Review Article

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Management of COVID-19 in intensive care units

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Abstract:

Coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 had already affected the whole world before the pandemic could be prevented and resulted in challenges to the development of an efficacious drug treatment. Intensive care admission is lower than the SARS and Middle East respiratory syndrome-CoV pandemics, although the rapid development and simultaneous contagion in society resulted in feasibility problems associated with intensive care units. The disease results in severe pneumonia, acute respiratory distress syndrome, cardiogenic shock, or multiorgan failure, causing mainly lung and myocardial damage. Decreasing the viral load and providing supportive treatment for organ failures are the main principles of treatment in such patients. One should take care to decrease the risk of transmission of the disease to the stuff providing care and treating patients in the intensive care unit. Precautions should be applied to the greatest extent possible, especially during aerosol-producing interventions.

Keywords:

Coronavirus disease-2019, intensive care unit, respiratory failure

Introduction

Coronavirus disease-2019 (COVID-19) had spread to more than 80 countries around the world by the end of March 2020 and affected over 1.4 million people, causing more than 80,000 deaths.[1] Mechanical ventilation and intensive care were required in 5%–10% of cases.[2] Although many guidelines have been published to guide infection control in the general population, there are only limited guidelines directed to the management of critical patients. This review is intended to be used by clinicians for the follow-up of patients in intensive care units.

Admission Criteria's for Intensive Care Unit

Patients with severe COVID-19 disease should be followed up in intensive care units. There is a male predominance in cases with severe forms of the disease (male/female: 2/1). Advanced age and the presence of comorbid diseases are the risk factors for the development of a severe disease course, with the most frequently seen comorbid diseases being hypertension and diabetes mellitus.[3] Severe disease may manifest as severe respiratory tract infection (severe pneumonia), acute respiratory distress syndrome (ARDS), sepsis, septic shock, myocarditis, arrhythmia, cardiogenic shock, or multiorgan failure. In a patient with fever and signs of respiratory tract infection, severe pneumonia is defined as respiration rate over 30, signs of respiratory distress (use of auxiliary respiratory muscles, paradoxical respiration, etc.),

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oxygen saturation below 90% at room air, or PaO_2/FiO_2 below 300. Respiratory failure frequently takes the form of hypoxemic respiratory failure, whereas hypercapnia is rare. In addition, decompensated cardiac failure and exacerbations of chronic lung disease may accompany in such patients.[4] If any respiratory distress developing in the past 1 week cannot be explained by cardiac failure or volume excess, there are bilateral opacities other than pleural effusion, collapse, and nodules in radiological appearance, and if the PaO_2/FiO_2 ratio is below 300, the patient is defined as having ARDS.[5] The staging of ARDS is as follows, according to the Berlin classification:

- Mild ARDS: 200 < PaO_2/FiO_2 ≤300 (positive end-expiratory pressure[PEEP] or CPAP ≥5 cmH_2O)
- Moderate ARDS: 100 < PaO_2/FiO_2 ≤ 200 (PEEP or CPAP ≥5 cmH_2O)
- Severe ARDS: PaO_2/FiO_2 ≤ 100 (PEEP or CPAP ≥5 cmH_2O).

Signs of organ failure accompanying a suspicious or proven infection are defined as sepsis. The main signs of organ failure are changes in consciousness, dyspnea, desaturation, decreased urinary output, increased creatinine, increased heart rate, weak pulse, cold extremities or low blood pressure, signs of coagulopathy, thrombocytopenia, acidosis, increased lactate level, or hyperbilirubinemia. The Sequential Organ Failure Assessment (SOFA) score helps in the definition of organ failure [Table 1]. SOFA (qSOFA) can be used to make a rapid diagnosis in a bedside evaluation in the emergency room and wards. The criteria of qSOFA are altered mental status, a respiratory rate of 22 or higher, and a systolic blood pressure of < 100. Each criterion receives 1 point. Hypotension resistant to fluid treatment, a requirement of vasopressors, and a lactate level above 2 mmol/L are defined as septic shock in such patients.[6,7] It should be kept in mind that myocarditis and associated arrhythmia and cardiogenic shock may accompany.

