REVIEW

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Current Methods of Treatment in Critical COVID-19 Patients

COVID-19 Kritik Hastalarında Güncel Tedavi Yaklaşımları

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ABSTRACT

A new type of coronavirus was detected in China at the end of 2019 and spread across continents in a very short time. The World Health Organization declared pandemic in March 2020 due to the virus, which is highly contagious and occurs with respiratory failure. The virus, which had serious economic consequences, made health systems inoperable with the increasing number of patients. The virus, which causes critical illness in 5% of patients, appears with severe respiratory distress and impairements in other organ systems, especially in people with additional diseases, and requires multi-disciplinary observation and treatment approaches. Our aim is to summarize current literature on Coronavirus disease 2019 in intensive care units.

Keywords: Coronavirus disease 2019, intensive care, mechanical ventilation

ÖZ

2019 yılı sonunda Çin'de ortaya çıkan ve kısa sürede kıtalar arasında yayılım gösteren yeni tip bir koronavirüs saptandı. Oldukça bulaşıcı olan ve solunum yetmezliği ile seyreden virüs nedeni ile Dünya Sağlık Örgütü Mart 2020'de pandemi ilan etti. Ciddi ekonomik sonuçlar doğuran virüs, artan hasta sayıları ile sağlık sistemlerini de çalışamaz duruma getirdi. %5 hastada kritik hastalık meydana getiren virüs, özellikle ek hastalığı olan kişilerde ciddi solunum sıkıntısı ve diğer organ sistemlerinde bozulmalar ile karşımıza çıkmakta olup, multi disipliner takip ve tedavi yaklaşımlarını gerektirmektedir. Amacımız yoğun bakımda izlenen Koronavirüs hastalığı 2019'a karşı güncel bilgileri derlemektir.

Anahtar Kelimeler: Koronavirüs hastalığı 2019, yoğun bakım, mekanik ventilasyon

Introduction

A new coronavirus, named as Severe Acute Respiratory syndrome virus-2 (SARS CoV-2), caused pandemic. By now, this novel Cov has resulted in 18 million confirmed cases and more than 600,00 deaths (1). Neither overwhelming health systems nor highly infectious virus has opened new doors for healthcare workers. In the latest World Health Organization's (WHO) surveillance report, it was informed that 20% Coronavirus disease-2019 (COVID-19) patients needed hospitalization and 2% were treated in intensive care unit (ICU) (2). Lack of knowledge obligated data sharing. After outbreak, many publications were transmitted. Our aim is to summarize information about intensive care treatment in COVID-19.

Characteristics of the Patients Treated in ICU

First case has been reported to WHO on December 31, 2019 in Wuhan, China. After cluster of pneumonia cases with unknown origin, Chinese government started to investigate the outbreak. It has been proved that the virus belongs to coronavirus family which caused two epidemics in past twenty years (3,4). After first cases in China, the new, very contagious virus spread all over the World and WHO declared pandemic in March, 2020 (5). Clinical manifestations are defined as COVID-19 disease. All age groups seem to be affected by SARS CoV-2 but severity of disease is variable. Although some cases are asymptomatic, severe and critical disease can occur in some cases. According to a report from Chinese Center for Disease Control and Prevention, incidence of mild cases is 81%, that of severe cases is 14%, and that of critical cases is 5% (Table 1) (3).

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Table 1. Laboratory findings related to negative outcomes (9,11,12)
Thrombocytopenia
Lymphopenia
Elevated ferritin, lactate dehydrogenase, D-dimer, C-reactive protein, creatine phosphokinase
Elevated liver enzymes
Serum lactate >2 mmoL/L
Elevated cardiac enzymes (e.g. troponin)
Acute kidney injury

Classification of COVID-19 Disease (3)

Asymptomatic: No clinical symptoms, COVID-19 polymerase chain reaction (PCR) is positive (1% of cases).

Mild: Patients have upper respiratory tract infection symptoms (fever, cough, myalgia etc.), with/without pneumonia development.

Severe: Dyspnea, respiratory frequency ⩾30/min, blood oxygen saturation ⩽93%, PaO_2/FiO_2 <300 mmHg, and/or lung infiltrates >50% within 24 to 48 hours.

