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Review

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Diagnostic and Therapeutic Approaches to Novel COVID-19 in Intensive Care Unit: A Narrative Review

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Abstract

This study aimed to compile the up-to-date information about the methods and pharmacological agents used in the diagnosis and treatment of coronavirus disease 2019 (COVID-19) and examine the methods used in the treatment of COVID-19 in patients in the intensive care unit by reviewing the treatment guidelines published by national health authorities worldwide. We surveyed the literature published on the novel coronavirus (severe acute respiratory syndrome [SARS] coronavirus [SARS-CoV-2]) before April 25, 2020, in PubMed. The results of the study identified serological and molecular methods (e.g., real-time reverse transcriptase polymerase chain reaction) used by physicians for diagnosing COVID-19 and identified thorax computed tomography along with other imaging methods used for determining the severity of the disease. However, it was concluded that the desired developments for treatment and vaccination have not been achieved till today, and many of the agents used and studied for the treatment were drugs previously used for the treatment of Middle East respiratory syndrome and SARS. COVID-19 has higher levels of transmissibility and pandemic risk. The available information revealed that, given the size and scope of the pandemic, to date, there has been no scientifically proven effective medicine and vaccines against SARS-CoV-2. There is also an urgent need for further research for finding an effective medicine and vaccine for COVID-19 to prevent the occurrence of an outbreak in future and manage such public health emergency of this magnitude in both short and long terms.

Keywords: Coronavirus disease 2019, diagnosis, intensive care unit, treatment

Introduction

In December 2019, in Wuhan City, China, a group of patients were found to have a febrile respiratory disease of unknown cause. A new coronavirus (severe acute respiratory syndrome [SARS] coronavirus 2 [SARS-CoV-2]) was detected as a result of bronchoalveolar lavage in patients (1). Within a span of months, coronavirus disease 2019 (COVID-19) had become a pandemic owing to its transmissibility, spreading across continents, with the number of cases and deaths rising daily. The pulmonary infection caused by SARS-CoV-2 was named COVID-19 by the World Health Organization (WHO) (2). On January 30, 2020, the WHO issued a worldwide public health alert on the emergence of a new epidemic viral disease (3). Till April 25, 2020, 2,849,133 confirmed cases (in 210 countries around the world) had been reported (https://www.worldometers.info/coronavirus/). The overall mortality rate of affected patients is approximately 7% (Table 1) (4-7). In our country, the first COVID-19 case was reported on March 11, 2020. As of April 25, 2020, a total of 104,912 laboratory-confirmed cases had been documented in Turkey.

The coronaviruses have envelopes, and the particles are round or oval, often polymorphic, with the diameter being 60–140 nm. Genetic analysis of SARS-CoV-2 revealed that the virus was similar to SARS coronavirus (8). Although most of the infected individuals exhibit mild illness, few have serious symptoms and about 5% have critical illness that requires intensive care unit (ICU) care, including invasive ventilation owing to acute respiratory distress syndrome (ARDS). Although mortality appears to be more common in older individuals and those with comorbidities such as chronic lung disease, cardiovascular disease and diabetes, young people with no comorbidities also appear to be at risk of critical illness, including multi-organ failure and death (8, 9).

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Table 1. Comparison of epidemiological data on SARS, MERS, and COVID-19

	Time of outbreak	Number of countries	Number of infected persons	Rate of fatality (%)
SARS	November 2002–June 2003	29	8,096	9.6
MERS	April 2002–November 2019	27	2,494	34.4
COVID-19 (until April 25, 2020)	December 31, 2020–ongoing	210	2,919,404	6.9
COVID-19 in Turkey (until April 25, 2020)	March 11, 2020–ongoing		107,773	2.5

SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; COVID-19: coronavirus disease 2019

Here, we investigated and compiled the methods used in the treatment of COVID-19 in patients in the ICU by reviewing the treatment guidelines published by national health authorities worldwide to assist and guide the patients, clinicians and other healthcare professionals in their decisions about the diagnosis and treatment of patients with COVID-19 infection.

Methods

We conducted a literature review of articles published on COVID-19 until April 19, 2020, in PubMed and investigated the national guidelines issued by local health officials in countries where the disease is common. We used clinical feature diagnostic methods for SARS-CoV-2, infection control and prevention, post-exposure management of COVID-19, pharmacological treatments and clinical research findings to collect up-to-date information about the methods and pharmacological agents used in the diagnosis and treatment of COVID-19 in patients in ICU.

