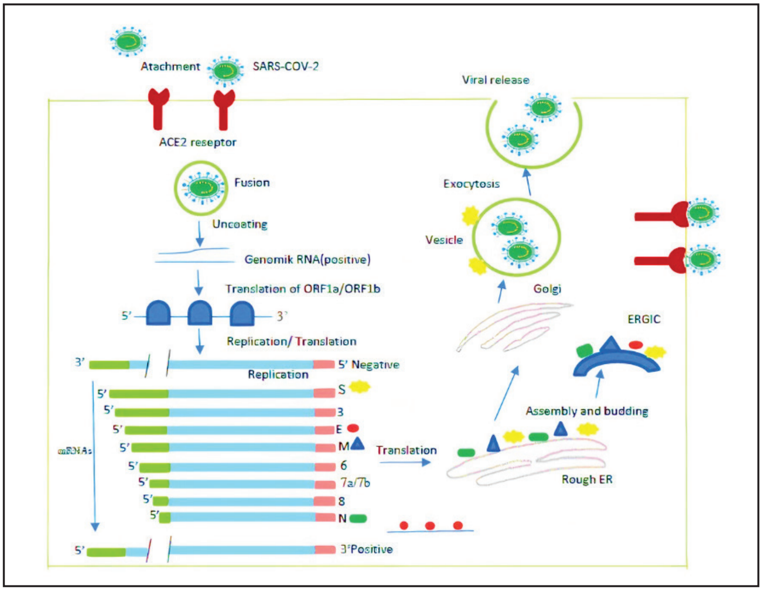

Figure 2: SARS-CoV-2 binding, cell entry and replication cycle

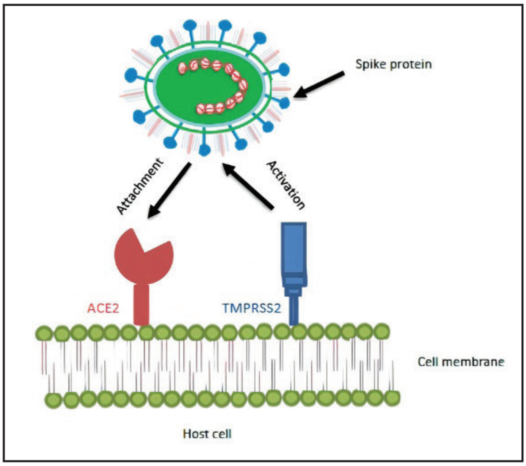

Figure 3: SARS-CoV-2 interaction with ACE-2 receptor and use of cellular protease TMPRSS2

5. Microbiological Diagnosis

5.1 Clinical Sampling, Storage, Delivery Laboratories

Taking an appropriate respiratory system samples in correct time and correct anatomical region plays key role in molecular diagnosis of COVID-19 infection. Nasopharyngeal (NF) and oropharyngeal (OF) samples representing the upper respiratory tract should be taken together in order to obtain higher accuracy levels of diagnosis, better patient tolerance, and for the safety of sampler. By using same swab, first nasopharyngeal (NF) and then oropharyngeal (OF) samples are taken and swab is placed in a single viral transportation media (VTM). For asymptomatic people who have not encountered infection before but also want to have a test to be sure and for epidemiological screenings nasal wash and saliva can also be used as an alternative upper respiratory tract sample when NF swab couldn't be taken. Phlegm, endotracheal aspirate and BAL (Bronchoalveolar lavage) samples produce more sensitive results than upper respiratory system samples. Phlegm and BAL samples which have high amount of viral load must be taken after intubation and delivered microbiology laboratories without using transportation media in follow-up of patients have COVID-19 and also in late phase of disease. Swabs that are produced from non-toxic dacron or polyester materials with aluminum or plastic cover must be preferred. It is not recommended to using of wood, cotton or calcium alginate swabs because of possibility of existence of PCR inhibitors in their content. The retching reflex while sampling from oropharyngeal walls and tonsils indicates correct sampling as region. It is suggested to insert the swab deeply into the nasal cavity and take samples from the nasal mucosa by rotation until teardrops come from the patient while the nasopharyngeal sample is taken. Samples must be delivered to clinical laboratories as soon as possible at +4 C. Nasopharyngeal, oropharyngeal and saliva samples can give negative results in early periods of infection. In this case, the test may need to be repeated or retested with lower respiratory tract samples. The viral RNA in serum and urine samples are often negative, regardless of the severity of the disease. A high amount of viral load is detected in the upper and lower respiratory tract in patients with COVID-19 within 5-6 days of the onset of symptoms (Table1). Sampling and laboratory staff must use personal protective equipment (PPE). Transfer of samples to lysis buffer and RNA extraction must be done in Level-II biosafety cabinet certainly. Level-III biosafety cabinet must be required for viral cultural studies. Commercial lysis buffers (Biomerieux easyMAG or QIAGEN EZ1) contain inactivating agents such as guanidium salt and detergent and can inactivate live coronaviruses. There are also POC (point of care) tests as closed systems which contains nucleic acid extraction, amplification and determination together. Using this kind of small devices helps to monitor SARS CoV-2 infections and control the epidemic with its capacity to give fast results within an hour. Although these types of tests have limitations, they allow clinical decisions by giving qualitative results. These bedside tests are useful and that can detect SARS CoV-2 in regional hospitals or clinics especially without a biosafety cabinet, in a manner of meeting the requirements. However, while the sampling and transferring the sample from the transport solution to the cartridge, the person taking the sample should wear PPE (gown, mask, gloves, eye protection) and be trained in their use.

Table 1: Collection of samples and storage conditions for the COVID-19 test.

Sample Type	Sampling Equipment	Delivery Conditions	Storage Conditions	Suggestions
URT: NF Swap, OF swap, NF aspirate	Dacron swap in VDM	4^0C	4^0C in 5 days >5 days -70 ^{0}C	
LRT: sputum	Steril container	4^0C	4^0C in 48 h. >48 h. -70^{0}C	
LRT: bronchial Wash	Steril container	4^0C	4^0C in 48 h. >48 h. -70^{0}C	Pathogen can be diluted.

LRT: tracheal aspirate, transtrakeal aspirate	Steril container	4^0C	4^0C in 48 h. >48 h. -70^0C	
LRT: lung biopsy	Steril container with Physiological Saline	4^0C	4^0C in 48 h. >48 h. -70^0C	
Serum	Serum tube	4^0C	4^0C in 48 h. >48 h. -70^0C	A double serum sample are taken for serological assays. Acute Phase: in 7 days after onset syptoms Convalescence phase: 14 days after taken at acute phase BSC-II or higher BSC must be used to separation of serum.

URT:Upper Respiratory Tract, **LRT**:Lower Respiratory Tract, **NF**: Nasopharyngeal, **OF**: Oropharyngeal, **VDM**:Viral Delivery Media, **PS**: Physiological Saline, **BSC**: Biosafety cabinet

5.2 Rapid Antigen Detecting Test Kits.

Antigen test which is a kind of rapid test detects existence of viral proteins (antigen) in a sample that is released by COVID-19 virus from a respiratory tract of a person. In the condition of sufficient concentrations of targeted antigen, then antigen binds specific antibodies that has been fixed to a strip paper and produce a typical visual signal in 30 minutes. Detected antigens are expressed only when the virus is replicated actively. For this reason, these kind of tests are used in diagnosis of acute and early stage of infection. Working capacity of depends on some aspects like as time onset of illness, viral concentration of sample, quality of sample individually, quality of processing and used reactive. Sensitivity of these tests for influenza is between 34-80, 1% for same type of sample and sampling.

5.3 Viral RNA Tests

The first preferred test method for the diagnosis of COVID-19 is viral nucleic acid determination by reverse transcription-polymerase chain reaction

(RT-PCR). RNA can be obtained from upper respiratory tract (oropharynx and nasopharynx) swabs as well as lower respiratory tract samples such as broncho alveolar lavage and sputum. It has been found that samples taken from the nasopharynx gave twice as better results than samples taken from the oropharynx. It is suggested to combine samples in a tube if each of these two samples had been taken. It is known that best results can be obtained when the two samples which are taken from upper and lower respiratory systems both. SARS-CoV-2 RNA has been isolated from feces, urine and blood, but these samples are less reliable than respiratory samples. It is recommended to collect the upper respiratory samples after few days later onset symptoms. It has been reported that the virus peaked in the upper respiratory tract at the end of the first week, and in the lower respiratory tract in more severe cases at the end of the 3rd and 4th weeks. PCR studies must conducted at Biosafety Level-II with personal protective equipment. It is known that the PCR test does not detect any viruses other than SARS-CoV-2 by cross-reaction, and therefore it has high specificity. Although there have not been given a specific value for sensitivity, it has reported between 63-78%. False negativities are common due to reasons such as small amount or displacement of viral load, improper sampling, early or late sampling, use of antivirals before testing, transport faults , presence of PCR inhibitors in the environment, viral genetic mutation. It is suggested to repeat test intermittently to increase the sensitivity of the test in case of negative results. It has crucial importance to evaluate the clinical findings of the patients together with the RT-PCR results. For instance, In a study which is conducted on 4880 cases in Wuhan, the city where the pandemic has started, it has been reported that the percentage of diagnosis of RT-PCR increased by 19% in the presence of fever findings, and the diagnostic capacity of the test increased in advanced age and male cases. A clinical study which is conducted in china with 82 cases, it was found that the sensitivity of RT-PCR increased from 79% to 94%, when evaluated together with computed tomography. This situation has showed that detection of lung involvement and other clinical finding has decreased false negatives in RT-PCR. RT-PCR is a gold standard method used in the confirmation of COVID-19 infections despite its limitations. It enables the amplification of nucleotide sequences in the targeted regions of the RNA of the virus to be visible in real time with fluorescent dyes. S (spike) and N (nucleocapsid) genes and non-structural RdRp and ORF 1a / b genes are often used as target regions because they are conserved, expressed and least crossreactive genes in the evolutionary process. Sensitivity and specificity of RdRp/Hel region is greater than RdRp-P2 region's in terms of diagnostic. Different numbers of gene regions are used in different kits and suitable RT-PCR protocols have been applied. In the collection and transportation of samples, international viral transport mediums can be used, as well as kit-specific viral nucleic acid buffers. Collected samples must be delivered laboratories as soon as possible preferably at +4 oC. The threshold cycle value (Threshold cycle / Ct) of target genes that can be evaluated at the end of PCR is below the limit value, which indicates the presence of viral nucleic acid and means a positive result. Test can be resulted in few hours. Reaction conditions of reactive, numbers of genes that has been analyzed can effect sensitivity of analyze. Optimization of PCR conditions by the laboratory is important. The clinical laboratory is required to perform routine quality control using validated negative and positive samples. Furthermore, the tested material is a RNA virus. RNA is a molecule that has a low stability, can be easily degraded by many enzymes after cell destruction and has high contamination risk. It is also known that RNA viruses have high tendency to mutation. Therefore, conducting the test run on an RNA virus is an important factor that can highly affect the specificity of the test. As a result, although Real-time PCR is the first test that is used the diagnosis of COVID-19, it should not be considered alone in decision of therapy and isolation because of false negative rates. The patient should be handled with a multidisciplinary approach; clinical findings, lung CT, etc. It should be evaluated together with all other findings.

