



**THE REPUBLIC OF TURKEY  
MINISTRY OF HEALTH  
DIRECTORATE GENERAL OF  
PUBLIC HEALTH**

**COVID-19  
(SARS-CoV-2 INFECTION)  
(Study of Scientific Board)**

**MANAGEMENT OF SEVERE  
PNEUMONIA, ARDS, SEPSIS AND  
SEPTIC SHOCK**

**THE REPUBLIC OF TURKEY  
MINISTRY OF HEALTH  
14 MAY 2020**

## **XV. SUPPORTIVE TREATMENT IN COVID-19 PATIENTS**

### **15.1. General Approach to Probable/Confirmed COVID-19 Infection**

1. Patient should be equipped with medical mask and taken in a separate place at least 1 meter away from other patients.
2. If possible, patient should be taken into a single room with bathroom and toilet and droplet isolation measures should be taken.
3. Fundamental personal protective measures should be taken for those individuals in contact with the patient (attendant and relatives). Room should be regularly ventilated and cleaned.
4. Vital findings of the patient (heart rate, rhythm, respiratory rate, blood pressure, body temperature, oxygen saturation) should be regularly monitored.
5. Complete blood count, lymphocyte count, C-reactive protein, procalcitonin, liver and lung parameters, cardiac enzymes, LDH, coagulation parameters, fibrinogen, D-dimer, ferritin, arterial or venous blood gas, lactate and lung x-ray should be demanded and results should be evaluated. Blood cultures and other cultures according to clinical symptoms should be taken prior to antibiotic treatment in case of fever or other indications.
6. Conservative fluid treatment should be initiated on patients with no shock status. Routinely maintained saline solution is not required. It must be remembered that fluid treatment applied in an uncontrolled manner may compromise oxygenation.
7. Surgical mask may be applied on nasal oxygen canula to reduce the risk of infection through droplets in hypoxemic patients.
8. Patients with severe respiratory infection, ARDS, hypoxemia or shock status may be initiated oxygen therapy with 5L/dk nasal or standard face mask. Target oxygen saturation should be titred as  $> 90\%$  (92-95% for the pregnant).
9. Oxygen therapy may be administered with conventional low flow ( $< 15$  L/min.) methods or high flow methods. At most 6 L/min oxygen may be applied with nasal canula and reached  $FiO_2$  may not exceed 45%. Therefore, patients who need oxygen 6 L/min should be applied oxygen with simple face mask and non-breather masks, respectively. Simple face mask should be started with 5 L/min of oxygen and increased up to 8 L/min at most. Reached  $FiO_2$  may not exceed 60%. Non-breather mask should be used at a flow of 10-15 L/min  $> 85\%$ . However, it should be remembered that  $6 >$  hours,  $FiO_2 > 60\%$  may also lead to oxygen toxicity itself. Venturi and diffuser masks should be carefully used with PPE as they may lead to aerosolization.
10. Patients, who are considered to be sepsis according to laboratory and clinical evaluations, should start appropriate antimicrobial treatment within one hour after admission to hospital. Antibiotic therapy should be selected according to the clinic conditions of patient (community-acquired pneumonia, healthcare related pneumonia, sepsis, comorbidities, immunosuppression, application for healthcare in the last 3 months, previous use of antibiotics) and local epidemiologic data and therapy guidelines. Antibiotic treatment should be planned to include atypical pneumonia in severe pneumonia. Neuraminidase

inhibitor may also be added for influenza according to risk factors and clinic status for influenza.

11. Samples should be taken from both upper airways (nasopharyngeal and oropharyngeal swab) and lower airways (phlegm, endotracheal aspirate) and if possible, respiratory bacterial and viral panels should be operated. Bronchoscopy should be avoided solely for sampling purposes.
12. Patients may manifest rapid clinic deterioration and therefore, they must be closely monitored for progressive respiratory failure and sepsis.
13. Patients should be evaluated in terms of comorbid diseases and their treatments related to such diseases should also be regulated.
14. Routine steroid treatment is not recommended but should be applied in accordance with any accompanying comorbid diseases and other reasons (chronic obstructive lung disease, refractory septic shock etc.).
15. Inhaler drugs to be implemented through nebulization should be applied if possible, through metered dose inhalers considering the risk of contamination.