Clinical features

On the basis of the current epidemiological investigation, the incubation period is on average 5-6 days, but can be as long as 14 days. Clinical characteristics of the patients who got infected with COVID-19 as well as influenza virus are as follows: common symptoms at the onset of illness included fever, cough, pharyngalgia, myalgia, fatigue and headache, and severe cases mostly developed dyspnoea and/or hypoxemia after 1 week. In severe cases, patients progress rapidly to ARDS, septic shock, metabolic acidosis that is difficult to correct, coagulopathy, multiple-organ failure and others. Some paediatric and neonatal patients may have atypical symptoms, manifested as gastrointestinal symptoms such as vomiting and diarrhoea or only manifested as low spirits and shortness of breath (7-10).

Main Points:

- In this narrative review, the literature published on the SARS-CoV-2 was surveyed. COVID-19 treatment guidelines published by national health authorities worldwide were reviewed.
- There are many ongoing clinical trials related to COVID-19 therapy, but desired developments for COVID-19 treatment and vaccination have not been achieved so far.
- Many of the agents used and studied for the treatment were drugs previously used for the treatment of MERS and SARS.
- For the world's public health, there is an urgent need for further research for finding an effective medicine and vaccine for COVID-19.

Most patients have good prognosis, and a small number of patients become critically ill. The prognosis for the elderly and patients with underlying chronic diseases is poor. The clinical course of pregnant women with novel coronavirus pneumonia is similar to that of patients of the same age (10).

Following are the ways in which the COVID-19 cases are clinically classified (8, 11-14).

1. Asymptomatic cases: The actual rate is unclear. This category seems to be the main cause of infectiousness.
2. Mild cases: Patients with mild symptoms and no signs in chest imaging fall under this category. It constitutes 81% of total diagnosed patients. The average time from baseline to clinical recovery is about 2 weeks.
3. Moderate cases: This category includes patients with fever and respiratory symptoms and imaging findings.
4. Severe cases: This category constitutes 13.8% of patients diagnosed with COVID-19 and includes the following: respiratory distress (≧30 minute^{-1}), SpO_2 ≤93% and PaO_2/FiO_2 ≦300 mmHg. This category includes cases showing more than 50% prominent lesion progression during chest imaging within 24–48 hours.
5. Critical cases: This category constitutes 5%–6% of patients diagnosed with COVID-19. Recovery for patients with severe or critical illness takes approximately 3–6 weeks. Mortality rate in critically ill patients is 49%. The total disease duration for the patients who die is 2–8 weeks. Following are the clinical findings.
   - Respiratory failure and mechanical ventilation required,
   - Sepsis/septic shock,
   - Multiple-organ failures.

Following are the ICU admission indications.

- Respiratory rate ≥30 minute^{-1},
- Dyspnoea and respiratory distress,
- PaO_2/FiO_2 <300,
- SpO_2 <90 and PaO_2 <70 despite 5 L minute^{-1} oxygen therapy,
- Increased oxygen demand during follow-up,
- Lactate >2 mmol L^{-1},
- Hypotension (systolic blood pressure (SBP) <90 mmHg, >40 mmHg drop from current SBP, mean arterial pressure (MAP) <65 mmHg, tachycardia >100 minute^{-1}),
- Patients with acute organ dysfunction development and immunosuppression such as acute kidney injury, impairment of acute liver function tests, confusion and acute bleeding diathesis,
- Elevated troponin and arrhythmia,
- Capillary perfusion disorder and the presence of skin disorders such as cutis marmaratus.

The incidence of ARDS is 35%–71% in patients diagnosed with COVID-19 with follow-up in ICU; 71% patients require non-invasive/invasive mechanical ventilation (15, 16).

Patients older than 60 years account for more than 80% of deaths. The mortality rate is 1.4% in patients without the comorbid diseases, 13.2% for those with cardiovascular disease, 9.2% for those with diabetes, 8.4% for those with hypertension, 8.0% for those with chronic respiratory disease and 7.6% for those with cancer (12).

It is reported that 53% of deaths occurred because of respiratory failure, 7% because of circulatory failure, 33% because of both respiratory and circulatory failures and 7% because of uncertain mechanisms (17). ARDS developed in 81% of patients who died, and the mortality rate of patients in need of mechanical ventilation is 94% (15, 16).