5.4 Sequence Analyze

Genome of virus has 14 ORFs region , 26-32 kb in length and codes 26 protein. Spike surface glycoprotein (S), envelope protein (E), matrix protein (M), nucleocapsid protein (N) are its main proteins. Similarity of previously known SARS-CoV (79%) and MERSCoV (50%) was revealed by sequencing the genome information of the virus. It has been observed that SARS-CoV-2 shows high level of homology to SARS-CoV except differences ORF1a and S gene. Phylogenetic studies that evaluate the RNA sequence has revealed that virus belongs to betacoronavirus. Thus, many information about the origin, evolution, mechanisms, transmission routes and treatment of virus could be predicted. The similarities and differences in the S gene, which encodes the spike protein, have given important clues about the binding of the virus to human ACE2 receptors and human-to-human transmission. It has been reported that the S protein has a high affinity for ACE-2 receptors by means of studies performing protein modeling of the obtained sequence. Data such as human-to-human transmission dynamics, immune response, viral replication rate and virus mutation rate were obtained by detecting the virus genome. On the other study 10 SARS-CoV-2 sequence from different countries are compared and it is found that there is no difference between M and N proteins. Two amino acid variants in the S protein sequence, one mutation in the E protein in one sample, and two possible SNPs (single nucleotide polymorphisms) were detected in the ORF1ab and ORF8 regions. Similar studies on viral RNA sequences are valuable for course of pandemic, prophylaxis and treatment of disease. Genome sequencing of SARS-CoV-2 has paved the way of vaccine technologies against to virus. Vaccination studies on other viral pathogens, especially on DNA and mRNA, paved the way for SARS-CoV-2 studies. ACE-Fc protein sequence is the candidate gene in treatment studies to be done.

5.5 Serology

Traditional serological analyzes such as enzyme-linked immunosorbent assay (ELISA) for specific IgM and IgG antibodies have an advantage of high efficiency and avoid of false negative results RT-PCR method. ELISA and chemiluminescence methods are used from serum samples to diagnos the concentration of antibodies (IgM and IgG) responsible for coronavirus S and N proteins in the serum. ELISA protocol is used to detect IgM, IgA and IgG antibodies against SARS-CoV-2 using purified recombinant N proteins (rNP) as coating antigens. Optimization of plasma dilutions and concentrations of rNP which are coated for ELISA is achieved by chess board titration tests. In order to settle the cut-off values of ELISAs, average values and SD of plasma taken from healthy individuals are determined. The optimal coating concentration of the antigen and optimal plasma dilutions are determined. Cut off values are calculated as the mean absorbance at 450 nm (A450) of negative serum and 3 times the SD values determined for IgM, IgA and IgG, respectively. Also determination of SARS-CoV-2 specific IgM and IgG antibodies can be used for diagnosis. COVID-19 infection can be diagnosed one of that by positive specific IgM, change of specific IgG from negative to positive and 4 times increasing in IgG titer. Additionally, combining more sensitive qPCR experiments with IgM ELISA's can improve diagnosis method. ELISA method was developed to detect antibodies based on double antigen sandwich immunoassay (Ab-ELISA) that contains HRP conjugated antigen and receptor binding domain (RBD) of immobilized SARS-CoV-2 spike protein. The IgM μ-chain capture method (IgM-ELISA) is used to detect IgM antibodies using the same HRP-conjugate RBD antigen as Ab-ELISA. IgG antibodies were tested using a recombinant nucleoprotein-based indirect ELISA kit (IgG-Elisa) and assay specificity for Ab, IgM and IgG was determined to be higher. Studies has showed that IgM and IgG antibodies can be detected at the early or later stages of disease and ELISA based IgM and IgG antibody tests have significant specificity in serological diagnosis of COVID-19. Specifically circulating antibodies can be detected by ELISA method. Therefore it can be possible to avoid false negatives caused by absence of virus in sample or in respiratory system.

Antibody tests for SARS-CoV-2;

1- It can be performed to trace the contact individuals.
2- It can be used to serological monitoring at local, regional or national level.
3- It is significant in to identify person who had met virus and has acquired immune.
4- It can be used to diagnose individuals who has clinical/radiological findings as well as has negative result in viral RNA test.
5- It can be used in prophylactic or therapeutic studies in plasm therapy.
6- It can be used to evaluate the vaccine studies response and determine the level of public immunity.

In bedside chromatographic tests, monoclonal antibodies (mAb) are used to detect viral antigens in clinical samples or cloned viral antigens to detect antibodies against the virus. In the “lateral flow” test method, there is a strip embedded in the cassette and the reagent fixed to the nitrocellulose membrane (a mAb for a viral antigen or a viral antigen recognized by the antibodies sought in the patient). The patient sample is added to the strip and reacts with the previously immobilized reagent. Samples to be studied may be serum, plasma or, in some cases, whole blood. Test generally can be performed with 2-3 drops of blood taken from patient’s fingertip. A colorful line is seen on strip in positive results. Most of tests have a control point or a control strip to evaluate the results. Enzyme immunoassay (EIA) tests, which take longer to develop, even though have less sensitivity and specificity than molecular methods, they are easy to use and give results in a shorter time. However, the inability to replicate the results obtained during their validation in clinical settings and the uncertainty of the results of the tests create serious diagnostic difficulties. In the enzyme immunoassay method, the antibody bound to the antigen-antibody complex is marked with an enzyme and antigen antibody reaction is determined by measuring the intensity of color change in reaction (enzyme-linked immunosorbent assay-ELISA) or measuring the intensity of emitted light (chemiluminescence immunoassay-CLIA). The direct method used in the search for antibodies by ELISA technique is also known as the "sandwich" or "double antibody" method. Proteins that are chosen frequently as target in tests are Nucleocapsid (N) protein which plays an important role in replication and transcription, and "Spike" (S) protein (S1 and S2 for some tests).

6. Results

Coronaviruses that are from the family of single-strand RNA viruses, may infect humans and animals and can cause respiratory, gastroinstentinal, hepatic and neurologic diseases. Up to now, six human coronaviruses that including alfa coronaviruses (HCoVs-NL63 ve HCoVs-229E), beta coronaviruses (HCoVs-OC43, HCoVs-HKU1), SARS-CoV and MERS-CoV have been defined. It has been confirmed with emerged evidences that 2019-nCoV can be transmitted from person to person with respiratory droplets, through contacts, and by inanimate objects. The virus enters human cells through receptors located on the surface of human cells. Genome sequence analysis using the spike protein, that determines the entry of the receptor binding site, shows that the dominant cell surface receptor for both SARs-CoV and SARs-CoV-2 is ACE-2. Considering the fact that ACE2 is the co-receptor for coronavirus, new therapeutics are being studied to block and reduce the expression of this enzyme in order to prevent cellular entry and SARS-CoV-2 infection in various tissues expressing ACE2 such as lung, heart, kidney, brain. In vaccine studies on SARS-CoV-1 and MERS-CoV, the S glycoprotein, which plays a role in the virus binding to the ACE-2 receptor of the host cell, was selected as the ideal target molecule. Antibodies to this protein block the virus from binding to ACE-2 and prevent the virus from entering its cell. Therefore, the S protein is considered the target antigen in vaccine study platforms, and it is very important that variations in this protein are closely monitored Although nucleic acid amplification (NAATs) is the main method of covid-19 diagnosis. serological tests also gained great importance, as they were easier to use and gave a better idea of all infected individuals compared to NAATs.

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CHAPTER 18

HIGH FLOW NASAL CANNULA OXYGEN THERAPHY IN THE 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 allover the world, and resulting in a pandemic being declared by the World Health Organization. COVID-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 (ARDS). SARS-CoV-2 is spread through respiratory droplets and contact with fomites. Airborne transmission has occasionally been implicated in patients with COVID-19 during procedures that are capable of generating aerosols. Nevertheless the effects and course of the disease differ from person to person, common symptoms are fever, drycough, myalgia, shortness of breath, weakness, confusion, loss of taste and smell, headache, sorethroat, vomiting and diarrhea. Inreference to the latest figures (17 March 2021), a total of 120.38 million people were caught the disease and 2.66 million people died. Although the majority of cases show mild symptoms, 25-34% of them have developed severe and critical diseases including respiratory failure, severe pneumonia, ARDS, septic shock, multiple organ dysfunction. SARS-CoV-2 mainly affects the respiratory system by attaching itself to the angiotensin converting enzyme 2 receptor (ACE2r) on pneumocytes and replicating with in that cell population. This may lead to acute severe hypoxemia without respiratory distress or to ARDS. Early recommendations suggested intubation at the first sign of hypoxemia and avoiding non-invasive ventilation (NIV) or high flow nasal cannula (HFNC) due tot he risk of viral aerosolization. The controversy surrounding timing of intubation remains; and the deleterious effects of invasive mechanical ventilation (IMV) coupled with the heterogeneity of the pulmonary manifestations of COVID-19 have prompted a rethink of HFNC Oxygen administration forms the basis of supportive therapy for hypoxemic patients.

The choice of oxygen supportive devices, as well as oxygen therapy, is essential in these patients in terms of effectiveness and aerosol dispersion HFNC is a respiratory support system that has become prominent in the treatment of respiratory failure and studies are available showing a reduction in intubation and mortality HFNC provides higher concentration and flow of oxygen, resulting in decreasing anatomic deadspace by preventing rebreathing and ensure positive end-expiratory pressure. However, in COVID-19, the usage of HFNC is much controversial due to concerns about the benefits and risk of aerosol-dispersion.

1. High-Flow Nasal Cannula (HFNC)

HFNC refers to high-flow oxygenated gas, heated and humidified to body conditions, that is delivered via nasal cannula at maximum flows ranging from 40 to 80 L/min depending on the manufacturer (**Figure 1**). It has not been around for as long as NIV, having gained traction over the past eight years or so. HFNC provides gas flow higher than the patient's inspiratory flow demand, which enables the delivery of a constant fraction of inspired oxygen (FiO2) without dilution by room air. The heating and humidification make it tolerable; a dry cool gas at those flow rates would rapidly desiccate the nasal mucosa, causing an uncomfortable burning sensation. It has the advantages of stable oxygen supply performance and constant oxygen output concentration. Moreover, it can maintain the air temperature in the range of 31-37°C and provide gas humidity of up to 100%. Therefore,the technology has the advantages of the common nasal tampon and mask.

The positive end-expiratory pressure (PEEP) it produces can increase the functional residual capacity and bring about almost the same partial function as noninvasive ventilation. Compared with the traditional oxygen therapy, it has the advantages of high comfort, good compliance, and an obvious therapeutic effect. Many studies have proved its application value in the treatment of acute respiratory failure. Therefore, the application of HFNC oxygen therapy may improve the prognosis of patients with COVID-19. Also enhancing tolerability is the soft, loosely fitting nasal interface that does not impede speech or eating during use. The heat and humidification also help to maintain hydration and mobility of secretions and to preserve mucociliary function. HFNC helps with oxygenation by flushing the nasopharynx during exhalations that the first bolus of air during inspiration is not just expired air but is partly freshened by the oxygenated HFNC gas. Also, compared with standard oxygen (SO) techniques, the high flow rate of HFNC comes closer to the inspiratory flow rates encountered in dyspneic patients, which may exceed 60 L/min. For example, the NRB mask provides oxygen flows up to only 15 L/min, so that air entrainment and dilution of FiO2 are greater than with HFNC. The flushing of the nasopharynx also washes out anatomic deadspace, improving ventilatory efficiency. That, and the reduction in respiratory rate probably caused by the slowing of exhalation by the inflowing gas, contribute to a reduction in work of breathing perminute. The expiratory impedance also creates positive expiratory pressure that peaks early during exhalation, amounting to roughly 1 cm H2O/10 L/min high flow and has been shown to increase end-expiratory lung volume. Thus, HFNC is more than just oxygen supplementation; it is a verywell-tolerated ventilatory assist device with multiple potentially advantageous physiologic attributes that is also easy and safe to apply.