Critical: Multi-organ dysfunction/failure, septic shock.

Restricted health sources necessitate reasonable usage of all resources. After exposure to virus, symptoms usually start within 4-5 days (6). All patients should be carefully examined for hospitalization and intensive care. Viral pneumonia can cause acute respiratory distress that leads to mortality and morbidity. Real time PCR test should be performed for diagnosis. Meanwhile, all the patients who have respiratory tract infection symptoms, for example, cough, fever, difficulty breathing, fatigue and myalgia, have a potential for COVID-19 .

ICU administration was 26%, ICU mortality was 31% and 59% of patients treated in ICU had comorbidities. The most common comorbidity was cardiovascular disease, followed by hypertension and diabetes mellitus. In Italy, 14. 2% of COVID-19 patients have died and mortality rate is higher in the elderly and those with comorbidities (7). In the United States of America, mortality rate is 3.2% and 90% of patients treated in hospital have one underlying medical condition (most frequently hypertension, obesity, cardiovascular diseases metabolic diseases and chronic lung diseases) (8). According to the latest Turkish Ministry of Health COVID-19 guideline, patients who have symptoms below should be evaluated for critical care (Table 2).

Table 2. Suspected ICU admission
Dyspnea and respiratory distress
Respiratory rate ⩾30/minute
PaO_2/FiO_2<300 mmHg
Increase in O_2 demand
Despite 5 L/minute O_2 PaO_2<70 mmHg, SpO_2 <90%
Hypotension[a]
Hypoperfusion
Tachycardia (heart rate >100/minute)
Acute organ failure
Patients with immunosuppression
Arrhythmia
Macrophage activation syndrome
>2 points increase in SOFA[b] score
[a]: SOFA: Sequential organ failure assessment, [b]: SBP <90 mmHg, MBP <65 mmHg, drop off 40 mmHg from usual ICU: Intensive care unit, SOFA: Sequential organ failure assessment

2. Critical Care Steps

COVID-19 can cause devastating results by Acute Respiratory Distress syndrome (ARDS), viral sepsis and hyper inflammatory syndrome. In severe cases, it should be carefully handled. COVID-19 treatment can be grouped as anti-viral therapies, immunmodulation and general support.

Recently, in a meta-analysis, nosocomial transmission of SARS CoV-2 is reported as 44% (9). In daily practice, various airborne factors are formed, which plays a major role in SARS CoV-2 transmission (e.g. endotracheal intubation, bronchoscopy, non-invasive mechanical ventilation, HFNC oxygen, open aspiration of mucus, nebulized drug application, manual ventilation, prone positioning, tracheostomy, cardiopulmonary resuscitation). Patients should be treated in negative pressure rooms to prevent spread of airborne particles if possible. In the lack of negative pressure rooms, isolated areas must be planned and increased patient numbers of COVID-19 obligated to cohorts (10). Viral exposure to health care providers can be decreased by using checklists before daily visits of patients.

Common complications of COVID-19 include acute respiratory distress, sepsis and septic shock, acute renal injury, cardiac injury (e.g. arrythmia, pericarditis, myocarditis, pericardial effusion) and hepatic dysfunction (11,12,13). Patients should be monitored carefully. Diagnostic tests should be performed to enlighten complications. To determine variance, daily ECG follow-up should be considered in patients who take medication that cause prolonged QT interval. Invasive arterial monitoring is determined to both blood gas samples and close blood pressure pursuit. Because of common usage of vasoactive drugs and fluids, central venous access should be applied. Current knowledge of hemodynamic approach is identical to latest sepsis guidelines.

During SARS CoV-2 infection, hypoxemic respiratory failure occurs in 19% of patients (6). To control hypoxemia, most cases require intubation and invasive mechanical ventilation. Up to this point, standard treatment therapies have not been designed.