Diagnostic methods for SARS-CoV-2

Laboratory findings

In the early stages of the disease, leucocyte and procalcitonin values were normal, whereas lymphopenia was observed at the rate of 80%–83.2%. Inflammatory markers such as C-reactive protein and interleukin (IL)-6 increased. In addition, liver function tests, levels of lactate dehydrogenase, myoglobin and troponin were elevated. Elevation of D-dimer and fibrin degradation products (FDPs) is one of the parameters to be followed in the treatment because they show poor prognosis (8-10, 18).

Molecular methods

Physicians multiplied (amplification) the specific nucleic acid segment of the agent with the real-time reverse transcriptase polymerase chain reaction (rRT-PCR) method to diagnose the viruses with the genome RNA. rRT-PRC is the gold standard for similar viral infections, including COVID-19.

Samples should be taken from patients with suspected COVID-19 infection regardless of the onset of symptoms (19). The sample can be taken from the nasopharyngeal and oropharyngeal regions, sputum and lower respiratory tract (8).

The accuracy of the molecular test varies depending on the sampling location, in other words, the anatomical level of infection in the respiratory system (20).

Following are the positivity rates with rRT-PCR.

- Bronchoalveolar lavage fluid sample 93%,
- Sputum 72%,
- Nasopharyngeal samples 63%,
- Fibrobronchoscope brush biopsy 46%,
- Pharyngeal samples 32%–59%,
- Stool 29%,
- Blood 3%,
- Urine 0% (21-23).

rRT-PCR positivity in the samples taken from the nasopharyngeal and oropharyngeal regions for diagnosis of SARS was between 65% and 70% (24). It is recommended to collect the tracheal aspirate sample from intubated patients instead of a nasopharyngeal or oropharyngeal sample (20). Although the viral load peak was detected in the oropharyngeal and sputum samples 10 days after the onset of the disease in SARS, it has been seen that in COVID-19 the detection is after 6 days of onset of the disease. In addition, viral loads in the samples from sputum and nasal region were generally higher than those from the oropharynx (25, 26).

It seems more accurate to take samples from sputum or lower respiratory tract owing to the high positivity rates (8). However, sputum induction and sampling with bronchoalveolar lavage should be avoided because of the high risk of aerosolization (19, 20). Bronchoscopy can rarely be applied to intubated patients whose upper respiratory tract samples are negative and for which alternative diagnosis can be changed, which may change the way of treatment (19). Tracheal aspirate sample with less risk of aerosolization can be preferred when sampling can be performed without removing the patient from the ventilator. Because the test positivity is not 100%, the diagnosis cannot be excluded with a single negative result obtained from the nasopharyngeal and oropharyngeal regions alone (20).

In high-suspect patients, additional samples, including lower respiratory tract samples, can be taken, if possible (20). If

both samples taken at least 24 hours apart are negative and immunoglobulin (Ig) M and IgG are negative 7 days after onset, COVID-19 diagnosis can be excluded (8, 11). However, because no false-positive results are observed, a single positive result can then be used to confirm the diagnosis of COVID-19. In addition, a positive test for another respiratory virus does not exclude COVID-19 (20). Insufficient sampling, taking samples from patients in the very early stage or at a later stage as well as mishandling of the sample can result in false-negative results (11).

Table 2. Clinical significance of rRT-PCR and serological test results

Stage of the disease	rRT-PCR	IgM	IgG
Window period	–	+	–
Window period	+	–	–
Early period of infection	+	+	–
Active infection	+	+	+
Late period of infection	+	–	+
Recovery period or PCR false negative	–	+	+
Previous recovered infection	–	–	+

rRT-PCR: real-time reverse transcriptase polymerase chain reaction; Ig: immunoglobulin; PCR: polymerase chain reaction

Table 3. Thoracic CT classification for COVID-19 by the British Society of Thoracic Imaging

Pattern	Description
Classic COVID-19 (100% confidence for COVID-19)	Lower lobe predominant, peripheral predominant, multiple, bilateral* foci of GGO ± Crazy paving Peripheral consolidation** Air bronchograms Reverse halo/perilobular pattern**
Probable COVID-19 (71%–99% confidence for COVID-19)	Lower lobe predominant mix of bronchocentric and peripheral consolidation Reverse halo/perilobular pattern** GGO scarce
Indeterminate COVID-19 (<70% confidence for COVID-19)	Does not fit into definite, probable or non-COVID-19 Manifests above patterns, but the clinical context is wrong, or suggests an alternative diagnosis (e.g., an interstitial lung disease in a connective tissue disease setting)
Non-COVID-19 (70% confidence for alternative)	Lobar pneumonia Cavitating infections Tree-in-bud/centrilobular nodularity Lymphadenopathy, effusions Established pulmonary fibrosis

*>1 lesion, but could still be unilateral, usually but not universally bilateral.