HFNC is very simple and safe to apply and is a favorite of respiratory therapists for that reason (**Figure 2**). Previous studies demonstrated that HFNC is associated with more ventilator-free time, lower mortality and decreased risk of intensive care unit ICU admission and lower reintubation rates in acute hypoxemic respiratory failures due to various causes. Besides, HFNC was applied for respiratory failure in patients with Middle East respiratory syndrome coronavirus (MERS-CoV), 2003 Toronto SARS-CoV outbreak and severe acute respiratory infection-related 2009 Influenza A/H1N1v. Although respiratory failure is common finding in patients with severe SARS-CoV-2 infection, COVID-19 related hypoxemia patterns are different compared with typical respiratory failurea nd ARDS. Patients with COVID-19 exhibits preserved lung compliance with low PaO2/FiO2 ratios. These differences in pathophysiology, may cause differences in the effectiveness of HFNC. Relevant to care givers, patientst end to leave the HFNC prongs inplace more than is the case with mask oxygen or NIV,reducing the number of needed visits into the room. Other advantages of HFNC include avoiding unnecessary intubation and protect much-needed ICU ventilators for the patients really needs it in resource-limited settings.

The major precautions that should be exercised in its application are related to putting an HFNC on unstable or severely hypoxemic patients and not monitoring the made quately. This may culminate in severe hypoxemia and an emergency intubation. This is catastrophic because it takes minutes for the code and intubation teams to apply appropriate personal protective equipment (PPE) and intubation is a high-risk AGP, not to mention the greater risk of morbidity and mortality to the patient.When using HFNC, especially unstable or severely hypoxemic COVID19 patients should be closely monitored due to possible respiratory arrest. In other respects, the depening of hypoxia and the urgent intubation may result in catastrophic consequences.

Some indicators have been shown to be useful in monitoring oxygenation status in patients with HFNC and in predicting the outcome of HFNC. Oxygen saturation index (SpO2/FiO2) and respiratory rate-oxygenation index (ROX) have been reported to be an efective monitoring indicator in the application of HFNC. The ROX index was first described and validated in subjects with respiratory failure prior to the outbreak of COVID-19. This index has also been applied to predict the need for endotracheal intubation after HFNC application in subjects with COVID-19. 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. However, its value for predicting HFNC failure in COVID-19 patients remains unknown. Many treatment protocols, from simple oxygen support applications to invasive mechavic ventilation applications in the treatment of patients with a diagnosis of Covid 19, are determined by health professionals according to the respiratory support needs of the patients (**Figure 3**).

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%. HFNC can reduce the requiring of intubation in patients with COVID-19, and it can decrease the length of ICU stay, and complications related to mechanical ventilation.

2. How I Do It: Technique and Monitoring of High-Flow Nasal Cannula

2.1.Technique

- Use in a negative-pressure room if available; if not, ask for a room with at least 6 (preferably 12) air exchanges/h, along with a HEPA filter,
- Fit nasal prongs, using fitting guides per manufacturer,
- Strap on firmly but not tootightly to nostrils,
- Initiate flow near maximum for manufacturer (50 L/min [60 L/minmax] used for initiation in key studies that used Fisher&Paykelequipment),
- Place droplet mask over nose and nasal interface to reduce aerosol dispersion,
- FiO2 as peroxygenation defect; if moderately severe to severe, start with 100% and adjust down to SaO2 target. If mild to moderate can start with 50%,
- Start with 37˚C temperature and adjust down to 34˚C or 31˚C if needed for better tolerance.

2.2 Monitoring

- Monitor RR and breathing pattern,
- Check ABG in 1/2 h,
- May consider alternating with NIV or using awake proning to improve oxygenation further

Figure 1: *AIRVO 2 Humidified High Flow System*

Figure2: *The patient with Covid-19 receiving high flow oxygen therapy*

STEP 1Simple Oxygen Supplementation

No respiratory distress O2 Via N/C @ 4-6 L/min

Spo2 < 92-94% RA or

Declining SpO2WorseningNRB mask @

Hipoksemia15L/min

STEP 2 **Noninvazive Strategies**

Mild to Moderate Respiratory Distress

Transfer to a continuously monitored setting

Observe patient closely and obtain ABG in 30 min

High Flow Nasal Cannula
(Preferred modality)
Minimal hypercapnia
(PaCO2 preferably
< 5 mm Hg above baseline)

Awake Proning
(Alone or with HFNC or NIV)
Useful with diffuse lung opacities-ARDS
No unstable spine fractures, hemoptysis, abdominal compartment syndrome, > first trimester pregnancy, anterior chest tubes

Noninvasive Ventilation
(Consider Helmet)
COPD with moderate hypercapnia or cardiogenic pulmonary edema or inability to carry out work of breathing
Low aspiration risk

STEP 3	**Invasive Mechanical Ventilation**
Severe respiratory distress	(Unless carries a Do Not Intubate order) ARDS net guidelines
P/F<150 or Spo2/PaO2<196 or hemodynamically unstable or at risk of impending respiratory arrest	

Figure3: *Algorithmic approach to respiratory failure in coronavirus disease 2019. ABG=arterialbloodgas; HFNC=high-flownasalcannula; N/C=nasalcannula; NIV=noninvasiveventilation; NRB= nonrebreather; P/F =PaO2/FIOCHEST 2020; 158(5):1992-20022 ratio; RA=roomair; SpO2=arterialoxygensaturation as determinedbypulseoximetry. (CHEST 2020; 158(5):1992-2002)*

Conclusion

HFNC therapy is used by many healthcare professionals during the Covid-19 pandemic. Its application is very practical and safe, and it is comfortable for the patient. The greatest danger when using HFNC, especially with patients with COVID-19, is to fail to monitor closely enough, leading to an unanticipated need for intubation with increased risk to the patient of respiratory arrest and increased risk of aerosol exposure to the intubating. However,all respiratory therapies represent a risk of aerosol generating procedures during the care of patients with COVID-19. Given the current circumstances it is not likely that there will be randomized controlled trials to confirm which noninvasive respiratory support is better to reduce the need for intubation in the context of COVID-19 pandemic.

In conclusion, HFNC provides high concentrations of oxygen to the patients, who can not reach with conventional devices. HFNC can reduce the requiring of intubation in patients with COVID-19, and it can decrease the length of ICU stay and complications related to mechanical ventilation. Also, HFNC is comfortable for patients due to mixing oxygen with warm water to humidify, bring the gas mixture to body temperature. On the otherhand, clinicians should carefully monitor the transformation from mild/moderate ARDS to severe ARDS to avoid delayed intubation during using HFNC. The use of HFNC can produce aerosols. So, HFNC treatment should be carried out in a negative pressure room; when it is not possible, devices should be undertaken in a singleroom. HFNC might be helpful in weaning COVID-19 respiratory failure. Effectiveness and comfort should be assessed between 2 and 48 hours. Clinical outcomes, oxygenation, and ROX index should be considered, to rule out the need for intubation. Manufacturers should be urged to create safer interfaces, viral proof circuitry and "newgeneration" noninvasive ventilators with integration of different therapies, specific monitoring and necessary safety features.

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CHAPTER 19

GUIDELINES FOR PROSTHETIC DENTAL TREATMENTS DURING THE COVID-19 PANDEMIC

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection, also called Coronavirus Disease 2019 (COVID-19), has caused a pandemic affecting the whole world. SARS-CoV-2, which causes pneumonia in humans, infected more than 169 million people worldwide from the outbreak to June 1, 2021, and caused approximately 3.5 million deaths worldwide. SARS-CoV-2 is an enveloped RNA virus with a magnitude of about 60 to 140 nanometers, with prominent spikes of 9 to 12 nm, with a "corona" appearance around it.

The saliva of infected people has been shown to contain enough live SARS-CoV-2 viruses to infect other people. Therefore, droplets containing saliva-borne viruses could cause the spread of the virus directly or indirectly.

Aerosols are liquid or solid particles smaller than 5 μm and can hang in the air for long periods. Instruments used in dental treatment applications have the potential to accelerate the spread of infection by causing aerosols.

In addition, prosthodontic treatments require laboratory procedures as well as general dentistry treatments. Therefore, there is a risk of cross-infection by transferring impressions or plaster models from the patients to the dental laboratory after contact with the virus-containing saliva.

Work on developing the SARS-CoV-2 vaccine is ongoing. Approximately 1.6 billion doses of vaccines have been administered worldwide as of June 1, 2021. However, existing vaccines can be administered in single or double doses, so the number of people vaccinated is relatively small. In addition, the effectiveness of different vaccines and their effects on SARS-CoV-2 variants vary according to each other. Consequently, the different efficacy of vaccine types, the emergence of new variants, problems in vaccine production and supply process continue the risk of COVID-19.

The aim of this guideline is to make recommendations to protect against infection and minimize cross-infection during the prosthetic treatment when the COVID-19 pandemic and normalization period.

2. Possible threats and transmission routes in prosthetic treatment

SARS-CoV-2 can be transmitted directly from person to person by respiratory droplets, it can also be transmitted by indirect contact, and the saliva of infected people can contain a level of virus that can infect other people.

Dentistry patients and professionals can be exposed to pathogenic microorganisms, including viruses and bacteria that infect the oral cavity and respiratory tract. Dental treatment is always at risk of COVID-19 infection due to its procedures, including face-to-face communication with patients, exposure to bodily fluids such as saliva, blood, and the use of sharp instruments.

Pathogenic microorganisms may be transmitted in the dental clinic as a result of inhalation of microorganisms that can hang in the air for a long time, direct contact with conjunctival, nasal or oral mucosa of droplets containing infected microorganisms caused by blood, oral fluids or other patient materials, inhalation of aerosols containing microorganisms originating from the infected person, coughing and unmasked speech at short distances, or indirect contact with contaminated instruments and surfaces. In addition, the transfer of impressions, models, and dentures used in prosthetic therapy between the laboratory and the clinic poses a risk of cross-infection by indirect contact.

Infection transfer pathways explained by Xian Peng et al. are revised and shown in Fig. 1 in terms of prosthetic treatment.