## 15.2. Management of Patient with Severe Pneumonia

Symptoms of COVID-19 infection might be of mild, moderate and severe form. Severe disease may manifest itself in forms of severe respiratory infection (severe pneumonia), Acute Respiratory Distress Syndrome (ARDS), sepsis, septic shock, myocarditis, arrhythmia and cardiogenic shock, metabolic acidosis and coagulation dysfunction and multiple organ failure. Respiratory failure is frequently displayed as hypoxemic respiratory failure and less frequently as hypercapnic respiratory failure. Furthermore, decompensated heart failure, myocarditis, arrhythmia, acute renal failure, chronic lung diseases inflammations may also accompany with these patients. Such patients should be monitored under intensive care.

Severe disease developing cases are more common in males (male/female: 2:1). While hypertension and diabetes mellitus are the most frequently type of comorbid diseases, advanced age is also another risk for development of severe disease.

**Severe respiratory tract infection (pneumonia): If patients with fever and respiratory infection symptoms have;**

- Respiratory rate  $\geq 30/\text{min}$

And/or

- Severe respiratory distress (dyspnea, use of extra respiratory muscles)

And/or

- Oxygen saturation in room air  $< 90\%$  (patient receiving oxygen  $\text{PaO}_2/\text{FiO}_2 < 300$ ), a thoracic CT should be planned.

Chest CT findings of COVID-19 pneumonia were likely to have peripheral distribution of bilateral lobular mode with ground-glass opacities.

CT findings in a series of 21 inpatient cases who have developed COVID-19 pneumonia were classified under four stages by their radiological prognosis:

1. Early period (days 0-4 days): ground glass opacities, lower lobe and frequently bilateral involvement
2. Progression period (days 5-8): Rapid progression, bilateral multi-lobular ground glass opacities
3. Peak time (days 9-13): more common consolidations with low progression in involvement zones
4. Resolution period (after day 14): regression of radiological densities up to 26 days upon controlling the infection.

### **15.3. Acute Respiratory Distress Syndrome (ARDS)**

- Respiratory distress occurring or deteriorating in the last week
- Bilateral ground glass densities or unexplained with pleural effusion or collapse in radiologic terms
- Respiratory failure unexplained with heart failure or excess volume (transthoracic echocardiography displaying left ventricle dysfunction)
  - Mild ARDS:  $200 < \text{PaO}_2/\text{FiO}_2 \leq 300$  (PEEP  $\geq 5$  cmH<sub>2</sub>O)
  - Moderate ARDS:  $100 < \text{PaO}_2/\text{FiO}_2 \leq 200$  (PEEP  $\geq 5$  cmH<sub>2</sub>O)
  - Severe ARDS:  $\text{PaO}_2/\text{FiO}_2 \leq 100$  (PEEP  $\geq 5$  cmH<sub>2</sub>O)

### **15.4. Sepsis;**

Availability of symptoms of organ failure coexisting with a suspicious or proven infection (changes in consciousness, respiratory distress, low oxygen saturation, decreased urination, increased creatinine, increased heart rate, weak pulse, cold extremities or low blood pressure, symptoms of coagulopathy, thrombocytopenia, increased level of lactate or hyperbilirubinemia)

### **15.5. Septic Shock;**

Hypotension resistant to fluid therapy, need for vasopressor to keep average arterial pressure at  $\geq 65$  mmHg and lactate level of  $> 2$  mmol/L

Please remember that patients may develop myocarditis and associated cardiogenic shock.