**Organising pneumonia patterns.

COVID-19: coronavirus disease 2019; CT: computed tomography; GGO: ground-glass opacity

Serological methods

In cases where molecular tests are negative and COVID-19 infection is highly suspected, serological tests such as enzyme-linked immunosorbent assay or rapid antibody tests that detect IgM/IgG, can be used (Table 2) (8, 11). The sensitivity of these tests is stated as 88.66% (18).

Thoracic imaging

Direct radiographs should be performed with portable devices. Special cleaning procedures should be performed before using them on the next patient's imaging. Computed tomography (CT) scans showing abnormal findings alone are not sufficient in the diagnosis of COVID-19, and normal CT findings do not provide definite diagnosis of the presence or lack of COVID-19. Therefore, CT should not be used as the first step in COVID-19 diagnosis. CT findings of 5 patients with combined COVID-19 and influenza infections were not different from the CT findings of those with pneumonia and COVID-19, therefore, proving that CT does not play a role in imaging in the diagnosis of COVID-19, except in special clinical situations in highly suspicious and symptomatic patients (Table 3) (27, 28).

The most common CT findings were shown as ground-glass opacities, consolidation and bilateral involvement, as well as widespread and peripheral involvements (22, 29). Pleural effusion is rare (8). Further research is needed to determine the correlation of sequelae of acute lung injury caused by COVID-19 detected by CT (29). Typical CT findings were observed in 88% of all patients in the 1,014 patients suspected of suffering from COVID-19 (22). Patients may have typical CT findings even when asymptomatic (30).

Infection control and prevention

Because the disease is transmitted by droplet, standard, contact and droplet isolation should be applied during the hospitalisation of COVID-19 suspected/definitive cases (11).

Patient room

If there is no negative pressure in single rooms, patients must be observed in single rooms. If there is no isolated room, the patient should be physically placed in a separate area from patients without COVID-19. Patients suspected of suffering from COVID-19 are kept in separate rooms (13).

To prevent the risk of contamination of the equipment through medical staff the following steps should be taken.

- First, disposable materials should be preferred.
- Personal materials should not be placed in the patient room.
- Medical supplies to be used should not be taken out of the room. However, if there are materials required to be used for more than 1 patient, such as a stethoscope, they should be disinfected with 70% ethyl alcohol before each use.
- The use of a stethoscope should be minimised while assessing patients (11, 13).

Personal protective equipment

All medical staff should be trained about the use of personal protective equipment (PPE) before contact with patients with COVID-19. This includes staff who provide cleaning and utilities (13). Access to patient room should be restricted to those medical staff assigned to patients' care (11).

PPE that are required for medical staff to come into contact with COVID-19 suspected/definitive cases are as follows:

- Gloves,
- Gowns (non-sterile, preferably liquid impermeable, and long sleeved),
- Surgical/medical mask,
- N95/FFP2 mask during procedures that cause aerosolization,
- Face shield,
- Eye protection,
- Liquid soap and
- Alcohol-based hand antiseptic (11).

In cases where the integrity of the glove is impaired and noticeably contaminated, the glove should be removed, hand hygiene should be provided and new gloves should be worn (11). It should be checked by an additional trained staff to ensure that PPE's dressing and removal procedures are carried out in proper order (13). To dispose of the used PPE, 2 separate medical waste bins should be kept at the entrance of the patient room and inside the patient room (11).

Masks

Medical/surgical masks were originally recommended to sick people to prevent transmission to other people (31). The medical/surgical mask is adequate to prevent transmission by droplet and large particles of droplets; however, it is less effective in blocking small particles (<5 μm). N95/FFP2 masks on the other hand prevent the transfer of 95%–99% of the aerosol particles (20). Therefore, N95/FFP2 mask is required in situations that cause aerosolization (31). It is not recommended to use non-standard PPEs because they pose a risk to the user (13).

While transporting the patient, a medical mask must be placed on the patient, and the medical staff must be equipped with medical masks, gowns, and gloves. According to the general condition of the patient, N95/FFP2 mask and goggles should be present if there is a condition that can cause aerosolization (11).