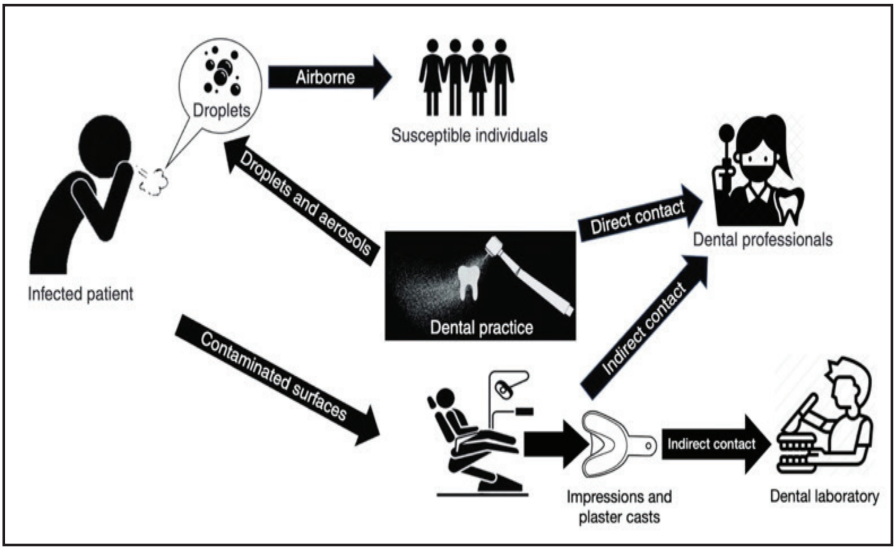

Fig. 1: Illustration of transmission routes of SARS-CoV-2 in dental clinic

2.1. Risk of prosthetic treatments

According to the American Dental Association, dental procedures are divided into two groups, emergency/urgent and routine/elective during the COVID-19 outbreak. Nonemergency prosthetic treatments can create aerosols, and some treatments can be completed without causing aerosols. Aerosol has the potential to accelerate the spread of infection. For this reason, routine prosthetic treatments can be divided into two groups as Aerosol-generating/Non-Aerosol. Prosthetic treatment groups organized according to ADA guidelines are listed in Table-1.

During the COVID-19 pandemic, routine dental treatments were delayed, and priority was given to emergency and urgent dental treatments. With the spread of vaccination and the normalization process, routine treatments that non-aerosol procedures can be done first, and then routine treatments generate aerosol.

Table 1: Treatment groups in prosthodontics

Emergency / Urgent Prosthetic Treatments	**Nonemergency Prosthetic Treatments**	
	Non-Aerosol Treatments	**Aerosol Generating Treatments**
Temporary prosthetic applications of patients with planned maxillofacial surgery Prosthetic treatment of patients undergoing or scheduled to undergo radiotherapy/ chemotherapy Patients who are asked for consultation due to their systemic condition Removal of fixed dentures on teeth with severe pain Cementation of fixed prostheses Tightening of loose abutment screws Denture repair in case of impaired function	Complete denture applications removable partial denture applications (no intra-oral preparation required) Lining or repair of denture Implant retained prosthetic treatments Splint treatments for TMJ disorders Maxillofacial Prostheses	Removable partial denture applications (requiring intra-oral preparation) Tooth preparation for Fixed Partial Denture (FPD) and crown treatment

2.2. Scheduling of appointments

Due to the rapid human-to-human transmission, face-to-face appointments should be stopped, and appointments should be made online or by phone to reduce patients' gathering within the dental clinic.

Table 2: COVID-19 screening questionnaire

Questions
1- Do you have fever or experienced fever within the past 14 days?
2- Have you experienced a recent onset of respiratory problems, such as a cough or difficulty in breathing within the past 14 days?
3- Have you, within the past 14 days, traveled intercity with a public vehicle (airplane, train, bus)?
4- Have you come into contact with a patient with confirmed COVID-19 infection within the past 14 days?
5- Are there at least two people with documented experience of fever or respiratory problems within the last 14 days having close contact with you?
6- Do you have confirmed COVID-19 disease?

Patients with appointments should be screened for COVID-19 risk before treatment. This screening is performed by phone or video call 24-48 hours before the appointment. During the conversation with the patient, the situations listed in Table 2 should be asked. When a positive answer is received to at least one of the questions, the patient's treatment should be postponed for at least 14 days. In addition, the patient's SARS-CoV-2 vaccination status should be asked to determine the COVID-19 risk status. All patients should be asked to come to their appointments wearing masks.

During the adjustment of appointments, at least 30 minutes interval should be considered between patient treatments.

Patients should come to their appointments alone, but there are elderly or patients in need of nursing in demand of prosthetic treatment. These patients should be told that they should only have a companion with them, and the companion should also be screened for the risk of COVID-19 by calling by phone before the appointment.

Patients who require dental procedures that cause aerosol should be given an appointment at the end of the day to minimize the risk of transmission.

2.3. The patient admission

Ensure that the patient who comes to the appointment comes wearing a mask; if not, the patient should be provided with a mask. High fever is the most prominent feature of SARS-CoV-2 infection, with 88.7% of cases occurring with high fever. The patient and the companion should be measured with a non-contact thermometer before entering the clinic and if it is below 37.3ºC, they should be taken to a separate waiting room. However, if the temperature measurement of the patient or companion is above 37.3ºC, it should be directed immediately to the nearest COVID-19 center.

When visitors arrive at the clinic, the questions shown in table 2 should be asked again and the patient's treatment should be postponed for 14 days if there is a risk of COVID-19.

Visitors should wash their hands with soap and water and disinfect with hand disinfectant containing 70-80% alcohol before entering the dental clinic. Clinical staff should take the patient's anamnesis by providing social distancing, and if signatures need to be obtained from the patient, who should be signed with a disinfectable pen. The companion should be asked to wait outside the clinic during the treatment of the patient. If the patient needs to wait before or after treatment, it should be single in the waiting room and maintain social distance with clinical staff.

2.4. Preparation of the treatment room

Symptomatic COVID-19 patients are the primary source of disease transmission. However, asymptomatic patients and incubators may also be carriers of SARS-CoV-2. It is necessary to evaluate all patients as potential carriers, and additional infection prevention practices should be used, as well as recommended standard practices, as part of routine healthcare delivery to all patients during the COVID-19 outbreak. The use of antimicrobial mouthwashes before treatment can reduce the microbial load in the oral cavity. Antiseptic mouthwashes can only reduce viral load, but they are not able to eliminate the virus from saliva. Chlorhexidine, which is routinely used in dental treatments, may not be effective against coronavirus. Therefore, since the coronavirus is susceptible to oxidation, it is recommended to use mouthwashes containing oxidative agents such as 1% hydrogen peroxide or 0.2% povidone-iodine to reduce the viral load of oral and saliva.

2.5. Personal protective equipment (PPE)

Clinicians must adhere to existing personal protective equipment protocols for contact and airborne infections. To protect the skin and mucosa from infected secretions, clinical staff should wear surgical gloves, appropriate masks, face shields, and isolation gowns according to the CDC's recommendations before starting treatment.

Dentists should wash their hands before examining the patient and starting dental procedures, after contact with the patient, after touching non-disinfected equipment and tools, and after touching the oral mucosa, skin, blood as well as other bodily fluids.

The isolation gown is an important PPE, which is especially necessary during the treatment of patients suspected of an infectious disease. Coverall gowns that provide protection against airborne pathogens have been shown to be the best choice for protection against COVID-19. Coverall gowns should be used, especially during aerosol-generating procedures, and should be replaced after each patient.

The standard surgical mask provides a protective barrier for the nose, mouth and respiratory system against large droplets and other liquids. However, it is loose and not protective against smaller particles in the air. Respirators called the N95 mask in the United States and the filtered facepiece (FFP) in Europe protect the user against smaller particles in the air in aerosol-forming procedures. FFP-3 respirators are recommended for aerosol-generating procedures and FFP-2 respirators are recommended during non-aerosol-generating procedures. A surgical mask is adequate for office staff working outside the operating room.

Respirators should be replaced if damaged, contaminated with blood, breathing, nasal secretions or other bodily fluids and after each patient visit. Long-term use of the mask is not recommended in the Dental clinical.

SARS-CoV-2 can also be transmitted through the contact of droplets with the ocular conjunctiva. Therefore, face shields should be used during treatment and then cleaned and disinfected between patients.

2.6. During dental treatment

During the epidemic period, dentists should avoid droplet and aerosol-generating procedures, such as the use of high-speed handpieces and ultrasonic scalers, as much as possible. The use of high-volume saliva suctions and rubber dams in aerosol-generating procedures can significantly reduce droplets and aerosols. Another effective method is to use an anti-retraction handpiece to reduce oral bacteria and virus backflow into the handpiece and dental unit tubes that reducing the risk of cross-infection.

2.7. Disinfection and sterilization

The standard post-treatment cleaning protocol involves first cleaning contaminated or potentially contaminated surfaces using a combination of water and irrigation solutions. This cleaning allows the removal of organic substances from the surface. After initial cleaning, surfaces should be disinfected with Environmental Protection Agency (EPA) registered hospital-grade disinfectant. Instruments and equipment must be disinfected according to who instructions. Since the coronavirus cannot live for more than 30 minutes at temperatures above 56ºC, common sterilization protocols are effective in preventing cross-infection. These protocols recommend sterilization of critical and heat-resistant semi-critical equipment.

Semi-critical equipment that cannot be sterilized must be disinfected. Standard cleaning is sufficient for non-critical tools; however, non-critical equipment should be cleaned and disinfected after spatter of saliva or blood or contact with contaminated gloves or hands. The disinfection protocol for instruments and equipment includes the use of antiviral solutions containing 70% ethyl alcohol. However, if emergency/urgent treatment is required for suspected or infected patients, the use of disposable tools and equipment should be prioritized. Nevertheless, if the use of disposable equipment is not possible, all equipment should be disinfected between patients.

All surfaces in the clinic should be effectively disinfected with hospital-grade disinfectants such as sodium hypochlorite. Regarding hospital-grade disinfectants, there are different concentrations recommended for different uses. The manufacturer's instructions for concentration and contact time must be followed. It is recommended to dilute 5.25-6.15% sodium in the ratio of 1:10-1:100 for the disinfection of blood. Constantly touched surfaces such as door handles, tables and light switches need to be disinfected. For this purpose, various disinfectant substances can be used, including alcohols, hydrogen peroxide, benzalkonium or sodium hypochlorite. Studies show that disinfectants containing 62-71% ethanol or 0.1% sodium hypochlorite can remove coronavirus from surfaces within one minute.

2.8. Transfer of impressions and dental casts to the dental laboratory

Dental staff should suitably disinfect impressions, plaster casts and dentures before sending them to the dental laboratory. In addition, the patient's COVID-19 status can be reported to the laboratory to take further precautions. The disposal of biomedical waste generated in the clinic is a necessary procedure and must be carried out according to established protocols.

The transfer of impressions to the dental laboratory must be in an airtight and watertight container. It should be considered that the notes that need to be forwarded to the dental technician should be sent by electronic mail or a similar digital method. Sending paper notes to a dental technician is unsafe for transmission by indirect contact. In addition, dentures and plaster casts from the laboratory to the dental clinic should be disinfected.

3. Conclusion

Consequently, the dental clinician is exposed to aerosols and contaminated surfaces during prosthetic treatment. In addition, dental laboratories and dental technicians through impressions, plaster casts and dentures are also at high risk of exposure to the new coronavirus due to indirect contact. For this reason, emergency treatments should be given priority and aerosol-generating procedures should be avoided. As a precaution, it is essential to reschedule suspected patients, disinfect surfaces and use respirators, disposable gowns and face shields.

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CHAPTER 20

COVID-19 PANDEMIC PROCESS AND ASPECTS RELATED TO DENTISTRY

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1. Introduction

At the end of December 2019, an outbreak with unknown background etiology occurred in Wuhan, China which cause severe pulmonary disease. This unidentified pathogen after analysis was officially described as Acute Respiratory Disorder Syndrome Corona Virus 2 (SARS-Cov2), or Corona Virus Disease 2019 (COVID-19) on February 11, 2020 by the World Health Organization (WHO). After the novel coronavirus spread throughout worldwide and become severe common sanitary disease, WHO officially declared a pandemic alert in March 11, 2020. SARS-CoV-2 virus can affect the multiple systems escalating mortality, primary the respiratory system. The WHO proclaimed SARS Cov-2 related coronavirus infection as "Public Health Emergency of International Concern" on February 1, 2020. As of April 1, 2021, SARS-CoV-2 virus infected more than 129 million people in whole countries around the world, and caused more than two and half million deaths, also keep increasing daily.