Infection Control in the Intensive Care Unit

According to the Chinese Center for Disease Control and Prevention data, 3.8% of the total cases were healthcare workers and 14.8% of those cases were defined as severe.[8] As of March 15, 2020, 2026 healthcare workers had been diagnosed with the disease in Italy.[3] These findings indicate a serious risk of contamination among healthcare workers. The risk is especially increased among stuff working in intensive care units where aerosol-producing interventions are performed usually. Protecting healthcare workers should be prioritized in intensive care units. All healthcare workers should be educated in hand hygiene and the wearing and removal of personal protective equipment. Waste management should be planned. Patients should be kept in isolated rooms, and personal protective equipment should be changed outside the room. Medical supplies and drugs should be available in the room and should not be taken outside the room. During interventions, a least number of healthcare professional should be inside the room. Personal protective equipment such as N95/FFP2 or FFP3 respirators, gloves, face shields or large safety googles, and gowns should be worn during aerosol-producing interventions, since surgical masks offer no protection against particles smaller than 5 μm. Aerosol-producing interventions should be carried out in negative pressure rooms, where possible, and air change ratio should be adjusted to 160 L/min/patient or 12 air changes/h. Portable HEPA filters should be used if no negative pressure room is available.[3]

Aerosol-producing interventions include:

- Endotracheal intubations
- Bronchoscopy
- Aspiration
- Nebulizer treatment
- Ambu ventilation of the patient
- Prone positioning
- Disconnecting ventilator circuits
- Noninvasive mechanical ventilation (NIV)
- High-flow nasal oxygen (HFNO) treatment
- Cardiopulmonary resuscitation
- Tracheostomy.

Endotracheal intubation should be performed carefully by the most experienced healthcare professional on the team. Standard monitorization, intravenous (IV) vascular access, and drugs, ventilators, and aspirators should be checked. Mechanical ventilator settings should be controlled before the operation, and a closed aspiration set, heating humidifier filter or active heat and humidifier filter, and hydrophobic virus/bacteria filter

Table 1: The Sequential Organ Failure Assessment score

	1	2	3	4
PaO_2/FiO_2 (mmHg)	<400	<300	<200	<100
Hypotension*	MAP <70	Dobutamine or dopamine ≤5 mcg/kg/min	Dopamine >5 or noradrenalin ≤0.1 mcg/kg/min	Dopamine >15 or noradrenaline >0.1 mcg/kg/min
Creatinine (mg/dl) or urine output (ml/day)	1.2-1.9	2-3.4	3.5-4.9 or <500	>5 or <200
Platelets (×10^3/mm^3)	<150	<100	<50	<20
Bilirubin (mg/dl)	1.2-1.9	2.0-5.9	6-12	>12
GCS	13-14	10-12	6-9	<6

*Vasoactive medications administered for at least 1 h. MAP: Mean arterial pressure, GCS: Glasgow Coma Scale

should be attached to the mechanical ventilator circuit, while ventilator is kept closed but ready for use. A rapid induction anesthesia should be planned, and a trained assistant should be ready to cricoid force. The rapid induction anesthesia should be modified if the alveolar–arterial oxygen gradient of the patient is high, and if the patient cannot tolerate 30 s of apnea, or if neuromuscular blocking agents are contraindicated. Preoxygenation with 100% oxygen for 5 min is recommended since the risk of aerosol production is high in manual ventilation with an Ambu ventilation. In need of Ambu ventilation, an additional bacterial-viral filter should be connected between the expiratory valve of the Ambu and mask. Ambu ventilation should be performed by two persons, two-handed; the patient should be ventilated slowly and in small tidal volumes. Video laryngoscopy is recommended for intubation to decrease the number of interventions and to limit exposure.[9] The cuff should immediately be inflated after the endotracheal tube is introduced. Mechanical ventilation should be started after the circuit is connected. The tightness of the connection points of the circuit should be checked to prevent any unwanted detachment. The endotracheal tube should be clamped in patients with no spontaneous ventilation if it is necessary to disrupt the circuit continuity.[10] One should refrain from using end-tidal capnography for the confirmation of the placement of the tube. The placement of the tube should be confirmed through auscultation, since the risk of droplet transmission is increased during the connection and disconnection of the apparatus. Open airway aspiration should be avoided before, during, and after intubation.