Procedures for generating aerosol are as follows:

- Endotracheal intubation,
- Extubation,
- Open suctioning,
- Nebulisation therapy,
- Manual ventilation before intubation,
- Prone position,
- Bronchoscopy,
- Disconnecting the patient from the ventilator,
- High-flow nasal oxygen use,
- Non-invasive mechanical ventilation,
- Tracheostomy,
- Respiratory sample collection and
- Cardiopulmonary resuscitation before intubation (11, 13, 20).

It is necessary to avoid aerosol-forming procedures as much as possible (13). In cases where it should be performed, it should be carried out preferably in negative-pressure rooms and only by the necessary health personnel (11). Negative-pressure rooms prevent the spread of infectious air pathogens from room-to-room. If this is not available, an isolated single room should be used (20).

Healthcare professionals performing these procedures should replace respirators (N95/FFP2) and other PPE with surgical/medical masks. It is recommended to use video laryngoscopy instead of direct laryngoscopy for endotracheal intubation, and it should be performed by the most experienced medical specialist in airway management to minimise the number of interventions and the risk of contamination (20).

Post-exposure management

Any negligence observed in the use of PPE should be considered as an occupational health and safety risk. In case of suspected contact, a risk classification should be made according to national guidelines. Accordingly, quarantine duration and other appropriate treatments should be initiated (26).

Staff at higher risk of developing COVID-19

Because of higher mortality due to comorbidities, medical staff who are pregnant, have major chronic respiratory diseases or are immunosuppressed are at high risk. Staff who are found to be at high risk should not be assigned to COVID-19 isolation areas (13).

Novel COVID-19 pharmacological treatments and clinical research

There is no disease-specific treatment scientifically proven to be effective treating COVID-19 (13, 20). However, many randomised controlled trials are underway regarding the use of some potential drugs in therapy (32). Many of these published studies relate to the potential therapeutic effects of drugs that were previously used to treat Middle East respiratory syndrome (MERS) and SARS. Some of these studies are expected to be completed in the coming months (11).

This review provides information about some popular agents, some of which have not yet been proven in the treatment of COVID-19, some of which are used by some centres and some that are recommended by local authorities.

Hydroxychloroquine/chloroquine

Hydroxychloroquine and chloroquine are used in the treatment of malaria and autoimmune diseases. Despite positive *in vitro* data on the antiviral activity of chloroquine and hydroxychloroquine, there is insufficient evidence to publish a recommendation on their use in the treatment of COVID-19 (33). The U.S. Food and Drug Administration (FDA) issued a warning to caution against using hydroxychloroquine or chloroquine for COVID-19 outside the hospital setting or in clinical trials owing to the risk of serious cardiac rhythm problems (34). The efficacy of hydroxychloroquine and chloroquine treatment in COVID-19 has not yet been demonstrated in well-designed clinical trials (35).

Hydroxychloroquine and chloroquine can prolong the QT interval and lead to ventricular tachycardia. This risk is higher in patients with advanced cardiac comorbidity and electrolyte disturbance and in patients taking other drugs that prolong QT, such as azithromycin and fluoroquinolones (36).

Remdesivir

Remdesivir is a broad-spectrum antiviral agent against RNA viruses. It is included in the beginning viral RNA chains, causing early termination of the virus. It was used clinically in the treatment of Ebola virus infection. *In vitro* studies of remdesivir have shown effective inhibition against SARS-CoV-2 (37). Besides the *in vitro* studies, there are several ongoing clinical trials for COVID-19 therapy using different doses of remdesivir. Some of these studies are related to the safety and antiviral activity of remdesivir in patients with severe COVID-19 (38).

Remdesivir is currently under investigation for use in the treatment of COVID-19. Remdesivir is one of the promising potential treatments for COVID-19 (20, 32).

Favipiravir

Favipiravir is an RNA polymerase inhibitor licensed in Japan. It is an antiviral drug currently used in Japan to treat influenza. It has a broad spectrum of anti-RNA virus activity *in vitro*. In a recent study, *in vitro* antiviral activity of favipiravir against SARS-CoV-2 has also been demonstrated (37).

The recommended treatment dose is 1,200–1,800 mg twice daily, followed by a loading dose of 2,400–3,000 mg twice daily (32). An alternative dosage schedule is 600 mg twice daily for 4 days, followed by an oral loading dose of 1,600 mg twice daily (11).