The outbreak of the novel coronavirus, and the following worldwide COVID-19 pandemic has substantial impact upon every country. Limitation of the SARS- Cov-2 related coronavirus infection spread and transmission subject became serious problem needs to be solved about all world governments and depending sanitary authorities. To prevent contagion and spread of SARS-CoV-2, social and physical distancing measures implemented. Social distancing which include decrease of unnecessary personal contacts and decreasing the contact with potentially contaminated areas, determined as 2 m of physical distance between individuals. Considering the social distancing measures, precautions that flexible work arrangements such as telecommuting, distance education, annulment of public events to prevent gathering, closure of redundant institutions, movement restrictions, staying-at-home order are taken.

Due to the contagion speed of COVID-19, health authorities recommended that the quick shut down about every educational institutions, particularly medical, and dentistry colleges. On the long view, these situations consisted the extension of school time, postponement of final exams and changing the graduation dates. COVID-19 lockdown for hindering social gathering occurred severe consequences about dental education. In consequence of COVID-19 pandemic, theoretical lectures had to be learned with online courses, though it is challenging to delivered practical courses by the instructors such as restorative dentistry with distance education on online, and particularly in order to learning for students staying-at-home without access to dental instruments. Under conditions of pandemic, it should be coming up solution for the continuation of practical education for dentistry universities.

On March 10, 2020, first COVID-19 case was announced by the Turkish Ministry of Health. Following the first reported case, several precautions were set especially about sanitary systems to not overload, such as the hospitals and intensive care units (ICUs) capacity. In Turkey, on March 13, 2020, all educational institutions were shut down, beside that any kinds of meetings, public gatherings and activities were cancelled or rescheduled. For the over the age of 65 and under 20, home isolation were performed to prevent virus transmission and spread. Except the only urgent treatments, routine and non-urgent procedures were postponed or rescheduled by the sanitary authorities. Urgent treatments were described as severe tooth pain, abscesses, dental trauma, and life-threatening or uncontrolled bleeding. After the first announcement about COVID-19 case, second phase named the controlled social life has begun. On the June 1, 2020, standard contagion preventive protocols were began to applied according to guidelines prepared by Turkish Ministry of Health. Considering these guidelines, only urgent treatments performed in case of necessity. In consequence of shut down and restriction about dental treatments, patients likely applied self-medication for their problems related tooth, in these process.

2. Information and Training Management

The most important stage to solve the healthcare crises are sufficient and well-timed sharing the information. Intend to keeping under control the present COVID-19 condition, number of positive cases infected with COVID-19, and occupancy rate due to ICUs must been updated daily basis. During the SARS epidemic recommended educations and trainings to lessen the burden shoulder of sanitary employee can be applied too in SARS-CoV-2 pandemic to improve the psychological. Beside that online conferences composed by various experienced professors as speaker should be scheduled. Health of sanitary personnel must be monitored every day due to COVID-19 infection, when infection suspect determined among the workers, in order to the protect patients and other employees, isolation have to applied. Addition to that, home office can be recommended to maintain the healthy environment, also rotation must be performed to reduced personnel numbers.

3. Transmission of SARS-CoV-2

Most known route in order to the transmission of SARS-CoV-2 is inhalation of Flügge micro droplets (droplets) and/ or core droplets (aerosol) that may occur in one meter radius through infected individuals or direct contacts. Droplets and/ or aerosols generating processes are such as coughing, gagging, sneezing and/ or direct contact to mouth, conjunctiva and nose by mucous. Transmission can be related on different factors such as particle size, relative humidity, and airborne flow. Flügge droplets which >5 μm diameter are transmitted through airborne up to 1 m. Large droplets because of their weight fall to the ground rapidly. On the other hand, small droplets which ≤5 μm diameter can diffused in the air farther than 1 m.

Even though the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) cannot survive on dry surface, van Doremalen et al. conducted that SARS-CoV-2 can be remain viable within the air up to 3 hours. Also, particles can stay viable up to 72 hours on plastic and/ or stainless steel areas.

COVID-19 infection entry the human body through mouth, nose, and eyes except exceptional conditions which may be spread with the oro-fecal route. COVID-19 contagion consist owing to contact by the contaminated individuals with or without clinical symptoms. Consequently, asymptomatic patients without clinical signs can transmitted the virus to another individuals. Considering the study, it has been reported that in the dentist practice air samples no SARS-CoV-2 virus detected where symptomatic patients were admitted. Nevertheless, more studies are needed to provide evidence of SARS-CoV-2 airborne transmission.

4. Incubation Time and Symptoms of COVID-19

It can be mentioned that the incubation period of SARS-CoV-2 varies from 2 to 14 days (approximately 5 days). Backer et al. conducted that virus can be detected as positive within human respiratory epithelial cells roundly 96 h behind exposure and/ or prior to 24–48 h the initial of symptoms. The most common symptoms are known as dry cough, fever, rhinitis, pneumonia, muscle pain, headache, sore throat, diarrhea, and vomiting. On the other hand, less typical symptoms are described as olfactory loss of patients or suffering from anosmia/hyposmia.

5. Mutation of COVID-19

The Spike (S) protein (SARS-CoV-2 key protein) which related receptor recognition, attachment, binding, and entry cause virus infection. There are two major domains named S1 and S2, which S1 related with attachment and binding to host receptor, while S2 mediates fusion to host membrane. These proteins have critical importance about entry into the host cells for the viruses.

Coronaviruses are known to mutation particularly on the S protein. Mutations are assist to gateway of virus from immune systems of individuals and accommodate with host. In particular, S proteins mutations may cause mutants and/ or variants that have cellular tropism or changed virulence. Furthermore, S proteins are main target considering the vaccine production and designing.

6. Etiology of COVID-19 and Entry Into the Host Cells

The novel SARS-CoV-2 was described first time in Wuhan using real-time polymerase chain reaction (qRT-PCR) and genomic sequencing with bronchoalveolar fluid taken from patient. SARS-CoV-2 related novel coronavirus COVID-19 belongs to the Coronaviridae family. There are four genus coronaviruses such as alpha, beta, gamma and delta coronaviruses, which the alpha and beta genus generally effected mammals, unlike gamma and delta generally effected birds. The alpha and beta genuses have six different variants. Four of these variants cause commonly infection similar to common cold. On the other hand, the two beta variants may cause severe respiratory illness which can be mortal such as SARS-CoV and the MERS-CoV. Zhou et al. conducted that both of SARS-CoV, and SARS-CoV-2 target angiotensin-converting enzyme 2 (ACE2) on the human cell walls, also similarity in terms of receptor-binding domain (RBD). SARS-CoV-2 utilize the ACE2 receptor to break into the human cells, therefore all cells that include the ACE2 receptor such as lung, heart, kidney, intestine, endothelium, oral mucosa and salivary glands are open to infection. According to the RNA sequencing data extracted from oral tissues demonstrated high affinity to expression of ACE2 to tongue and the oral mucosa epithelial cells. Moreover, considering the another study, it is discovered that expressed ACE2 and an enzyme that simplify entry of SARS-CoV-2 in cells on oral mucosa. Considering all these results, it can be concluded that the oral cavity is the likely route for the entry of SARS-CoV-2 into the body.

7. Transmission Risks of COVID-19 in Dentistry

During the dental treatment, there is a biological risk among the dentists, dental nurses, hygienists and patients. Infection prevention process for routine dental procedures cannot protect against SARS-CoV-2 transmissions. Meng et al. conducted that among the 169 dental practitioners 9 of them infected with COVID-19 which these results showed the high risk of contagiousness.

During the dental treatment utilizing burs with highspeed handpiece occurs excessive heat which causing the damage on hard dental tissue and these outcomes lead to pathological side effect on pulp tissue. To prevent these heat-induced damages, it is general rules to use a water coolant, which also cause the aerosols generating, during the dental procedures such as cavity or crown preparations. These aerosols combined with the blood and/ or saliva (body fluids) in oral cavity, named as bioaerosols which is contaminated with bacteria and viruses, and can be inhaled by patients and dental personnel through in the airborne. Transmission of COVID-19 through inhalation during the dental treatment is high due to diffusion of aerosol particles of saliva, blood, and secretions caused using handpieces or ultrasonic scalers. Furthermore, dental environments, surfaces, areas and dental instruments can be contaminated by generated aerosols through the dental practices. Therefore, during the dental treatments, novel rules must be applied prevention of transmission infection among the patients or dental personnel (cross-infection), also, it should be recommended various procedures reducing the airborne transmissions.

8. Contamination Preventive Protocols

To maintain herd immunity in community widespread immunization with vaccination generally takes a long period, therefore it is precisely significant to utilized preventive protocols during dental practices within SARS-CoV-2 transmission.

8.1. Patient Triage

Due to increase of infected people with COVID-19, American Dental Association (ADA) recommended to postpone dental practices except the emergency situations, also advised various route for the dental treatments. One of the route is telephone triage which is the identify dental emergencies and initial patients screening. Virtual/telecommunication triage can assist the dentist with anamnesis, photographs and videos initial diagnosis before admitting patient to the practice. If there is dental emergencies such as tooth pain, swelling and redness, can be recommended locally applied analgesics and/ or antimicrobials. When the palliative medication does not effective perfectly in symptoms pass to acute phase, dental treatment is necessary. In this instance, it has to be questioned patients about positive for COVID-19 PCR test, any symptoms such as cough, shortness of breath or sore throat, recent travel history, and contact with infected individuals. Also, temperature must be measured with contact-free forehead thermometer. If the patient infected with COVID-19 or contact with positive case, all treatments must be cancelled and reported to healthcare authorities immediately.

8.2. Waiting Area

Waiting areas have excessive risk due to cross-infection among the patients, patients' relatives, dental practitioners and dental nurses. Therefore, dental personnel have to admitted patients to dental practice with no accompanying person, in waiting areas, social distance must be applied among the patients.

Sitting environments in the waiting areas must be composed considering the social distance (approximately 2 m, which is provided to distance among the patient that due to recommendation chairs should be taped. All unnecessary materials such as magazines, furniture, and flyers should remove from waiting areas. Patients and accompanying individuals must wear mask correct way and use hands sanitizer. Elevator buttons must be disinfected daily avoid the cross-infection among patients.

8.3. Personal Protective Equipment (PPE)

Masks

Due to contagion route of COVID-19, respiratory protection devices are extremely necessary to avoid from aerosols, chemical and biological materials. While respiratory devices known as particle filtering face-piece respirators (FFRs are classified at nine different predicament such as N95, N99, N100, P95, P99, P100, R95, R99, and R100 by US National Institute for Occupational Safety and Health (NIOSH, they are divided into three categories by European Standard (EN 149:2001 such as FFP1, FFP2, and FFP3 due to filter effectiveness (particle size up to 0.6 µm respectively 80%, 94%, and 99%. Differences in categories made by these institutions are related their filter capacity, and quality. According to these two different classification methods, FFP2 is acceptable relatively equal to N95. Beside that surgical masks are generally used to prevent droplets among particle size above 1 µm, and must be continually wear by patients admitting to dental practice to protect themselves and personnel.