Laboratory Diagnosis and Samples

All intensive care patients with respiratory tract infections should be treated as suspicious. The incubation period of the pathogen is 5 days, and while viral transmission can vary depending on the anatomical location involved, a lower respiratory tract sample should be taken from intubated adult. Tracheal aspiration samples should be preferred over bronchial lavage or bronchoalveolar lavage. Real-time reverse transcription-polymerase chain reaction is the gold standard method, offering a high positive predictive value and a low negative predictive value (47%). A single sample from the upper respiratory tract is insufficient to exclude severe acute respiratory syndrome-coronavirus 2 infection. Repeated samples should be obtained from the lower respiratory tract in an intubated patient. It should be kept in mind that the detection of other respiratory tract viruses does not exclude a diagnosis of COVID-19.[3]

Whole blood count, lymphocyte count, C-reactive protein (CRP), procalcitonin, renal and liver parameters, cardiac enzymes, lactate dehydrogenase, coagulation parameters, fibrinogen, D-dimer, ferritin, arterial blood gases, lactate levels, and a chest X-ray should be ordered, and the results were evaluated.

Monitorization

A central venous catheter, inserted preferably into the jugular vein, a urinary catheter, and a nasogastric tube should be placed upon admission to the intensive care unit to decrease the number of entries to the patient's room. Noninvasive, and if available, invasive arterial pressure monitorization, and monitorization of oxygen saturation, electrocardiogram (ECG), and urine outputs should be carried out. The corrected QT interval should be measured by ECG for the follow-up of any adverse effects of the drugs used. Continuous central venous pressure (CVP) monitorization, invasive hemodynamic monitorization, and continuous temperature monitorization are optional.

Hemodynamic Support

The prevalence of shock in adult patients with COVID-19 can vary considerably, depending on the variability of the population studied, severity of the disease, and definition of shock (1%–35%). The rate of shock was detected to be 1.1% in a study performed in China involving 1099 patients.[11] The incidence of shock has been observed at 20%–35% in studies of patients in intensive care units.[12,13] Data on the risk factors for shock are limited; however, advanced age, diabetes mellitus, cardiovascular system comorbidities, decreased lymphocyte count, and increased level of D-dimer have all been found to carry a risk of cardiac damage and death.[12,14]

Fluid Treatment

Balanced solutions should be selected for fluid treatment in intensive care patients in the presence of hypotension or hypovolemia at admission. The amount of infusion should be adjusted according to the perfusion targets (urine output 0.5 ml/kg/h, lactate <2 mmol/dl, and capillary filling time) rather than on static parameters (CVP, mean arterial pressure, or appropriate for early targeted treatment such as 30 ml/kg). Passive leg raising test and pulse pressure variation directed therapy were found to be superior to other methods. A positive fluid balance might be accepted during the first 48 h until the patient is stable, since the chance of developing renal failure is high in the early period. One should remember, however, that conservative fluid management decreases the number of ventilator days and the number of days of intensive care. Hydroxyethyl starch, gelatins, and dextran should not be used due to their adverse effects and the cost-effectiveness. There is a lack of evidence supporting albumin use. Balanced-buffered crystalloid fluids should be preferred.[3]

Vasoactive Agents

The first-line drug should be norepinephrine, as a vasopressor agent, in patients with continuing hypotension, despite the appropriate fluid replacement. The administration of the drug should be started in a dose of 0.05–0.1 mcg/kg/min and tittered so that the mean arterial pressure is above 60–65 mmHg. The risk of arrhythmia should be remembered in case when the target mean arterial pressure is kept higher. Vasopressin or adrenaline should be selected when noradrenaline is unavailable. It should be kept in mind that vasopressin treatment may lead to digital ischemia and that adrenalin infusion may result in elevated lactate levels. Vasopressin is also recommended as a second-line treatment when high-dose noradrenaline is required. However, dopamine in a dose of 4–10 mcg/kg/min may be added to the treatment if vasopressin is unavailable and if the patient has no tachycardia. Dobutamine should be added to the treatment and be titrated in patients with cardiac dysfunction and persistent hypotension with no tachycardia.[3]