### **15.6. Approaches and methods applicable in case of severe respiratory infection, hypoxemic respiratory failure or ARDS:**

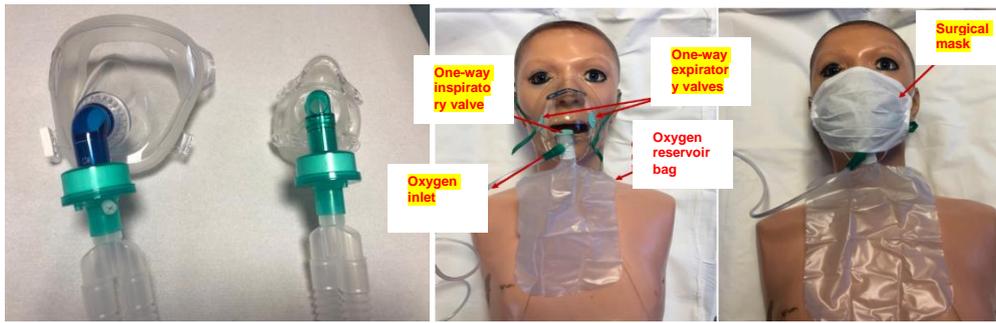
1. Hypoxemic respiratory failure must be diagnosed in the early period. Patients, who have indications for admission to intensive care, should be taken into intensive care upon the decision of intensive care unit expert or supervisor.
2. In cases where it is not possible to improve oxygenation through conventional methods, high-flow nasal cannula (HFNC) therapy should be initiated, if possible. Flow should be increased (at most 60 L/min) and oxygen is applied in way that  $\text{FiO}_2$  is  $< 60\%$ . Patient, to whom HFNC is applied, should wear medical/surgical mask. In particular due to the aerosolization risk of

high-flow oxygen application, it should be applied in negative pressure rooms, if possible, and if this is not possible, it should be applied with maximum PPE in single rooms.

3. Awake prone position may be tried for those patients, who have gravity-dependent lung consolidation in lung images at each stage of hypoxia. At least 4 hours of application is recommended for each time. Prone position may be considered several times a day depending on its effect and tolerance of patient. Patients, who cannot tolerate prone position, should be positioned in right and left lateral position. Meanwhile, availability of tachypnea and respiratory distress should be closely monitored.

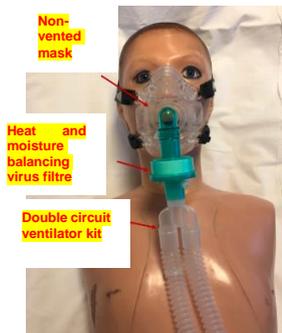
4. Mechanic ventilation should be considered for those patients, who develop deepening hypoxemia and increased respiratory stress under oxygen therapy (tachypnea, increased respiratory depth, dyspnea, use of extra respiratory muscles, paradoxical respiration respiratory alkalosis).

5. If patient is not in need of immediate intubation, noninvasive mechanic ventilation (NIMV) may be tried. Helmet or full-face mask, if these are not possible then oronasal mask should be worn during the application of NIMV. Full face mask and oronasal mask should fit completely unto face and patient must not have any facial hair. If possible, non-vented masks should be applied with intensive care ventilators or double circuit ventilators; circuits should be equipped with viral/bacterial filters on inspiration and expiration outlets. If single-circuit non-invasive mechanic ventilators are to be used, then the filter should be placed between exhalation port and masks, as seen in the Picture below, and non-vented masks and sets with activated expiratory valves should be preferred. No humidifiers should be used during the use of NIMV. NIMV may be applied in 8-15 cmH<sub>2</sub>O CPAP or BIPAP (inspiratory pressure 8-10 cm H<sub>2</sub>O, PEEP 5-10 cmH<sub>2</sub>O). Those patients, who have been applied NIMV, should be closely monitored for clinical deterioration and if no positive response is received within the first one-two hours, (failure criteria: refractory hypoxemia, tachypnea, deep breaths, tidal volume >9 ml/ideal kg, increased SOFA score >2), patients should be considered for invasive mechanic ventilation. For patients, who have uncontrolled secretions, risk of aspiration, hemodynamic disturbance, multiorgan failure or mental disorders, NIMV should be avoided. NIMV should be applied in negative pressure rooms, if possible, and if not possible in single rooms with maximum PPE due to the risk of aerosolization. NIMV may be applied in prone position to hypoxemic patients, if they are conscious.