Dentist always must be wear surgical mask when close contact is required (less than 2 m, and dental treatment must be performed wearing an FFP2 or FFP3 mask however under conditions which is not provided these respiratory devices, surgical masks utilized with face shield. Masks are remove with a new pair of gloves no touching the contaminated surface.

Gloves

During the procedure disposable gloves (double pair) must be used, and before putting the gloves on for prevent the infection any cuts or scars above hands are covered. Gloves after use might be removed rolling from wrist avoiding the touch the skin, also with no contact any environment.

Hand hygiene and sanitation

Routine hand washing is one of the most crucial protocol in order to prevent COVID-19 transmission through the individuals. Considering the dental examination occurs that is close contact with patients, in particular dental practitioners must be excessively attentive about oral fluids or aerosols generating process, also have to utilized antiseptic among the each patient treatments. In many antiseptic solution products, ethanol-based antiseptic solutions are preferred (in particular concentration over the 70%) due to their non-toxic property above the human skins, however soap and water is exceedingly recommended due to their effectiveness.

Face and eye protection

Eyes protection can be provided with goggles, visors and face shield during the process generating aerosols. After use, they must sterilized, disinfected or disposed among the each patients, and only medical loups and prescription glasses have to used.

Uniforms and surgical gowns

Uniforms must be long sleeves, changed daily, and before washing disinfected with chlorine solution (0.5 g/L) about 30 s, furthermore surgical gowns must be wear above the uniforms to reduce the transmission risk. After use, gowns are removed without removal gloves, and disposed immediately.

8.4. Disinfection of Potentially Contaminated Surfaces/Air

After the dental procedures, patient's disposable gown must be carefully removed by personnel without touching external part, and all contaminated instruments collected to disinfection. It is known that SARS-CoV-2 is sensitive at heat increase, ultraviolet light, and can be deactivated at 56 ◦C for 30 min which can be used common autoclaves to disinfection of dental instruments. On the other hand, it can be disinfected with lipid-based solvents, 75% ethanol, disinfectants containing chlorine, and chloroform, except chlorhexidine. Except from all these methods, ozone can be use as disinfectant considering the their properties similar to liquid sanitizer, to improve distribution on surfaces. Dental unit and surroundings must be sanitizing cautiously, in particular spittoon environment. When the units or environments are disinfected, solutions containing hypochlorite 1% or alcohol 70% must be spray on surfaces and leave at least 1 min.

Furthermore, due to SARS-CoV-2 virus is remain in the airborne up to 3 h, it is obligated to change air periodically to prevent transmission in the dental practice, in particularly after using the high-speed handpieces or ultrasonic scalers. The air change which is required in dental clinics with no windows or ventilation, might be performed through various methods such as air suction, plasma cluster ion technology using fixed devices, UV lights, HEPA filters, or in special negative pressure rooms.

Window opening for 20 square meters room must be minimum 2 square meters to obtain effective air exchange along 10 min. Considering the property of SARS-CoV-2 virus remaining in airborne couple hours, it has to be disinfected every place contact by individuals such as door handles, waiting room chairs, PC keyboards, mouse, desks, filing cabinets. At the end of day, ground sanitizing can be performed with 1% hypochlorite solutions, daily.

Use of air conditioning might still not be safe considering the distribution of novel coronavirus. According to a study, it was shown that air conditioning can be directed the particles in the airborne through the different direction, which these outcomes might be useful managing the aerosols generating in the dental practice.

8.5. Rubber Dam

During the dental treatments, rubber dam is exceedingly recommended to reduce generating aerosols, infected biological materials. Samaranayake et al. conducted that rubber dams could be decrease aerosols up to 70% surrounding 1 m of operating areas during the use of high-speed handpieces. Even though rubber dam is recommended to decrease aerosols, it cannot be applied each procedures such as periodontal scaling and must use hand scaler.

9. Treatments Recommendations

Endodontics

When the patients are applied with emergency situation to dental practices, during the endodontic treatment must be used manual instruments instead of rotary systems, and rubber dam has to placed.

Restorative and pediatric dentistry

During the cavity preparations instead of the high-speed handpieces, chemo chemical caries removal or atraumatic restorative techniques with manual instruments should be used in restorative and pediatric dentistry.

Periodontics

Manual scaling must be preferred to ultrasonic scalers during the periodontal operation.

Prosthodontics

To lessen the contamination risk, materials and impressions must be disinfected in the prosthodontic laboratories. During the impression taking, oral mucosa might be anesthetized to avoid gag reflex. Rubber dam is advised during the preparation fixed partial denture or single crown to decrease generating aerosols. If it is occurred discomfort during the use, to maintain its properties can be applied soft lining to removable prosthesis.

Oral and maxillofacial radiology

Diagnostic radiographs taken from patients should be extraoral radiographs such as Dental Panoramic Radiographs (DPR) or Cone Beam Computed Tomography (CBCT), unless it is required intraoral radiographs.

Oral and maxillofacial surgery

During the tooth extraction, it must be used high volume suctions. Antibiotic therapy is advised in case of abscess or pericoronitis. During the treatment, if there is excessive tooth pain, it must be preferred extraction of teeth instead of conservative approach.

10. Conclusion

Given the characteristics of COVID-19 transmission, dental practitioner and personnel are highly exposed at infection risks, by profession nature. Considering the continuing SARS-CoV-2 global pandemic devastating the healthcare systems, economics and social relations, with stated above precautions to prevent transmission of COVID-19 to avoid the side-effects at dentistry, might be protect for patients and dentists during the dental treatments.

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CHAPTER 21

COVID-19 AND LIVER

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by the recently identified coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) , which first reported in humans in Wuhan, China, in December 2019. SARS-CoV-2 is a single, positive-stranded RNA virus has since spread rapidly worldwide as a global public health threat. The novel coronavirus SARS-CoV-2 is most similar to the beta-coronaviruses, SARS-CoV and MERS-CoV that are causative agents of the SARS outbreak in 2002-2003 in southern China and the MERS outbreak beginning in 2012 in Saudi Arabia, respectively.

The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Symptoms associated with COVID-19 are mostly fever, cough and shortness of breath. Some patients also develop symptoms including, headache, myalgia, nasal congestion, sore throat and loss of smell or taste. A significant proportion of COVID-19 patients can present initially with only digestive complaints. The most common digestive symptoms are anorexia, nausea, vomiting, and diarrhea. While symptoms remain mild throughout the course of infection in the majority of patients, older patients were identified to be at higher risk of a fatal disease course, with hypertension, diabetes and coronary heart disease being the most frequent comorbidities.

There has been growing concern about pre-existing chronic liver disease (CLD) might predispose to poor outcomes following SARS-CoV-2 infection, especially due to the overlapping risk factors for severe COVID-19 and CLD, for example, advancing age, obesity and diabetes. Moreover, advanced liver disease is associated with immune dysregulation and coagulopathy, which could contribute to a more severe COVID-19 course. We aim to summarize the pathogenesis and consequences of SARS-CoV-2 infection in patients with CLD , the utility of liver biochemistry as a prognostic tool during COVID-19, the evidence for direct viral infection of liver cells and explore the likely mechanisms underlying SARS-CoV-2-related liver injury.

Hepatotropism of SARS-CoV-2

SARS-CoV-2 is internalized into target cells through angiotensin-converting enzyme 2 (ACE2), which acts as a functional receptor. The virus spike protein binds ACE2 to gain cell entry and transmembrane serine protease 2 (TMPRSS2) and paired basic amino acid cleaving enzyme (FURIN) are also important for infection. It has been shown that gene expression levels for ACE2 are highest in cholangiocytes, followed by hepatocytes. TMPRSS2 expression levels are highest in cholangiocytes, hepatocytes and periportal liver sinusoidal endothelial cells and FURIN expression levels are similar from hepatocytes to all populations of liver resident cells. Zhao et al. demonstrated ACE2-expressing and TMPRSS2-expressing human liver ductal organoids that were able to recapitulate SARS CoV-2 infection, suggesting that the bile duct epithelium could support pseudoparticle entry. Human pluripotent stem cell-derived liver organoids comprising mostly albumin-expressing hepatocytes have also been shown to express ACE2 and permitted SARS-CoV-2 pseudoparticle entry.

Studies before covid-19 found a 34-fold increase in ACE2 mRNA levels and this was associated with a 97-fold increase in ACE2 protein, while ACE2 activity was increased 2.4-fold in the liver of patients with hepatitis C virus-related cirrhosis compared with healthy controls. ACE2 expression is significantly increased in liver injury, possibly in response to increasing hepatocellular hypoxia, and may modulate renin angiotensin system (RAS) activity in cirrhosis. Furthermore, liver mRNA expression of ACE2 and TMPRSS2 was upregulated in patients with obesity and nonalcoholic steatohepatitis (NASH) but not with steatosis alone. These results suggest that advanced stages of non-alcoholic fatty liver disease (NAFLD) may predispose individuals to COVID-19. Liver injury and inflammation might potentiate SARS-CoV-2 hepatotropism by interferon-driven upregulation of ACE2 being identified as an interferon-inducible gene in human respiratory epithelia.

Coronavirus particles have been identified in the cytoplasm of hepatocytes associated with typical histological evidence of viral infection. Several autopsy series have demonstrated SARS-CoV-2 within hepatocytes confirming that direct hepatic infection in COVID-19 occurs. Typical histological evidence of viral infection in these hepatocytes has also been seen; however, the impact of direct SARS-CoV-2 hepatocyte infection on liver failure or the course of COVID-19 remains unclear. An American autopsy series demonstrated histologic findings of macrovesicular steatosis, mild acute hepatitis (lobular necroinflammation) and mild portal inflammation. Cholestatic features including bile duct proliferation and canalicular/ductular bile plugs have been reported. In addition, SARSCoV-2 viral RNA was detectable by PCR in 55% of liver samples that were interrogated. An Italian autopsy series showed minimal hepatic inflammation but extensive portal and sinusoidal thrombosis. Considering the degree of cholangiocyte viral entry receptor expression, the absence of histological evidence of biliary damage is remarkable. SARS-CoV-2 was also detected in 68% of samples by in situ hybridization. Postmortem liver examination by electron microscopy identified typical coronavirus particles, characterized by spike structures, in the cytoplasm of hepatocytes in 2 COVID-19 cases. SARS-CoV-2-infected hepatocytes displayed conspicuous mitochondrial swelling, endoplasmic reticulum dilatation and glycogen granule decrease. Histologically, massive hepatic apoptosis and some binuclear hepatocytes were revealed. Consequently, both ultrastructural and histological evidence indicated a typical lesion of viral infection.

Liver biochemistry in COVID-19

Patterns and frequency of liver biochemistry abnormalities in COVID-19

Although the precise influence of COVID-19 on the liver remains unclear, abnormalities in liver biochemistries in hospitalized patients with COVID-19 ranges from 14% to 83%. The wide range in these reported frequencies could be attributable to different definitions of upper limit of normal,varying laboratory values considered as liver enzymes, and geographical variability in the prevalence and type of underlying CLD.