Lopinavir/ritonavir

Lopinavir is an antiretroviral protease inhibitor that inhibits the protease activity of the coronavirus. It is used in combination with ritonavir to provide adequate lopinavir exposure in the treatment of human immunodeficiency virus infection. It was found that lopinavir shows *in vitro* activity against SARS and MERS (39). Lopinavir/ritonavir is considered a potential agent for the treatment of COVID-19 in WHO's list of research priorities of therapeutic agents (40). There are some ongoing clinical trials, but there is insufficient evidence to publish a recommendation on the use of lopinavir/ritonavir in critically ill patients with COVID-19 (20, 41).

The recommended treatment dose for lopinavir/ritonavir is 400 mg/100 mg twice daily for up to 10–14 days (8, 11).

Lopinavir/ritonavir was associated with some common side effects such as gastrointestinal intolerance, nausea, vomiting and diarrhoea. Less common but more dangerous side effects include pancreatitis, hepatotoxicity and cardiac conduction abnormalities. Lopinavir/ritonavir is a potent cytochrome P3A4 inhibitor and can interact with many drugs commonly used in critically ill patients, such as apixaban, betrixaban, clopidogrel and vitamin K antagonists.

Ribavirin

Ribavirin is an RNA polymerase inhibitor that inhibits the viral RNA-dependent RNA polymerase. Its antiviral properties against fighting MERS and SARS are well known, but for these findings to come into effect, it should be used in high doses, especially in the treatment of COVID-19. Ribavirin can cause severe haematological and liver toxicity. Haematological toxicity effect is dose dependent, so most of the ongoing ribavirin studies include combination therapy with recombinant interferon.

Because the side effects such as haemolytic anaemia and transaminase elevation are frequently seen in the therapeutic dose, the use of combining therapies is thought to be better in terms of clinical efficacy rather than individual drugs (32). In

addition, ribavirin is a teratogenic drug; its use is contraindicated in patients who are pregnant.

There is insufficient evidence to publish a recommendation on the use of ribavirin in the treatment of COVID-19 (20).

Oseltamivir
It is a neuraminidase inhibitor used in the treatment of influenza. Oseltamivir is not recommended for the treatment of COVID-19 (11, 20, 42). Oseltamivir should be given to patients with clinical findings that are compatible with influenza, as well as to patients who are positive for the influenza diagnostic test.

Umifenovir
It is an antiviral drug used in influenza treatment in Russia and China, but it is not approved for use in other countries. Umifenovir is thought to inhibit the viral entry into target cells and stimulate the immune response. A limited number of studies have been described from China, but there is no sufficient evidence to publish a recommendation on COVID-19 treatment yet (32).

Azithromycin
Azithromycin is one of the macrolide antibiotics. It inhibits RNA-dependent protein synthesis, which causes an antibacterial effect. Although a non-randomised study (36) with a small number of participants found that the combination of hydroxychloroquine and azithromycin in patients with COVID-19 is significantly related to viral load reduction or loss, there is insufficient evidence about the therapeutic effect of azithromycin on COVID-19. (20, 41). Some local guidelines recommend the combination of hydroxychloroquine and azithromycin in patients with critical illness in COVID-19. The recommended treatment dose for azithromycin is a 500-mg loading dose once daily, followed by a 250-mg dose once daily for 4 days (11).

Both azithromycin and hydroxychloroquine prolong the QT interval and may be prone to ventricular tachycardia.

Antimicrobials/antibacterial agents
If the diagnosis of COVID-19 is uncertain or if a co-infection is suspected, antibiotics showing activity against both typical and atypical respiratory pathogens can be added to the treatment for community-acquired pneumonia (43). Because the etiological agents that cause pneumonia vary according to the country where the patients live, the origin of the patient should be taken into account during the selection of the antibiotic type. Empirical antimicrobial/antibacterial agents are recommended for COVID-19 and mechanically ventilated patients with respiratory failure (20, 43).

Tocilizumab
The underlying pathophysiology of organ damage in patients with severe COVID-19 infection is thought to be due to an increased immune response and cytokine release (cytokine storm). IL-6 is thought to play a key role in irregular inflammation in the cytokine storm. Tocilizumab is a recombinant monoclonal antibody. It functions as an IL-6 receptor antagonist. Tocilizumab is already approved for the treatment of cytokine release syndrome and rheumatoid arthritis. Studies on the use of tocilizumab in COVID-19 infections include Italian anecdotes and case series from China. Some randomised controlled trials on the use of tocilizumab in patients with COVID-19 are still ongoing. The China diagnosis and treatment guideline for COVID-19 recommended a single intravenous dose of 4–8 mg kg^{-1} (maximum 400 mg) (8). Tocilizumab may increase the risk of developing other respiratory infections and tuberculosis as well.