Non-vented full-face mask (left), non-vented oronasal mask (right)

Non-rebreathing oxygen mask. Higher oxygen fraction ( $FiO_2 > 0,6$ ) can be provided with low flow. Inspiration and expiration may be divided into single-way valves to prevent rebreathing expiration air. Surgical mask may be equipped on mask to minimize exposure to aerosol.

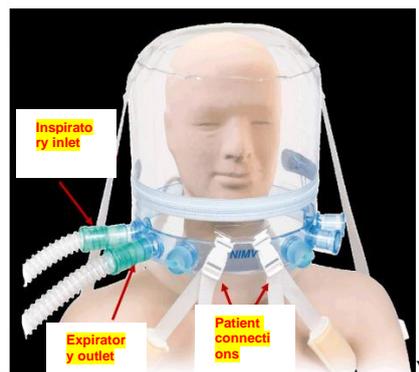
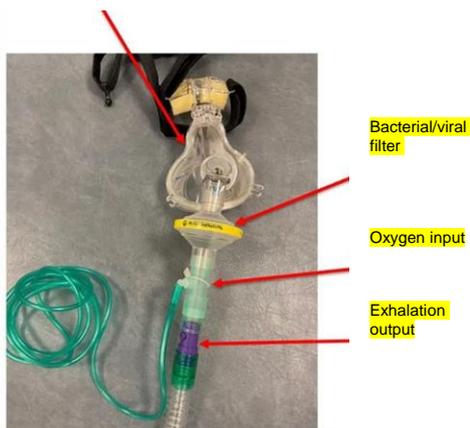


NIMV application with double circuit closed system ventilator. Mask should be fit completely on face and air leaks must be prevented. Virus filters must be installed to inspiration and expiration circuits.



Virus filter should be placed between respirator and mask during simple manual respirator application.

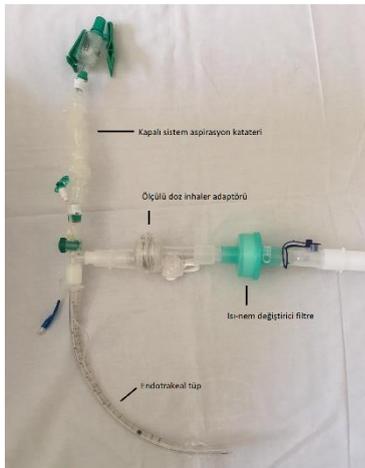
Non-vented oronasal mask



Single circuit NIMV application mechanism with non-vented oronasal mask. Mask should be installed with filter, oxygen input, exhalation output, and circuit, respectively.

Helmet mask: there are three each input on both sides. Inspiratory line, expiratory line, and a line for nasogastric catheter and other apparatuses. The inputs on patient's side where ventilator is placed should be used. Inspiratory and expiratory lines should be equipped with virus filter.

