Literature Review

The Role Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome

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Abstract

Treatment of oxygen therapy should be based on appropriate indication and dose of administration. British Thoracic Society (BTS) recommends oxygen therapy were administered with a 94–98% saturation target in most acute patients and for patients with hypercapnic respiratory failure, BTS recommends 88-92 saturation target or spesific saturation target. Acute respiratory distress syndrome (ARDS) is characterized by acute, diffuse, inflammatory lung injury leading to increased capillary permeability in the alveolus with clinical manifestations of hypoxemia and bilateral opafication. The use of extracorporeal membrane oxygenation (ECMO) along with mechanical ventilator can be useful for ARDS patients and can improve survival.

Keywords: acute respiratory distresss syndrome (ARDS), Extracorporeal Membrane Oxygenation (ECMO)

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INTRODUCTION

Oxygen is a therapy that is often used in emergencies in the medical field. Thirty-four percent of patients receive oxygen therapy on their way to the hospital, and 15–17% of inpatients receive long-term oxygen therapy. The wrong perception is about the safety of oxygen therapy. Many people are not aware of the dangers of hyperoxemia; many believe that oxygen therapy is used to relieve shortness of breath even without hypoxemia. There is no evidence to suggest a benefit of oxygen administration in normothermia or mild hypoxemia. Shortness of breath can occur not only due to cardiorespiratory disease. However, it can also occur in metabolic acidosis, anxiety, and pain, so oxygen therapy is not indicated in these cases.[1]

Optimal oxygen therapy at the time of patient delivery is of paramount importance in addition to assessment by physicians in the emergency department and treatment of disease. Most patients need to get adequate oxygen therapy according to the patient's needs. Too little oxygen can result in hypoxia. Inadequate administration of oxygen therapy can cause cardiac arrhythmias, tissue damage, kidney failure, and brain damage. Giving excess oxygen therapy can also result in death in patients with respiratory failure.[2]

The British Thoracic Society (BTS) recommends that oxygen therapy be administered with a saturation target of 94–98% in most acute patients and a saturation target of 88–92% or specific targets for patients suffering from or at risk of developing hypercapnic respiratory failure. Patients with cystic fibrosis frequently experience exacerbations, and their characteristics resemble those of chronic obstructive pulmonary disease (COPD), namely hypoxemia, hypercapnia, and acidosis. Management of oxygen therapy in cystic fibrosis using a non-invasive ventilator (NIV) is significant in severe cases; NIV is needed to reduce

symptoms of increased respiratory effort and shortness of breath and help clear the airways.[3] Extracorporeal membrane oxygenation (ECMO) is a method of assistance living outside the body; its efficacy has been proven and accepted for managing respiratory and cardiopulmonary failure in the neonatal and pediatric population. In the adult population, there is still much debate regarding the advantages of using ECMO but it has an advantage in the postcardiotomy heart failure population.[4]

PHYSIOLOGICAL EXTRACORPOREAL MEMBRANE OXYGENATION

Diffusion law

Ficks' law explains the process of diffusion through the tissue; namely, the speed of air exchange through the tissue will be directly proportional to the tissue surface area and the difference in partial air pressure between the two sides and inversely proportional to the thickness of the tissue. The surface area of the blood gas barrier in the lungs is around 50 – 100 m^2, and the thickness is 0.3 microns, so the barrier is ideal for the diffusion process. The velocity of air exchange is proportional to the diffusion constant, which is influenced by the tissues and gas components in the air. The diffusion constant is proportional to the solubility of air and inversely proportional to the square root of the molecular weight.[5]

Diffusion process

The diffusion process based on Ficks' law has three principles. First, the rate of gas diffusion through the tissue is directly proportional to the area of the tissue and inversely proportional to the thickness of the tissue. Second, the rate of diffusion of gases is directly proportional to the difference in partial pressure. Third, the rate of gas diffusion is directly proportional to the solubility of the gas in the tissue but is not related to the molecular weight of the gas. This statement explains that the diffusion speed of carbon dioxide (CO2) is 20 times faster than oxygen (O2) because CO2 has a more excellent solubility than O2, even though it has almost the same molecular weight.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is an inflammatory lung injury that causes an acute and widespread increase in capillary permeability in the alveoli. Increased lung weight and reduced oxygenation to lung tissue seen in clinical manifestations of hypoxemia and bilateral opacity on chest X-rays are associated with decreased lung compliance, increased venous flow velocity, and increased physiological dead space. Acute respiratory distress syndrome is a life-threatening condition. This condition can be caused by pulmonary disorders such as pneumonia and aspiration or nonpulmonary disorders such as sepsis, pancreatitis, and trauma, which cause nonhydrostatic pulmonary edema.[6]