Liver biochemistry abnormalities in COVID-19 are generally characterized by mild (1–2 times the upper limit of normal) elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, reported in an estimated 29–39% and 38–63% of patients, respectively. Elevations in alkaline phosphatase and gamma glutamyl transferase are seen in 6% and 21% of COVID-19 patients, respectively. Low serum albumin on hospital admission is a marker of COVID-19 severity. Abnormalities in liver biochemistries are reported in similar frequencies regardless of the presence of pre-existing liver disease. Liver injury occurs more commonly in severe COVID-19 cases than in mild cases. Rare cases of severe acute hepatitis have been described in patients with COVID-19. Predictors of peak abnormal liver tests >5x upper limit of normal (ULN) include age, male gender, body mass index, diabetes mellitus, medications (e.g., lopinavir/ritonavir, hydroxychloroquine, remdesivir, tocilizumab), and inflammatory markers (IL-6, ferritin). Acute liver failure secondary to Herpes Simplex Virus-1 has been reported in COVID-19 patients following tocilizumab and corticosteroid therapy.

Underlying causes of elevated liver enzymes in COVID-19

There are a number of potential contributors to elevated liver enzyme levels in COVID-19. In most cases, abnormal biochemistries are likely multifactorial with potential contributions from immune-mediated inflammatory response, drug induced liver injury, hepatic congestion and extrahepatic release of transaminases as well as possible direct infection of hepatocytes. In hospitalized patients with COVID-19, elevations of serum AST levels positively correlate with levels of ALT but not with markers of muscle breakdown (such as creatinine kinase) or systemic inflammation (such as C-reactive protein (CRP) and ferritin). These findings suggest that elevated liver enzymes in COVID-19 result from direct hepatic injury, although COVID-19- associated rhabdomyolysis is rarely reported. During the course of COVID-19, AST is often found to exceed ALT, which would be atypical for a classic hepatocellular pattern of liver injury outside of specific contexts such as alcohol-related liver disease, certain drug-induced liver injuries (for example, lamotrigine), ischaemic hepatitis and cirrhosis. The mechanisms responsible for an AST-predominant aminotransferase elevation may include COVID-19-related mitochondrial dysfunction, SARS-CoV-2-induced hepatic steatosis, decreased hepatic perfusion secondary to microthrombotic disease and systemic hypoxia in parallel with diminishing peripheral oxygen saturations.

Venous and arterial thromboses are a well-known consequence of COVID-19, including in the liver which could contribute to elevations in liver biochemistries. The pooled incidence of drug-induced liver injury in patients with COVID-19 is 25.4% (95% CI 14.2-41.4). Therapeutic agents used to manage symptomatic COVID-19 may be hepatotoxic but rarely lead to treatment discontinuation. These include remdesivir and tocilizumab. It is difficult to distinguish whether the increases in liver biochemistry are due to the SARS-CoV-2 infection itself or its complications including myositis (particularly with AST>ALT), cytokine release syndrome, ischemia/hypotension; and/or drug-induced liver injury.

Prognostic significance of elevated liver enzymes in COVID-19

COVID-19 patients with elevated liver biochemistries are at increased risk of death and severe COVID-19 compared to COVID-19 patients without elevated liver biochemistries. Especially, AST and ALT level elevations greater than five times the upper limit of normal, are associated with an increased risk of death. AST is usually higher than ALT and is associated with severe COVID-19 and mortality, which may reflect non-hepatic injury. Alkaline phosphatase peak values are correlated with risk of death and may be predictive of a worse prognosis. It has been proposed that the prognostic significance elevated liver enzyme levels could be due to a more strong host response and aggressive therapies in those with severe illness. Nevertheless, these studies could be prone to bias if patients with severe disease received more intensive laboratory monitoring, increasing the likelihood of detecting liver injury. Some studies have reported that there is no apparent association between liver enzyme level elevations and mortality. Liver injury in mild COVID-19 cases is usually transient and does not require specific treatment beyond supportive care.

Guidance For Evaluation of COVID-19 Patients With Elevated Liver Biochemistries

- Consider etiologies unrelated to COVID-19, including other viruses such as hepatitis A, B, and C, and drug-induced liver injury when assessing patients with COVID-19 and elevated liver biochemistries.
- To limit unnecessary exposure to COVID-19, ultrasound or other advanced imaging (e.g., MRI/MRCP) should be avoided unless it is likely to change

management, e.g., clinical suspicion for biliary obstruction or hepatic/portal venous thrombosis.

- Consider other causes of elevated liver biochemistries, including myositis (particularly when AST>ALT), cardiac injury, ischemia, drug-induced liver injury, and cytokine release syndrome.
- Consider cholangiopathy or secondary sclerosing cholangitis of critically ill patients in patients with severe COVID-19 with worsening cholestasis.
- The presence of abnormal liver biochemistries should not be a contraindication to using investigational or off-label therapeutics for COVID-19, although AST or ALT levels >5x ULN may exclude patients from consideration of some investigational agents.
- Regular monitoring of liver biochemistries should be performed in all hospitalized COVID-19 patients, particularly those treated with remdesivir or tocilizumab, regardless of baseline values.
- In patients with AIH or liver transplant recipients with active COVID-19 and elevated liver biochemistries, do not presume disease flare or acute cellular rejection without biopsy confirmation.

SARS-CoV-2 infection and liver disease

In patients with CLD, especially cirrhosis, there are multiple mechanisms of immune dysfunction that can lead to increased susceptibility to infection and an abnormal inflammatory response during infection. This immune dysfunction includes reduced components of the complement system, decreased macrophage activation, impaired lymphocyte and neutrophil function, Toll-like receptor upregulation, and intestinal dysbiosis. Electronic health record data from the USA has shown that patients with cirrhosis actually have a lower risk of testing positive for SARS-CoV-2 infection. It is unlikely that cirrhosis will be protective against SARS-CoV-2 acquisition, and thus this low positive test rate is likely due to the patient's increased compliance with preventive measures (eg, social distancing, hand washing). It has been shown that patients with cirrhosis with infections of all kinds have worse clinical outcomes than patients without underlying liver disease and SARS-CoV-2 infection seems to follow a similar pattern. American non-Hispanic Black and Hispanic CLD patients have an increased risk of SARS-CoV-2 infection with socioeconomic disparities.

CLD is not more prevalent among hospitalized patients with COVID-19, but it is associated with severity of COVID-19 and mortality. A meta-analysis that included 73 studies and 24,299 patients reported the prevalence of CLD was 3% among hospitalized COVID-19 patients, which was similar to the COVID-19-negative population. CLD was associated with COVID-19 severity (OR 1.48) and mortality (OR 1.78). In a large cohort study of electronic health record data from over 17 million patients (>100,000 with CLD) in the United Kingdom, CLD was a risk factor for in-hospital death from COVID-19. CLD was associated with significantly higher mortality (RR 2.8) in a cohort of 2780 US patients with COVID-19, and the mortality risk was higher in patients with cirrhosis (RR 4.6). In a retrospective Italian study of 50 patients with COVID-19 and cirrhosis, patients with cirrhosis had a higher 30-day mortality rate compared to patients without cirrhosis (34% vs 18%). In a multicenter study of inpatients with cirrhosis and COVID-19 compared with age/sexmatched patients with COVID-19 alone and cirrhosis alone, patient with cirrhosis and COVID-19 had a higher risk of death compared to patients with COVID-19 alone (but not significantly higher than the risk of death from cirrhosis alone without COVID-19). Mortality from COVID-19 is higher in more advanced liver disease and strongly associated with hepatic decompensation. In a large international registry study, patients with Child-Turcotte-Pugh class C cirrhosis and COVID-19 had a 4.6-fold increase in mortality compared to patients with Child-Turcotte-Pugh class A cirrhosis. Acute hepatic decompensation is common, occurring in 46% of patients with cirrhosis and COVID-19, and typically manifests as worsening ascites and encephalopathy. Hepatic decompensation could be the first and only indication of SARS-CoV-2 infection in patients with cirrhosis, with 21% having no concurrent pulmonary symptoms. Hepatic decompensation (hazard ratio [HR] 2.91), alcohol-related liver disease (ALD) (HR 2.42), and hepatocellular carcinoma (HCC) (HR 3.31) were independent risk factors for mortality in a multicenter, observational US cohort of patients with COVID-19 and cirrhosis. Although the acute mortality associated with COVID-19 in patients with cirrhosis is high, in those who survive the initial insult, the rates of death and re-admission at 90-days are comparable to those with cirrhosis alone. Therefore, beyond the acute infective period, SARS-CoV-2 infection does not seem to precipitate liver disease progression over and above the natural history of cirrhosis. A low threshold for testing SARS-CoV-2 should be considered in patients with new complications for cirrhosis.

Chronic hepatitis B or C have not been associated with mortality from COVID-19. Patients with autoimmune hepatitis (AIH) were associated with increased risk of hospitalization but not increased risk of ICU admission or death despite immunosuppressive treatment (83% of AIH subjects in this study were on immunosuppressive drugs) compared to other causes of CLD and to matched cases without liver disease. This finding should reassure clinicians and provides a clear rationale not to routinely reduce immunosuppression in these patients during the course of COVID-19. The impact of nonalcoholic fatty liver disease (NAFLD) on COVID-19 is controversial but metabolic risk factors such as obesity, diabetes mellitus, and hypertension are associated with COVID-19 severity. One retrospective series of 202 consecutive patients with SARS-CoV-2 infection identified NAFLD as a risk factor for progressive COVID-19, abnormal liver enzyme levels and longer viral shedding time. NAFLD is associated with progressive COVID-19 and worse outcomes independent of obesity and comorbidities. It is unknown whether SARS-CoV-2 infection exacerbates cholestasis in those with underlying cholestatic liver disease such as primary biliary cholangitis or primary sclerosing cholangitis or with underlying cirrhosis. Secondary sclerosing cholangitis of critically ill patients and cholangiopathy have been reported in patients with severe COVID-19 and during recovery. Treatment for hepatitis B, hepatitis C, AIH, or primary biliary cholangitis (PBC) sould be continued if already on treatment. There is no contraindication to initiating treatment of hepatitis B, hepatitis C, AIH, or PBC in patients without COVID-19 as clinically warranted. Initiating treatment of hepatitis B in a patient with COVID-19 is not contraindicated and should be considered if there is clinical suspicion of a hepatitis B flare or when initiating immunosuppressive therapy. Initiating treatment of hepatitis C or PBC in a patient with COVID-19 is not routinely warranted and can be deferred until recovered from COVID-19. Patients with CLD and AIH on immunosuppression without COVID-19 should be encouraged for COVID-19 vaccination.

The majority of deaths in patients with cirrhosis and COVID-19 are due to respiratory failure, but the exact mechanisms supporting this observation remain unclear. However, it is reasonable that pulmonary venothromboembolic disease, a hallmark of critical COVID-19, has a contributing role given the additional hypercoagulable state associated with cirrhosis. While routine thromboprophylaxis in hospitalized COVID-19 patients is universally recommended, unified risk classification models and treatment algorithms, which vary widely in clinical practice and between international guidelines, have yet to emerge. Acute portal vein thrombosis has been reported in patients with COVID-19; however, a causal link to COVID-19 has not been definitively established. Considering both cirrhosis and coagulopathy associated with COVID-19, the coexistence of these conditions may pose a cumulative risk of thrombotic complications. An awareness of the high rate of thrombotic events in COVID-19 is necessary as this could potentially adversely impact the outcomes in those with chronic liver disease and anticoagulation may improve outcomes in hospitalized patients. Based on a systematic review and meta-analysis, patients with cirrhosis and PVT who receive anticoagulant therapy have increased recanalization and reduced progression of thrombosis, compared with patients who do not receive anticoagulants, with no excess of major and minor bleedings and less incidence of variceal bleeding.