6. Rapid sequence intubation protocol should be followed by healthcare workers, trained and experienced in endotracheal intubation, for those patients to be applied invasive mechanic ventilation. In order to ensure balanced anesthesia in these patients, who are to be applied endotracheal intubation electively, induction should be performed with anesthesia agents to be elected based upon patient characteristics. Neuromuscular blockers ~~may~~ should be used to suppress cough prior to intubation. Positive pressure ventilation should not start before inflating endotracheal tube balloon. If possible, the use of balloon-mask should be avoided during preoxygenation. Filter should also be used in balloon-mask application. If intubation is possible, then it should be applied with video laryngoscope. Patients with airway problems may be intubated in accompany with flexible bronchoscopy. However, bronchoscopy may also pose a great risk of aerosolization. Intubation should be applied in negative pressure rooms, if possible, or if this is not possible, in single rooms with maximum PPE due to the risk of aerosolization.
7. Heat-moisture exchanger (moisturizing) filter may be used but active moisturizing should be preferred in case of increased plug and dead-space.
8. Mechanic ventilator circuit should not be disconnected unless necessary, and if so, then personal protective equipment must be used. Closed system aspiration method should be used if possible, and circuit, closed aspiration and filters should not be changed on routine basis. Bronchoscopic processes should be avoided unless actually necessary and metered dose inhalers should be preferred instead of nebulization in bronchodilator treatment.



A sample of closed system circuit mechanism. Bacteria/viral filter is installed at the inspiratory outlet and expiratory input of ventilator (not shown in figure). Normally, a metered dose inhaler adaptor or nebulizer is installed on inspiration line however, in case of heat-moisture exchanger filter, adapter is placed in front of the filter to maintain integrity of circuit. If heat-moisture exchanger filter is to be replaced with heated active humidifier, then metered dose inhaler adaptor should be placed on inspiration line.

9. Lung protective mechanic ventilation should be applied in cases where invasive mechanic ventilation is applied due to ARDS.
10. It is crucial to balance ventilation and oxygenation demands with mechanic ventilation-related lung damage risk in the treatment of COVID-19 pneumonia.

Ideal kg to calculate tidal volume

Male  $50 + (0.91 \times [\text{height cm} - 152.4])$

Female  $45.5 + (0.91 \times [\text{height cm} - 152.4])$

ARDS network PEEP protocol:

Low PEEP protocol

FiO <sub>2</sub>	30	40	40	50	50	60	70	70	70	80	90	90	90	100
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

High PEEP protocol

FiO <sub>2</sub>	30	30	30	30	30	40	40	50	50	50-80	80	90	100	100
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22	24

- Tidal volume should be adjusted as 4 - 8 ml/ideal kg.
- Plateau pressure should be <30 cmH<sub>2</sub>O and driving pressure should be (plateau pressure– PEEP [positive end-expiratory pressure]) <15 cmH<sub>2</sub>O. PaO<sub>2</sub> 60- 85 mmHg, SO<sub>2</sub> 88-95% will be sufficient.
- If compliance is good (static compliance > 40 mL/cmH<sub>2</sub>O) recruitment and high PEEP values may not be necessary. However, patients with lower compliance should be treated like traditional ARDS, in particular PEEP should be applied in a way to ensure best compliance and oxygenation under pressures that may not disturb hemodynamics and cause overstress while preventing atelectotrauma and ensuring alveoli aperture in particular in moderate-severe ARDS. ARDS protocol may be used for this purpose.
- Ventilation frequency may be adjusted at 16-24/min. In case of pH < 7.15 and hypercapnia, respiratory rate may increase up to 30/min. Permissive hypercapnia may be applied unless pH < 7.15.
- If tidal volume, plateau pressure and driving pressure is too high, and if patient is in compliance with ventilator, sedation and analgesia may be applied. Although routine use of neuromuscular blocking agents is not recommended, it may be applied in case of ventilator in compliance, persistent hypoxemia or hypercapnia despite sedation in moderate-severe ARDS (for a period of less than 48 hours) Excessive sedation should be avoided.
- Prone position for more than 12 hours a day should not be applied in moderate-severe ARDS cases (PaO<sub>2</sub>/FiO<sub>2</sub><150).

11. Extracorporeal membrane oxygenation (ECMO) may be considered in patients with refractory hypoxemia despite lung protective ventilation and appropriate patients should be referred to experienced facilities (please see the file attached for ECMO indications).