Steroids

Low-dose corticosteroids (hydrocortisone 200 mg/day, methylprednisolone 40 mg/day, or dexamethasone 7.5 mg/day) in divided doses or as a 24-h infusion can be started in patients with refractory shock. In refractory shock, corticosteroids have been demonstrated to shorten the length of stay in the intensive care unit, although no difference in mortality has been reported. However, there is insufficient evidence supporting their use in patients with COVID-19 with respiratory failure alone.[3]

Management of Respiratory Failure

The prevalence of respiratory failure was found to be 19% in patients with COVID-19. NIV and invasive mechanical ventilation were applied in 5%–14% and 2%–12% of the patients, respectively, according to the latest data from China.[11,13,15]

The observation of different compliance and shunt fraction when compared to ARDS in intubated patients with COVID-19 pneumonia suggests different mechanisms of hypoxia in those patients. Different thoracic computed tomographic findings have been observed in patients with the same PaO_2/FiO_2 ratio. The starting symptoms and radiological findings are uncorrelated with ARDS–Berlin criteria. Hypoxemia was explained by Gattinoni *et al*. using three different mechanisms, being the dysregulation of pulmonary perfusion, microthrombi in lung parenchyma, and noncardiogenic pulmonary hypoxemia (similar to ARDS), and the patients were divided into two phenotypes as H and L. The mechanism was explained by the dysregulation of pulmonary perfusion and microthrombi in patients with phenotype L, while the elastance and ventilation–perfusion ratio of these patients were observed to be low, and the patients were found irresponsive to recruitment, prone positioning, and high PEEP. The application of high PEEP, which may affect right heart venous filling in such patients, can also increase the vasoactive agent requirement, since the shunt fraction is high in this group of patients. On the other hand, the elastance was found to be high and compliance low in patients with phenotype H. Recruitment, prone positioning, and high PEEP were observed to exert the positive effects such as ARDS in those patients. A crossover from phenotype L to phenotype H has been reported in the advanced stages of the disease.[16,17]

The predictive factors in the management of respiratory failure of the patients are response to oxygen treatment and decreased respiratory workload. Oxygen treatment should be started when saturation is below 90% at room air and should be increased to maintain a target saturation of between 90%–95%. The target value should be above 92% in a pregnant patient. Prone positioning has been demonstrated to have positive effects on hypoxia in nonintubated patients with lung involvement. HFNO therapy and NIV support can be applied in selected cases of hypoxemic respiratory failure. These patients should be followed up closely for worsening and the need for invasive mechanical ventilation within the 1st hour. Refractory hypoxemia, tachypnea, and tidal volume over 9 ml/ideal body weight are the signs of NIV failure. NIV should be avoided in patients who cannot expectorate, with hemodynamic instability, multiorgan failure, or altered mental status.[3,4,17] A helmet-type mask should be preferred in cases of application of noninvasive ventilation, and patients should be monitored closely for clinical improvement within 1–2 h.

Patients should be intubated if the present noninvasive oxygen treatment methods fail to increase oxygen saturation although FiO_2 is higher than 50% and the respiratory workload is severe. The volume control mode should be preferred to overcome the risk of volume trauma. Mechanical ventilation should be started with an initial tidal volume of 6 ml/kg and a PEEP of 8 cmH_2O, and the tidal volume (4–8 ml/kg), respiratory rate, and PEEP changes should be made according to the target values. PEEP titration can be performed according to the ARDS network table [Table 2] at the bedside for the physician's time management.[3,4,17]

The target values are as follows:

- $P_{plato} < 30$ cmH_2O
- pH > 7.30

Table 2: Acute Respiratory Failure Network (ARDS-net) PEEP Table

Lower PEEP/Higher FiO_2														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24
Higher PEEP/Lower FiO_2														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5-0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22-24	

PEEP: Positive end-expiratory pressure

- $PaO_2 > 60$ mmHg
- $SaO_2 > 90\%$
- Driving pressure (Pplato –PEEP) < 15cmH_2O.