Healthcare associated infections have been reported at the

rate of 44.5% in COVID-19. Longer length of ICU and hospital stay and higher mortality rate have been found to be related to HAI. In this paper, multidrug-resistant *Acinetobacter baumanii* has been isolated most commonly (9). According to current knowledge, HAI is more frequent in SARS Cov-2 patients (14). Deficiency in adaptation to bundles, exhausted medical staff, insufficient medical equipment, and high rate of intubated patients may bring on higher HAI incidence.

2.a Respiratory Support

Recent reports showed that 40-80% of patients required oxygen support, 2.5-5% required intubation and the prevalence of hypoxemic respiratory failure was 19% (11,15). Patients with underlying comorbidities, obesity, and smoking develop respiratory failure more frequently. WHO advises target SpO_2>90-92%, in pregnant patients as >92% (16).

According to surviving sepsis campaign, mechanically ventilated COVID-19 patients should be treated like acute respiratory distress syndrome (10). Nonetheless, Gattinoni reported that L type and H types of COVID-19 pneumonia were defined. According to this report, in L type, at the beginning of illness, low elastance, low ventilation/perfusion ratio, low lung weight, low lung recruitability and near normal compliance were described. In H type, high elastance, high right to left shunt, and high lung weight were observed (17). Following L type, clinics of patients can improve or worsen. Increased transmural pressure shifts by high respiratory drive may cause vascular oedema. Occurrence of dyspnea has been accused for clinical worsening. This phenomenon is called Patient self-inflicted lung injury (P-SILI) (18). Early intubation was suggested to reduce P-SILI (19,20). L type cases can reply to conventional oxygen therapies which include nasal cannula, high flow nasal cannula (HFNC) and non-invasive mechanical ventilation (NIV) support, although Actinon remarked this benefit as "questionable". In the recent paper, L type intubated patients should be ventilated with higher tidal volumes (<6 mL/kg). Prone positioning is defined only as rescue maneuver and high levels of positive end expiratory pressure (PEEP) (>8-10 cmH_2O) should be avoided because of low recruitability and hemodynamical side effects (17).

In literature, HFNC is associated with lower mortality rate, decreased ICU administration and decreased reintubation (21,22). Potential benefits of HFNC are high patient consistency, stable FiO_2 and reduced dead space. Surviving sepsis campaign suggests HFNC in patients unresponsive to supplemental oxygen and WHO recommends the usage of HFNC in selected patients (10,23). ROX index can be beneficial to diagnose failed HFNC (24). NIV can be preferred in patients with cardiogenic pulmonary oedema and chronic obstructive pulmonary disease. In the presence of hypercapnia, FNC is not recommended. Both HFNC and NIV could cause airborne transmission of SARS CoV-2, until the spread of virus is still undetermined (25). To define excessive transpulmonary pressure swings in spontaneous breathing patients, usage of work of breath and transpulmonary pressure measurement and lung imagining with computerized tomography or ultrasound can be beneficial. Both NIV and HFNC should be closely monitored. Up to this point, no certain timing for intubation has been settled. Non-uniform characteristic of disease should be kept in mind. Delayed intubation can cause clinical worsening. Stigmas of respiratory failure are mentioned in Table 3 (26,27).

In 2012, ARDS was defined by Berlin criteria (Table 4, the Berlin definition of ARDS) (28). In the light of current information, COVID-19 patients developing ARDS should be treated according to lung protective ventilatory interventions. Both volume and pressure controlled ventilatory modes can be applied. Tidal volume target should be 4-8 mL/kg of predicted body weight, plateau pressure should be below 30 cmH_2O, peep titration should be applied (Table 5, protective ventilatory strategies) (29). Despite lack of certain data about driving pressure, it can be useful for PEEP titration) (29). Neuromuscular blockade and prone positioning should be applied to patients with $PaO_2/FiO_2 \leqslant$ 150 mmHg (30). Prone positioning could improve oxygenation in mild and severe cases and should last more than 12 hours (31,32). There are few ongoing studies about extracorporeal membrane oxygenation (ECMO). According to extracorporeal life support organization COVID-19 Interim Guideline, patients should be unresponsive

Table 3. Respiratory failure indicators

Increased work of breath,
Rapid clinical worsening
Hypoxemia despite maximal oxygen support[a]
Hyper carbic respiratory failure
HFNC flow demand >40/L and FiO_2>0.6
Hemodynamic instability