Currently, both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) support the resumption of HCC surveillance in high-risk patients (for example, advanced cirrhosis, chronic hepatitis B virus infection) during the COVID-19 pandemic but recognize potential feasibility issues due to the strain on imaging and radiology resources. The AASLD, therefore, recognises that an arbitrary delay of 2 months might be reasonable following the discussion of risks and benefits with the patient. If HCC surveillance is deferred indefinitely, it is inevitable that the proportion of patients presenting with HCC not amenable to curative treatments will increase. Liver cancer treatments or surgical resection should be done when able rather than delaying them because of the pandemic.

SARS-CoV-2 İnfection and Liver Transplant

The complex decision making involved in whether or not to proceed with transplantation has been more challenging because of the COVID-19 pandemic. COVID-19 has had a significant impact on the transplant waiting list and transplant center practice patterns.

Country-wide data from Spain and the UK suggest that the incidence of COVID-19 is higher in liver transplant patients than among the general population. The most plausible explanations are chronic immunosuppression and increased comorbidities, which would make them more vulnerable. Fortunately, not all LT recipients diagnosed with SARS-CoV-2 infection develop severe COVID-19. For example, in the Spanish series, 6% were described as asymptomatic, and in a multinational series, 14% had neither respiratory nor gastrointestinal symptoms. In a German study using serology to identify LT recipients who had previously been exposed to SARS-CoV-2, 5 out of 8 people with a detectable IgG response reported no previous symptoms consistent with COVID-19. The most common presenting symptoms were fever, cough, and dyspnea developing around 1 week following SARS-CoV-2 infection. Two-thirds of the patients had moderate to severe disease. Among LT recipients seems to be a high frequency of gastrointestinal symptoms, with diarrhoea reported in 42% and 31% of two early cohorts, respectively. In 149 liver transplant recipients and 529 patients in the comparison cohort, the proportion of patients with gastrointestinal symptoms (abdominal pain, diarrhoea, nausea, or vomiting) was higher among liver transplant recipients (30%) than among the comparison cohort (12%) ($p<0.0001$). However, the presence of respiratory symptoms at diagnosis did not differ significantly between the liver transplant cohort (77%) and the comparison cohort (81%) ($p=0.248$). In propensity score-matched models, the frequency of gastrointestinal symptoms differed whereas rates of respiratory symptoms were similar between groups. Evaluation of liver transplant-related outcomes among individuals infected with SARSCoV-2 is complex due to the demographic and comorbidity pattern within the population. LT recipients are more likely to be male and more likely to have kidney failure, type 2 diabetes mellitus, and obesity than the general population. In the United States, based on data from the United Network for Organ Sharing on adults , the mean age of liver transplant registrants increased from 51.2 to 55.7 years between 2002 and 2014. All of these factors are well established to be associated with an increased risk of adverse outcomes following SARS-CoV-2 infection, and for LT recipients, age and comorbidity burden are strongly associated with death or severe disease course. Overall, mortality in liver transplant recipients in the COVID-19 pandemic is around 20%. In prospective nationwide study including a consecutive cohort of liver transplant patients with COVID-19, mortality rates were lower than those observed in the age- and gender-matched general population, thereby suggesting that chronic immunosuppression could exert a certain protective effect against the most severe forms of COVID19.

An argument put forward to justify delaying some transplants is a concern with immunocompromised patients during the COVID-19 pandemic. However, immunosuppressed patients may not be at increased risk for severe COVID-19.

Nevertheless, immunosuppressed patients have higher viral titers and may be more infectious than immunocompetent individuals. It is impossible to weigh the value of the life of a patient with COVID-19 against that of a patient in need of life-saving liver transplantation. Transplant decisions should ideally be made in consultation with local medical ethics committees. All recipients and donors for SARS-CoV-2 should bet tested before transplantation. There is a significant false negative testing rate and transplant programs should consider symptoms of COVID-19 in a potential donor or recipient to be strongly suggestive of infection despite negative testing. SARS-CoV-2 PCR may remain positive for months after resolution of infection and infectivity. Organs from donors with a prior history of COVID-19 but asymptomatic and infected 21 to 90 days prior to donor evaluation may be eligible for donation. “Reactivation” of SARS-CoV-2 after solid organ transplantation has not been reported to date. Transplantation in SARS-CoV-2-positive transplant candidates is currently not routinely recommended until at least 14 days after clinical recovery.

The immune response and “cytokine storm” may be the main driver for pulmonary injury attributable to COVID-19 and that immunosuppression may be protective. Corticosteroids improve survival in critically ill patients with COVID-19 requiring supplemental oxygen. Baseline immunosuppression containing tacrolimus was associated with better survival in liver transplant recipients with COVID-19. Baseline immunosuppression containing mycophenolate was an independent predictor of severe COVID-19 in liver transplant recipients. Lowering immunosuppression, primarily antimetabolites, in liver transplant recipients with COVID-19 during a period of active infection has not been shown to increase the risk of rejection as long as liver biochemistries are monitored. Reducing the dosage or stopping immunosuppressants without monitoring liver biochemistries may cause a flare in a patient with AIH or precipitate acute rejection in a liver transplant recipient. A complete immunosuppression withdrawal after the diagnosis of COVID-19 may not be justified. However, in patients receiving mycophenolate, dose reduction, or temporary conversion to calcineurin inhibitors or everolimus may be considered until complete recovery from COVID-19. Lowering immunosuppression to the most acceptable level appears reasonable in infected liver transplant patients, in particular, in the setting of lymphopenia or clinical worsening of infection. The COVID-19 treatment guidelines recommend that oral corticosteroid therapy used prior to COVID-19 diagnosis for another underlying condition should not be discontinued. Anti-IL-6 therapeutics have not been shown to increase the risk of acute cellular rejection. All liver transplant recipients should be encouraged for COVID-19 vaccination (ideally at least 6 weeks post liver transplantation).

In addition clinicians have to be aware of drug–drug interactions in the transplant setting. In particular immunosuppressive drugs and ritonavir-boosted antiviral therapies exhibit relevant interactions through CYP34A which lead to increased levels of calcineurin and mTOR inhibitors. Accordingly, chloroquine-based regimes or remdesivir appear to be safe, while boosted protease inhibitors should be avoided.

Drugs for COVID-19 and Liver

Given the fact that the liver is involved in the metabolism of many drugs, including nucleoside analogs and protease inhibitors that are currently used to treat COVID-19, hepatotoxicity from these drugs can arise.

- Lopinavir/Ritonavir are protease inhibitors approved for HIV. In the single center experience of Fan et al., patients with abnormal liver function had a significantly higher rate of receiving lopinavir / ritonavir after hospitalization compared with patients with normal liver function. Importantly, liver function tests elevation during the hospital stay was associated with prolonged length of hospitalization. It should not be co-administered with mTOR inhibitors (sirolimus, everolimus). When used with calcineurin inhibitors (cyclosporine, tacrolimus) drug level should be closely monitored.
- Chloroquine, an old drug with a potential of repositioning for new treatment indications, has recently been tried in patients infected with SARS-CoV-2. The pharmacodynamic activity of this drug in COVID-19 may be in the form of inhibition of the cytokine storm, activation of CD8+ cells or inhibition of endocytosis-mediated uptake of the virus. Hepatotoxicity related to chloroquine or hydroxychloroquine has been rarely reported.
- Favipiravir, is a guanine analogue and a RNA-dependent RNA polymerase (RdRp)- inhibitor, approved for influenza in Japan. Metabolised by aldehyde oxidase and xanthine oxidase. CYP450 isoenzymes are not involved in the metabolism. Elevation of ALT and AST possible. No data in cirrhosis available. Few cases have been published about rarely causing cholestatic hepatitis.

- Remdesivir is a nucleotide analogue with demonstrated activity against SARS-CoV-2 in human cell lines. No mortality benefit has been demonstrated, but remdesivir shortens duration of illness and hospitalization and appears to be most effective when given to patients on supplemental oxygen within 10 days of symptom onset. No benefit observed in those requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO. No efficacy of treatment duration beyond 5 days has been observed. Remdesivir should be offered for a 5-day duration to hospitalized patients with liver disease or liver transplant recipients hospitalized with COVID-19 and requiring supplemental oxygen. In patients who require high-flow oxygen or non-invasive mechanical ventilation, remdesivir should be considered. Remdesivir should not be used in patients with liver disease or liver transplantation requiring mechanical ventilation. Baseline testing of liver biochemistries should be performed prior to initiating remdesivir and testing should be repeated frequently during treatment with drug discontinuation for elevations >10x ULN or signs or symptoms of liver inflammation.
- Dexamethasone given at 6 mg daily for up to 10 days decreases mortality in hospitalized patients with COVID-19 requiring supplemental oxygen. The greatest benefit was seen in patients requiring mechanical ventilation, a trend toward harm was observed in patients who did not require supplemental oxygen, and no benefit was seen in those more than 7 days from onset of symptoms. Very few patients with severe liver disease were included in the RECOVERY trial (<3%) and the number of solid organ transplant patients included is not reported. If patients already receiving corticosteroids at lower than an equivalent dose of 6 mg daily of dexamethasone (prednisone 40mg), dose should be increased to equivalent of 6 mg daily of dexamethasone and if dexamethasone is not available, an alternative corticosteroid at equivalent doses may be substituted. In patients with decompensated liver cirrhosis, the risk of other infections (eg. SBP) and viral shedding may be increased. The risk of HBV reactivation should be considered.
- Tocilizumab and sarilumab are IL-6 inhibitors approved by the FDA for treatment of autoimmune diseases (e.g., rheumatoid arthritis) and chimeric antigen receptor T cell induced cytokine release syndrome. Early in the COVID-19 pandemic, case series suggested that IL-6 inhibition of the inflammatory state occurring in some patients with COVID-19 might improve outcomes. While tocilizumab may benefit a subset of deteriorating

critically ill patients already receiving corticosteroids, no recommendation about use in patients with liver disease or solid organ transplantation can be made based on currently available data. In previous clinical studies for other indications, tocilizumab has been reported to cause mild elevations of liver function tests in 10-50% of patients, usually transient, usually beginning 2 weeks after exposure and resolving within 6-8 weeks.

- Baricitinab is FDA approved for the treatment of refractory rheumatoid arthritis and may have direct antiviral properties. Baricitinab could be considered in patients with liver disease or in transplant recipients who are unable to tolerate corticosteroids and who otherwise meet indications for corticosteroids.
- Emapalumab is a monoclonal Ab targeting interferon-gamma approved for hemophagocytic lymphohistiocytosis. Treats the cytokine release syndrome observed in COVID-19. Typically occurring a few weeks after the start of treatment, mild and transient ALT elevations may occur. There may be a risk of reactivation tuberculosis, p.jirovecii, herpes zoster.
- Umifenovir (Arbidol) can inhibit viral entry into target cells and stimulate immune response. It was used in the treatment of influenza in some countries. There is a risk of interaction between Arbidol and drugs metabolised by CYP3A4. Caution should be exercised in patients with liver cirrhosis.
- Anakinra is an interleukin 1 receptor antagonist. It is used in macrophage activation syndrome developing in the course of COVID-19. It has minimal hepatic metabolism.

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