Gattinoni *et al*. suggested adjusting the tidal volume of the patients to maintain the driving pressure below 15 cmH_2O by keeping tidal volume at 4–8 ml/kg. Patients with a static compliance above 40 have been reported to be compatible with the L phenotype and did not benefit from a high PEEP. On the other hand, patients with a static compliance of below 40 were reported to be compatible with the H phenotype, and so, a high PEEP was suggested.[17]

The level of sedation should be deepened, and neuromuscular blocker treatment and prone positioning should be attempted in patients with a PaO_2/FiO_2 ratio of <150 mmHg, regardless of the optimal mechanical ventilator setup. Prone positioning should be applied for 12–16 h daily, and medical personnel should be careful to manage pressure sores, catheter and endotracheal tube removal, hemodynamic instability, and brachial plexus injury. Prone positioning should not be performed in the presence of a vertebra fracture, instability, or an open abdomen. Neuromuscular blocking agents should be administered intermittently in the IV bolus form or should be applied as an infusion for up to 48 h in case of ventilatory asynchrony or high plateau pressure. Extracorporeal membrane oxygenation (ECMO) may be considered in patients with a ratio of $PaO_2/FiO_2 < 100$ mmHg in spite of these rescue maneuvers. Before starting ECMO treatment, the healing potential of the patient's pathology, comorbidities, possible complications, and the long-term rehabilitation course should be considered before a decision is made. Such patients should be referred to ECMO centers. The management scheme is shown in Figure 1.

The administration of methylprednisolone for 5–7 days at a dose of 1–2 mg/kg is recommended with a low level of evidence in patients with ARDS, while routine IV corticosteroid treatment is not recommended in patients with respiratory failure.[3] Available evidence is inadequate on the risk of increasing viral contagion.

Pharmacologic Intervention

No specific treatment with proven safety and efficacy is currently available for COVID-19. Nevertheless, due