[a]: Nasal cannula demand >6/, non-breather mask demand>10/L, HFNC: High flow nasal cannula

Table 4. The Berlin definition of ARDS

The Berlin definition of ARDS	
On set	The presence within 7 days of a known clinical insult, new or worsening respiratory symptoms
Chest imagining	Bilateral opacities not fully explained by heart failure or volume overload
Oxygenation	**Mild:** 200 mmHg<$PaO_2/FiO_2 \leqslant$300 mmHg with CPAP or PEEP ⩾5 cmH_2O
	Moderate: 100 mmHg< $PaO_2/FiO_2 \leqslant$200 mmHg with PEEP ⩾5 cmH_2O
	Severe: $PaO_2/FiO_2 \leqslant$100 mmHg with PEEP ⩾5 cmH_2O

ARDS: Acute Respiratory Distress syndrome, PEEP: Pasitive and expiratory pressure

to conventional ARDS therapies involving prone positioning. Veno-arterial ECMO should be applied to patients who have cardiac complications. Contraindications and indications for ECMO in SARS CoV-2 infection are similar and defined in Table 6 and Table 7. In overwhelmed capacities of ECMO and health care systems, triage becomes essential (32). Despite the absence of precise information, inhaled Nitric oxide (i NO) could dilate pulmonary vessels, may improve oxygenation and ventilation perfusion ratio, and has immunomodulatory effects. Routine usage of i NO is not recommended (32,33,34).

Table 5. Protective ventilatory strategies

Tidal volume	6 mL/kg PBW (range: 4-8 mL/kg PBW)
Plateau pressure	Less than 30 cm H_2O
Respiratory rate	Up to 35 breaths per minute, goal of pH 7.30-7.45 but may allow permissive hypercapnia with a pH >7.15
PEEP	Initiate at ⩾5 cm H_2O Titrate according to ARDS set lower PEEP/higher FiO_2 table
Oxygenation target	Titrate FiO_2 to: PaO_2 55-80 mmHg, SpO_2 88-95%

PBW: Predicted body weight, PEEP: Positive end expiratory pressure, ARDS: Acute Respiratory Distress syndrome

Table 6. Contraindications for ECMO in SARS CoV-2 infection

Relative contraindications	Absolute contraindications
Age ⩾65 years	Advanced age
Obesity BMI ⩾40 kg/m²	Clinical Frailty scale category ⩾3
Immunodeficiency	Mechanical ventilation>10 days
Lack of testamentary guardian	Significant underlying comorbidities[b]
Advanced chronic systolic heart failure	Severe acute neurologic injury, e.g., anoxic, stroke
High dose vasopressor requirement[a]	Uncontrolled bleeding
-	Contraindications to anticoagulation
-	Inability to accept blood products

[a]: Not under consideration for VA or V-VA ECMO, [b]: Cirrhosis, dementia, disseminated malignancy, Advanced lung disease, Uncontrolled diabetes with chronic end-organ dysfunction, severe deconditioning, protein-energy malnutrition, severe peripheral vascular disease, severe multiple organ failure, ECMO: Extracorporeal membrane oxygenation, SARS CoV-2: Severe Acute Respiratory syndrome virus-2, BMI: Body mass index

Table 7. Indications for ECMO in SARS CoV-2 infection

PaO_2/FiO_2<60 mmHg 6 hours[a]
PaO_2/FiO_2<50 mmHg 5 hours[a]
Ph <7.20 and $PaCO_2$>80 mmHg for >6 hours[a]

[a]: Without contraindications for ECMO, ECMO: Extracorporeal membrane oxygenation, SARS CoV-2: Severe Acute Respiratory syndrome virus-2

2b. COVID-19 Specific Treatment and Cytokine Storm Syndrome

Currently, no specific antiviral treatment is recommended. So far, lopinavir/ritonavir, hydroxychloroquine, remdesivir, umifenovir, favipiravir and many other drugs have been used. Consensus on standard treatment has not been established. Many ongoing trials may enlighten this issue.