Acetaminophen
It is well known that most patients with COVID-19 will develop fever during hospitalisation. Acetaminophen remains the best option for the treatment of fever owing to the unproven reports on ibuprofen and non-steroidal anti-inflammatory drugs but confusing the preliminary reports (20).

Corticosteroids
There is not yet sufficient evidence that corticosteroids are useful in COVID-19 treatment. Therefore, the recommendations are based on indirect evidence from critically ill patients, especially patients with ARDS. The purpose of using corticosteroids in patients with ARDS is to reduce the host inflammatory response in the lungs. However, the negative side effects of corticosteroids may outweigh this benefit. Common side effects of corticosteroids include respiratory and blood delay of viral clearance, hyperglycaemia, avascular necrosis, and psychosis.

Current evidence has reported that low-dose corticosteroid therapy does not change mortality rates but shortens the length of stay in the ICU and hospital (20). Corticosteroids are not recommended for routine use in patients with acute respiratory failure with COVID-19 (13, 20, 41). Patients with special conditions, such as the presence of septic shock or refractory shock and exacerbation of chronic obstructive pulmonary disease, will have alternative clinical indications suitable for the use of corticosteroids. Low-dose corticosteroid therapy is recommended for refractory shock. The recommended treatment dose is 200 mg day^{-1} as an infusion or intermittent doses (20).

Convalescent plasma
It is believed that administration of plasma, serum or immunoglobulin concentrates derived from the recovered patients

Table 4. Heparin prophylaxis dosage schedule

D-dimer <1,000 ng mL^{-1}	D-dimer >1,000 ng mL^{-1} or severe disease
BMI <40 kg m^{-2}: Enoxaparin 40 mg day^{-1}, once a day SC BMI >40 kg m^{-2}: Enoxaparin 40 mg day^{-1}, twice a day SC	Enoxaparin 0.5 mg kg^{-1} day^{-1}, twice a day SC
If CrCl <30 mL min^{-1}, the dose should be reduced.	
BMI: body-mass index; CrCl: creatinine clearance; SC: subcutaneous.	

may be effective in the treatment of COVID-19. Application of convalescent plasma to patients for therapeutic purposes can be defined as passive immune transfer. This potential adjunctive therapy was used in SARS and MERS. On April 13, 2020, the FDA issued guidance on the application of convalescent plasma collected from the individuals recovering from COVID-19 (44).

Fluid therapy, hemodynamic support and vaso-active agents

Because there is no direct evidence for patients with COVID-19 and septic shock, the recommendations are generally based on indirect evidence from critical patients.

Recommendations to evaluate fluid responsiveness offer the use of dynamic parameters such as skin temperature, capillary refill time and/or serum lactate measurement. It should be noted that high lactate levels may also be due to mitochondrial dysfunction, liver failure, beta-agonists, mesenteric ischaemia or epinephrine. Considering that fluid resuscitation is necessary in patients with COVID-19 and septic shock, conservative fluid therapy is recommended by guides first. The recommended fluid type for acute resuscitation of adults with COVID-19 is primarily crystalloids. Hydroxyethyl starches, gelatines, dextrans and albumin are not recommended (20).

The vaso-active agent recommended for COVID-19 and adult patients with septic shock is norepinephrine. If it is unavailable, vasopressin may be an alternative. Dopamine is no longer preferred as an alternative. If the target MAP cannot be achieved only with norepinephrine, vasopressin can be added as a second-line agent. Despite fluid resuscitation and norepinephrine administration, if cardiac dysfunction and persistent hypoperfusion still exist, it is recommended to add dobutamine instead of increasing the norepinephrine dose (20).

Despite fluid resuscitation, vasopressor support should be given in the presence of a septic shock or severe hypotension. Target MAP should be set to 65 mmHg (11, 20).

Coagulopathy management

In a relatively small single-centre study in China, the coagulation results of 183 consecutive patients with COVID 19 were retrospectively analysed. Non-survivors showed significantly higher D-dimer and FDP and longer prothrombin time and activated partial thromboplastin time than the survivors in the application (45). Disseminated intravascular coagulation appeared in most of the deaths.