Table 1. Berlin criteria for ARDS[7]

Criteria	Rational
Onset within 7 days of clinical cause or new or worsening respiratory symptoms	*Acute respiratory distress syndrome* may occur within 72 hours in the majority of patients at risk for the syndrome and within 1 week in all patients at risk.
Bilateral opacities consistent with pulmonary edema on chest X-ray or chest CT	The Berlin criteria are clearer in making the criteria for opacity i.e., not an effusion, atelectasis of the lung or lobe, not a mass or nodule
Degree of severity ARDS	
Light	PaO_2/FiO_2 201–300 mmHg, Mortalities 27%
Moderate	PaO_2/FiO_2 101–200 mmHg, Mortalities 32%
Heavy	$PaO_2/FiO_2 \leq 100$, mortalities 45%
Minimum PEEP setting or Continuous Positive Airway Pressure (CPAP). Assessment of PaO_2/FiO_2 in invasive mechanical ventilation.	In the use of *high flow nasal cannula* (flow ≥ 45 L/minute); The need for a high PEEP setting does not increase the severity of ARDS on the Berlin criteria

The prevalence of ARDS in the United States reaches 200,000 patients annually and contributes to 75,000 deaths annually. This figure is higher than breast cancer and Human Immunodeficiency Virus (HIV) infection. Worldwide data states that ARDS affects 3 million patients annually, contributing to

10% of Intensive Care Unit (ICU) care and 24% of ARDS patients receive mechanical ventilation in the ICU. Supportive therapy with mechanical ventilation remains the mainstay of management for ARDS, although the mortality rate remains high at 35–46%. The mortality rate is related to the degree of lung injury and the onset of ARDS.[6]

The diagnosis of ARDS continues to be updated to date. ARDS criteria in 1967 are based on clinical syndromes of the severity of shortness of breath, tachypnea, and cyanosis that persists on oxygen therapy accompanied by decreased lung compliance and bilateral wide infiltrates on chest radiographs. In 1994, the definition of ARDS, according to the American-European Consensus Conference (AECC), was the acute onset of hypoxemia with bilateral infiltrates on chest X-ray with no clinical evidence of left atrial hypertension when pulmonary capillary wedge pressure (PCWP) ≤18 mmHg was measured. The degree of hypoxemia is measured by the arterial partial pressure of oxygen (PaO_2) divided by the fraction of inspired oxygen (FiO_2). ≤200 mmHg is considered ARDS, while the limit for Acute Lung Injury (ALI) uses the criteria (PaO_2/FIO_2) ≤300 mmHg.[6]

The 2012 Berlin definition established clinical criteria, namely the degree of shortness of breath worsening within 7 days with minimal positive end-expiratory pressure (PEEP) settings, bilateral opacity on chest X-ray and chest computed tomography (CT), and PaO_2/FiO_2 ≤ 200 to diagnose ARDS. PaO_2/FiO_2 criteria are divided into three levels: mild criteria if PaO_2/FiO_2 is 201–300 mmHg, moderate criteria for PaO_2/FiO_2 is 101–200 mmHg, and criteria for severe PaO_2/FiO_2 ≤100 mmHg. The cause of ARDS, whose onset appears seven days is pneumonia or sepsis. ARDS symptoms can also be found in other diseases called mimic ARDS, but the onset of ARDS appears more slowly.[7]

ARDS Pathogenesis

Injury in the distal part of the lung to the alveoli can be caused by direct or indirect causes that cause microvascular injury. In the exudative phase, alveolar macrophages are activated to release inflammatory mediators and chemokines, resulting in neutrophils and monocytes congregating at the injury site.[7]