12. Despite lack of sufficient evidences in COVID-19 induced moderate and severe ARDS cases, nitric oxide inhalation may be applied if possible.

13. In the absence of tissue hypoperfusion symptoms, conservative fluid replacement should be provided. However, if the patient's clinical picture and general fluid intake is not sufficient prior to admittance to intensive care, then fluid therapy should be planned carefully.

The use of diuretic (furosemide) should be avoided unless there is hypervolemia and patients should be kept euvolemic. It will be useful to apply dynamic tests and ultrasonographic methods if possible, in order to evaluate fluid status.

14. Enteral nutrition should be initiated in hemodynamically stable patients in the early period. Prone position does not inhibit enteral nutrition. However, there should be a break one or two hours before changing position. Hypocaloric nutrition may be sufficient in patients who do not have malnutrition risk within the first week. Patients should be supplemented with vitamins and trace elements at daily recommended doses.

## 15.7. Tracheostomy Application in COVID 19 Patients

Tracheostomy in Covid-19 patients, who are applied invasive mechanic ventilation and are not appropriate for extubating, requires very careful decision-making. Tracheostomy is the leading aerosolization process. No optimal timing has been defined for the application of tracheostomy. However, disease process, prognosis of patient, the best use of healthcare services and safety of healthcare worker are of great importance in defining such time. General approach requires the application of tracheostomy before 14<sup>th</sup> day of intubation. Certain sources suggest that tracheostomy should not be decided before day 21. These applications aim at decreasing the viral load of patient. Despite the repetition of or negative PCR or antibody test before tracheostomy is suggested by certain sources, it is not an accepted practice to repeat PCR test before tracheostomy.

Maximum PPE (N95/FFP3 mask, eye protection/face protection, impermeable surgical apron/overalls, double-insulated gloves and if possible powered air purifying respirator) should be used for the safety of healthcare workers. Tracheostomy must be performed by the most experience physician and in a negative pressure operating room or negative pressure patient room. If it is to be applied in the operating room, patient must be transferred in accordance with the necessary rules.

It is not clear which of either surgical or percutaneous methods would be preferred in tracheostomy and which method generates less aerosol. The use of electrocautery in surgical tracheostomy and the use of bronchoscopy in percutaneous tracheotomy, separation of circuit and the use of positive pressure ventilation may trigger aerosolization. Intensive care doctor and ENT doctor should decide together to which method should be preferred taking into consideration the hospital resources and experiences. General approach suggests surgical tracheostomy.

- Mechanic ventilation values of the patients to be applied tracheostomy should preferably be  $FiO_2 \leq \%50$  ve  $PEEP \leq 10$  mmHg.

- In case of prolonged intubation, it is recommended to measure endotracheal tube cuff pressure on daily basis until tracheostomy. Cuff pressure should be kept between 20 and 30 cmH20 to prevent any possible air leaks (suggested by Dr. Murat. Is it appropriate here?)

- Tracheostomy cannula should be non-fenestrated and cannula should have cuffs. It would be useful to keep available various sizes of tracheostomy cannula and to check the integrity of cuffs prior to operation.

- A minimum number of healthcare workers should be present in the operation room or patient room and all materials should be prepared in the room prior to operation.

- $FiO_2$  should be adjusted at 100% before application.

- Full-dose neuromuscular block and deep sedation should be applied to the patient at a level to prevent cough and straining.

- The use of electrocautery and aspirator should be avoided as much as possible during tracheostomy due to aerosolization.

- Tube should be fully inflated and adjusted to prevent any leaks during tracheostomy

and strict attention should be paid to avoid cuffs from any damages during operation.

- When the front wall of trachea is in sight, anesthesia tube should be pushed towards bronchus as deep as possible to prevent cuff from cutting. Make sure that tube cuff is fully inflated. Surgeon must be able to perform the incision and open tracheal window without damaging cuff.