Remdesivir has shown beneficial effects in patients of varying initial severity. A reduction in mean time for recovery resulted in higher probabilities of recovery on the 8-level sequential scale at day 15 and a statistically non-significant reduction in mortality in mild to severe COVID-19 patients. It also resulted in a statistically insignificant reduction in clinical recovery time with no effect on mortality rate in severe COVID-19 patients (35).

According to the latest Turkish Ministry of Health COVID-19 guideline, patients developing pneumonia should be treated with hydroxychloroquine with/or favipiravir (Figure 1). Current knowledge promotes early administration of antiviral therapies. If patients worsen under hydroxychloroquine, favipiravir should be added to the treatment. Multidrug and electrolyte imbalance can cause prolonged Qt and sudden cardiac death in intensive care unit. Other risk factors for prolonged Qt are hepatic and renal dysfunction, and sepsis. Drug interactions must be reviewed (36). All patients should be evaluated with electrocardiogram before hydroxychloroquine. During pregnancy, lopinavir/ritonavir is recommended for the treatment. Any potential benefits have been shown (37).

Defining superinfections and coinfections in COVID-19 is problematic. Both WHO and Surviving Sepsis Campaign recommend empiric antimicrobials in mechanically ventilated COVID-19 patients. Antimicrobial therapies should be daily evaluated for de-escalation, duration and appropriateness (10).

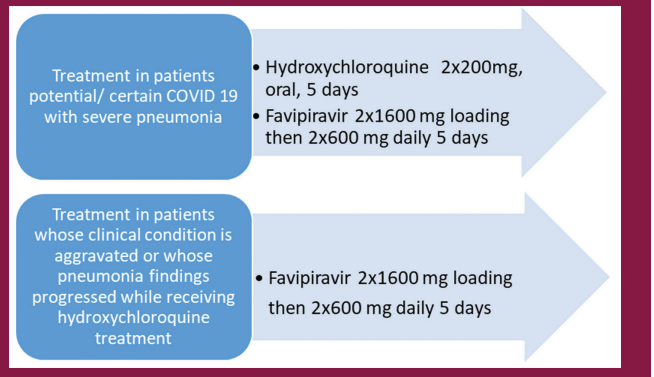

Figure 1. COVID-19 Treatment in adult patients (Adapted form: T.C. Sağlık Bakanlığı COVID-19 [SARS-CoV-2 Enfeksiyonu) (Bilim Kurulu Çalışması) Erişkin Hasta Tedavisi.; 2020].

SARS CoV-2: Severe Acute Respiratory syndrome virus-2, COVID-19: Coronavirus disease-2019

Table 8. COVID-19 immune (convalescent) plasma clinical use criteria
Fever >7 days
In 24-48 hours >50% infiltration increase in lung imaging
Respiratory rate >30/min
PaO_2/FiO_2<300 mmHg
Oxygen saturation <90%
Mechanical ventilation support
Two or more points increase in SOFA
Stigmas for rapid clinical worsening
Vasoactive drug administration
COVID-19: Coronavirus disease-2019, SOFA: Sequential organ failure assessment

Table 9. Thromboprophylaxis		
D-Dimer <1000ng/mL	**BMI <40 kg/m²**	**BMI >40 kg/m²**
CrCL ⩾30 mL/min	Enoxaparin 40 mg/day	Enoxaparin 40 mg/day twice
CrCL <30 mL/min	Standard heparin 5.000 U 2 or 3 times a day	50% of low-molecular weight heparin dosage
D-dimer ⩾1.000ng/mL	**BMI <40 kg/m²**	**BMI >40 kg/m²**
CrCL ⩾30 mL/min	Enoxaparin 0.5 mg/kg day	-
CrCL <30 mL/min	Standard heparin 5.000 U 2 or 3 times a day	-
BMI: Body mass index, CrCL: Creatinine clearance		

In recent years, convalescent plasma has been used to treat viral infections. In Mair-Jenkins metanalysis, convalescent plasma can reduce mortality by passive immunoterapy (38). At the beginning, in China, convalescent plasma has been given in small groups of COVID-19 patients and clinical improvement has been reported (39). Because of limited donor pool, efficiency in COVID-19 and effective dosage clinical approach remains still in dark. In cases with immunoglobulin A deficiency, cytokine storm syndrome and elongated SARS CoV-2 infection, convalescent plasma is not recommended (40). Indications of convalescent plasma are mentioned in Table 8 (40).