Thromboembolic event is an anticipated complication in the clinical course of patients with COVID-19. Virus-induced endothelial damage, microthrombotic disease observed in sepsis or immobility-related stasis may be responsible for this specific situation (11).

The Turkish diagnosis and treatment guideline for COVID-19 typically recommends starting coagulopathy monitoring and administering heparin prophylaxis in various doses to all patients with COVID-19 (Table 4) (11).

Oxygen therapy, non-invasive support and invasive mechanical ventilation

Lung damage seen in patients with COVID-19 has unique histopathological features: cellular fibromyxoid exudates and bilateral widespread alveolar damage, desquamation of pneumocytes, pulmonary oedema and hyaline membrane formation. Lung disease associated with COVID-19 can show different dynamics than typical ARDS; some patients show significantly higher compliance than typical for shunt fractions. Despite this high compliance, clinically severe hypoxemia is observed. This can be explained by the loss of lung perifusion regulation and hypoxic vasoconstriction. Considering all these aspects, some researchers have proposed a new ventilation strategy-buying time with minimal additional damage-which is the lowest possible positive end-expiratory pressure (PEEP) and gentle ventilation (46).

The recommended threshold value of peripheral oxygen saturation to initiate oxygen supplementation is specified as 90%. Target SpO_2 is not higher than 96%. Despite conventional oxygen therapy, if acute hypoxemic respiratory failure is still present, high-flow nasal cannula (HFNC) is recommended instead of non-invasive positive pressure ventilation (NIPPV) (13, 20). If HFNC is unavailable and there is no immediate indication for endotracheal intubation, NIPPV can be used with close monitoring. There is not yet enough data to make a recommendation on the use of the helmet NIPPV compared with the mask NIPPV (20).

In invasive mechanical ventilation, it is recommended to use low tidal volume (Vt) ventilation (Vt 4-8 mL kg^{-1} estimated body weight); the purpose of the low Vt is to minimise the risk of ventilator-induced lung damage. For mechanically venti-

lated adults with COVID-19 and ARDS, it is recommended that the target plateau pressures be <30 cm. However, some aspects remain uncertain about PEEP. There are 2 different suggestions about target PEEP values. Although some researchers suggest high values as in typical ARDSs, some recent studies have suggested that high PEEP values may increase the lung damage (11, 13, 20, 47).

Prone positioning

Prone positioning reduces ventral alveolar distension and dorsal alveolar collapse, resulting in more homogeneous ventilation. This can reduce lung compression, improve perifusion and reduce the difference between dorsal and ventral transpulmonary pressure.

Prone positioning is recommended not only for patients with mechanical ventilation but also for patients who are not intubated. Recommended prone position time is 12–16 hours day^{-1} (8, 11, 13, 20).

Mesenchymal stem cell therapy

Mesenchymal stem cell (MSC) can be obtained from many tissues such as adipose tissue, bone marrow, placenta, amniotic fluid and umbilical cord, and the stem cells can be stored for use in the treatment of various diseases. Many clinical studies have demonstrated the efficacy and safety of MSC therapy. Treatment of COVID-19 mainly depends on the patient's immune system. In this disease, cytokine storm caused by the overactivated immune system results in the damage of various organs, especially the lung. Pulmonary damage formation is expected to be prevented from MSC, which has a strong cellular level of anti-inflammatory and immunomodulatory effect. Although the MSC supply source creates treatment limitation, there is no MSC treatment protocol proven in COVID-19 treatment or prophylaxis yet (48-50).

Conclusion

The COVID-19 pandemic, which has been progressing rapidly since the first case was detected in China, has caused a major crisis in the world. Rapid progress was made in diagnosing the disease. There are many ongoing clinical trials related to COVID-19 therapy. A number of randomised controlled trials are underway regarding the use of some potential drugs for therapy, but, to date, there is no treatment scientifically proven to be effective in treating COVID-19.

COVID-19 has higher levels of transmissibility and pandemic risk. The available information revealed that, given the size and scope of the pandemic, to date, there has been no scientifically proven effective medicine and vaccines against SARS-CoV-2. There is also an urgent need for further research into finding an effective medicine and vaccines for COVID-19 to prevent the occurrence of an outbreak in future and manage public health emergency of this magnitude in both the short and long terms.

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