- The riskiest time in tracheostomy is the stage when endotracheal tube is pulled and tracheostomy cannula is placed. At this stage, if patient's condition allows (if no critical hypoxia is present) ventilation should be ended at expiratory-end. Endotracheal tube is pulled up to incision yet not completely removed but clamped instead.

- Tracheostomy cannula should be placed after equipped with HME filter and mechanic ventilation circuit. Once cannula is placed, cuff must be inflated before initiating ventilation and then patient should be ventilated; endotracheal tube should be pulled and placed into a plastic bag for disposal.

- The location of tracheal cannula should be verified with end-tidal CO<sub>2</sub> measurement; it is not recommended to verify through auscultation in regard to spread of infection.

- If percutaneous tracheostomy method is used, bronchoscopy may not be required to minimize aerosolization. Moreover, after placing guidewire, if patient's condition is suitable (no critical hypoxia), mechanic ventilation should discontinue by expiratory-end and operation spot should be enclosed with gauze before proceeding to tracheal dilatation.

## 15.8. Weaning from Mechanical Ventilation

A number of objective criteria should be checked in order to initiate the process of weaning from mechanical ventilation.

These criteria include:

1-Better oxygenation:

PEEP  $\leq$  5 cm H<sub>2</sub>O and PaO<sub>2</sub> / FiO<sub>2</sub> > 200.

2-Hemodynamic stability:

Unavailability of continuous vasopressor infusion.

3-Sufficient level of consciousness:

Patient is awake or easily arousable

4-Management of sufficient cough and secretion:

Effective coughing in response to endotracheal aspiration.

5- Respiratory physiology criteria:

Rapid shallow breathing index (RSBI)\* <100 after 2 minutes of spontaneous breathing trial (SBT)

\*(RSBI index is the ratio of respiratory frequency to tidal volume after 2 minutes of spontaneous breathing trial)

\*RSBI: respiratory frequency (minutes) /Tidal Volume(liter)

### Spontaneous Breathing Trial (SBT)

1-SBT may be ideally performed without or with less support of ventilator (low inspiration pressure support or CPAP).

2- Inspiratory pressures support (up to 7 cmH<sub>2</sub>O) decreases the work of respiration and gives an idea about the process after extubating.

3-It is suggested to avoid T-pierce during SBT.

### SBT Period

1-30 minutes is sufficient in most of the patients to determine if SBT is either successful or unsuccessful.

2- However, SBT may be extended up to 120 minutes in patients with a high risk of re-intubation (COPD, heart failure, neuromuscular disorders, advanced age etc.)

### **SBT Success Criteria**

1-Respiratory rate <35 / minutes

2-Heart rate <140 / minutes or heart rate variability < 20%

3-FiO<sub>2</sub> <0,4 SpO<sub>2</sub>>% 90 or PaO<sub>2</sub>> 60 mmHg

4-Systolic blood pressure > 80 and <180 mmHg

### **SBT Failure Criteria**

1-Perspiration

2-Nasal flaring

3-Increased ventilatory effort

4-Tachycardia (increase in heart rate > 40 pulse/ minute)

5-Cardiac arrhythmia

6-Hipotension

7-Apnea

### **Extubating**

Following a successful SBT, endotracheal tube extubating is suggested.

Corticosteroid treatment is recommended with a **poor level of evidence** at 1-2 mg/kg/day, methylprednisolone for 5-7 days in ARDS cases solely with mechanic ventilation in the Sepsis Guidelines by European Society of Intensive Care adopted to COVID-19 published on 20.03.2020 and is not recommended in pneumonia with no ARDS.

“Immune Plasma may be applied subject to permission of relevant boards of the Ministry of Health in ARDS cases with COVID-19 positive clinic symptoms and bilateral infiltration manifested on tomography.”

“Alternative treatments such as stem cell may be tried subject to permission of relevant bodies of the Ministry of Health on COVID-19 patients.”.