During viral infections, exaggerated immune response can cause endothelial damage or dysfunction and tissue edema and shock. Hyperinflammatory response can trigger multiorgan failure and causes mortality. Cytokine storm is thought as a major underlying clinical feature in severe cases. In a recent paper, IL-6 and IL-2 receptor levels have been found to be significantly higher in severe COVID-19 cases. In contrast, there were no statistically significant differences in serum tumor necrosis factor alpha (TNF-a), IL-1, IL-8, or IL-10 (41). In further investigations, higher concentrations of granulocyte colony stimulating factor, interferon-inducible protein 10, monocyte chemoattractant protein-1 and TNF-a were found in patients who required admission into an intensive care unit (42,43). Due to cytokine storm, ARDS and macrophage activation syndrome (MAS) may occur. Clinical and laboratory features of MAS are persistent fever, high/increasing CRP, high levels of ferritin (>700 mg/L), elevated D-dimer, lymphopenia, thrombocytopenia and elevated liver enzymes (44).

In RECOVERY trial, hospitalized patients receiving dexamethasone up to 10 days had a lower 28 mortality rate (45). In the latest treatment guideline of WHO, corticosteroid usage has been recommended. Corticosteroids can decrease mortality in severe and critical COVID-19 patients. Daily 6 mg dexamethasone or equivalent dosage is given intravenously or orally. Duration should be 7-10 days and glucose levels should be monitorized (46). Turkish Ministry of Health recommends the usage of 6 mg/day dexamethasone or 0.5-1 mg/kg prednisolone or equivalent methylprednisolone up to 10 days in patients who need oxygen therapy. Considering the risk factors of the patient, a higher dose of glucocorticoid (pulse, 250 mg/day methyl prednisolone) may be decided in patients whose need for oxygen has increased within 24 hours despite the treatment or whose acute phase response has increased (44).

In cases unresponsive to glucocorticoid, tocilizumab, which inhibits IL-6 or anakinra, IL-1 inhibitor, can reduce inflammatory response. Increased risk for infections should be kept in mind in those patients. Clinical response should be monitored with CRP, IL-6, fever and O_2 demand. Contraindications for toculizumab are pregnancy, neutropenia, active infections (tuberculosis, hepatitis B and C), allergy and hypersensitivity (47). Tocilizumab 8 mg/kg dos can be applied. In severe cases, when initial dose of 400 mg is administered, the dose can be repeated in the form of 200-400 mg within 12-24 hours according to the changes in values in clinical and laboratory findings. After treatment, patients should be carefully monitored for complications like infections, gastrointestinal perforation and ARDS like syndrome (44).

2c. Thromboprophylaxis

Although thromboprophylaxis is not a specific treatment for COVID-19, it is widely thought to be important considering the pathophysiology of the disease. Microvascular thrombosis may develop due to increased endothelial damage in COVID-19 patients. Increased fibrinogen and D-dimer levels and hypercoagulability also increase severity of disease. These patients are thought to have a high risk of developing pulmonary embolism. Therefore, low molecular weight heparin should be administered to every patient at prophylactic dose and to patients with high clinical thrombosis at the therapeutic dose except thrombocytopenic patients. At active hemorrhage and

thrombocytopenia states, intermittent pneumatic compression can be beneficial. In case of heparin induced thrombocytopenia, thromboprophylaxis can be ensured by fondaparinux. Without any drug interactions, oral anticoagulation is kept similiar (44). Thromboprophylaxis according to the body weight and renal function is summarized in Table 9.

Conclusion

Fight against pandemic still goes ahead. Although specific treatment has not been found, ongoing

trials and development of COVID-19 vaccine may enlighten our ways to a non-pandemic COVID-19 world. Until that day, the prevention of COVID-19 will play a major role.

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