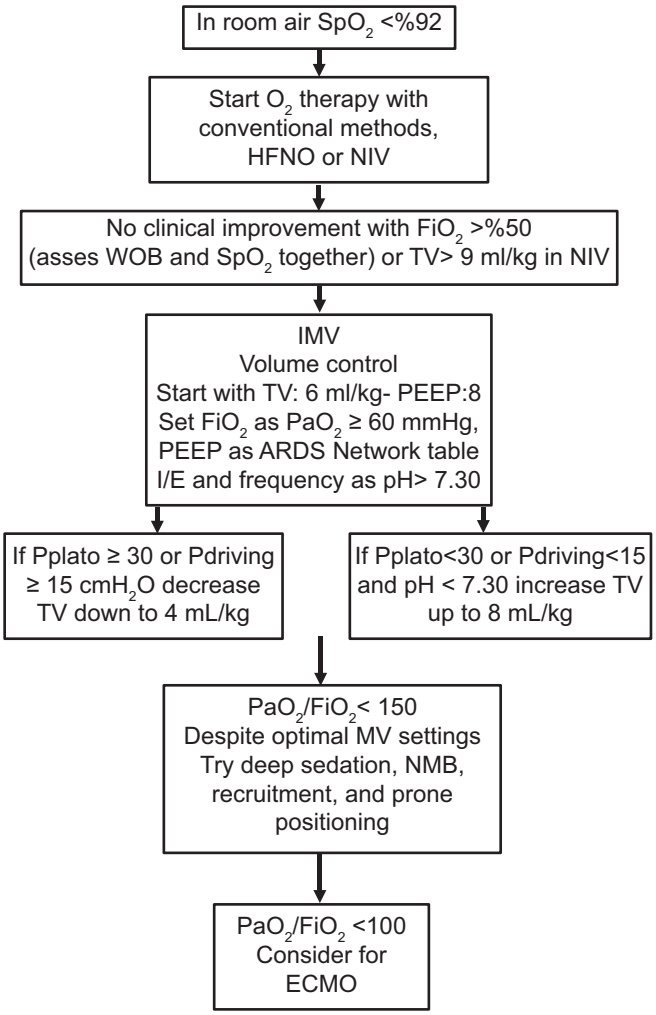

Figure 1: Management of respiratory failure in coronavirus disease-2019

to the emergent nature of the current status and the limited availability of scientific data, treatment options with any data present on the possible efficacy of the treatment, albeit limited, are used widespread globally in these patients. The combined use of possible treatment options in patients with COVID-19 should be decided individually for each patient, considering all related literature, and physicians should be cautious about the drug interactions and adverse effects of the drugs used.

For severe cases, a combination treatment of hydroxychloroquine, favipiravir, and azithromycin is suggested by the Public Health Directorate of the Ministry

of Health of Turkey.[4] An appropriate antimicrobial treatment should be started within the 1st h of admission in patients considered to have sepsis based on laboratory and clinical evaluations. The selection of the antibiotic treatment should be based on local epidemiological data and the clinical status (community-acquired pneumonia, health care-related pneumonia, pneumonia developed in hospital, pneumonia developed in immunosuppressed patients, and suspicion of another focus of sepsis or prior antibiotic use) of the patient. Patients should be evaluated for comorbid diseases, and the treatment should be regulated depending on the drugs they are already using. Bronchodilator drugs should be applied by metered dose inhalers considering the risk of transmission.[4]

The efficacy and safety of plasmapheresis treatment performed using plasma obtained from recovered patients are as yet unclear.[3]

Cytokine storm syndrome is a hyperinflammatory state that is characterized by increased cytokine levels and fulminant multiorgan failure. Cytokine storm in patients with COVID-19 has been found to be associated with a clinical course similar to the secondary hemophagocytic lymphohistiocytosis (HLH) in a study from China.[18] Among signs and findings are persistent fever, elevation of acute-phase reactants such as CRP, hepatosplenomegaly, and cytopenia. Despite optimal treatment, worsening of these parameters may indicate cytokine storm. In such cases, corticosteroids, IV immunoglobulin (Ig), tocilizumab, anakinra, and JAK inhibitors may be used. That said, the possibility of immunosuppression with these drugs should be considered. High-dose corticosteroids are not recommended for routine treatment, since sepsis is already an immunosuppressive disease. IV Ig treatment may be administered for a total of 2 days in a dose of 2 g/kg/day. However, it should not be used in the presence of IgA deficiency. The risk of anaphylaxis, acute renal failure, aseptic meningitis, thromboembolism, and transfusion-related lung injury should be considered. Tocilizumab has been reported to exert positive effects on COVID-19-associated HLH. Tocilizumab can be administered via the IV route in a dose of 400 mg, and the dose can be repeated within 12–24 h. This drug, however, has been reported to cause ARDS, and hence, it should be kept in mind that the routine use of the drug may be undesirable. Contraindications should always be evaluated in each patient before the administration of the drug. Specialists in rheumatology and/or hematology should be consulted to confirm a diagnosis of macrophage activation syndrome, and treatment should be instituted as soon as possible in diagnosed patients.[4]

In the selection of treatment, various factors should be considered related to sepsis as being an immunosuppressive disease with high mortality generally secondary to bacterial infections. It should be kept in mind that the single application demonstrated to increase survival in the treatment of ARDS is lung preserving mechanical ventilation.

The plasma of recovered patients or hyperimmune Ig use has come to light as another potential auxiliary treatment in patients with COVID-19. The antibodies of recovered patients are considered to lessen the viral load. This method has been reported to decrease the mortality in H1N1 and SARS outbreaks in some studies.[19,20] It is considered to be effective theoretically between the 7th and 10th days of infection with a weak level of evidence.[21]

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Conflicts of interest
There are no conflicts of interest.

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