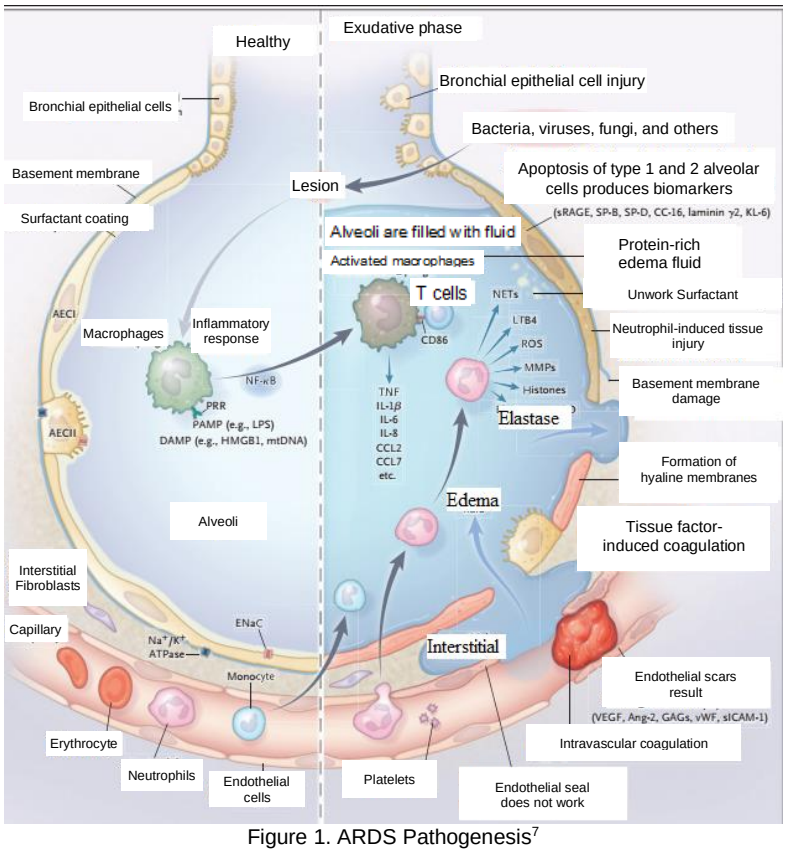


Figure 1. ARDS Pathogenesis[7]

Activated neutrophils play a vital role in causing alveolar tissue injury because they produce toxic mediators which cause loss of insulating function so that the interstitial and interalveolar layers are filled with fluid. Tissue-derived tumour necrosis factor (TNF) causes platelet aggregation, micro thrombus formation, interalveolar coagulation, and the formation of hyaline membranes (Figure 1).[7]

Management

The current management of ARDS is still relatively limited; the final stage of management is mechanical ventilation with the ultimate goal of minimizing the incidence of ventilator-induced lung injury (VILI). VILI events are iatrogenic and cause secondary injury with systemic inflammation leading to multi-organ failure. The ARDS management algorithm starts with optimizing ventilation that does not injure the lungs and increasing interventions based on the physiology of gas exchange. Additional management is individual, based on the cause and availability of facilities at the place of care. Current management of ARDS includes extracorporeal carbon dioxide removal (ECCO2R), prone position, administration of statins, and high-frequency oscillatory ventilation (HFOV).[6]

Prevention of lung injury can reduce morbidity and mortality due to ARDS. Platelets play a role in the injury process, so it is hypothesized that anti-platelet anti-aggregation therapy can prevent ARDS in high-risk patients. VILI events can occur even though the lung-protective ventilation method has been used. This method aims to reduce tidal volume and can reduce the incidence of VILI. This method can increase carbon dioxide and cause respiratory acidosis, so $ECCO_2R$ is needed, which can remove CO_2 from the blood through gas exchange devices outside the body.[6]

The incidence of VILI can be reduced by placing the patient in a prone position. This position facilitates the expansion of the lungs simultaneously so that the mechanical stress load can be distributed evenly in all parts of the lung. Several studies have shown that the prone position can benefit ARDS patients. A multicentre randomized controlled trial (RCT) of ARDS patients with PaO_2/FiO_2 ≤150 mmHg stated that the prone position for at least 16 hours/day significantly reduced mortality in 90 days with a hazard ratio (HR) value 0.44 (95% CI=0.29–0.67).[6]

Table 2. Risk factors for ARDS[7]

Direct lung injury risk factors	Indirect lung injury risk factors
1. Pneumonia (bacterial, virus, fungal, or opportunistic)	1. Sepsis (source of infection outside the lungs)
2. Gastric fluid aspiration	2. Hemorrhagic shock and extra thoracic trauma
3. Pulmonary blunt trauma	3. Pancreatitis
4. Inhalation injury	4. Big burn
5. Sink	5. Drug overdose
	6. Transfusion reaction
	7. *Cardiopulmonary bypass*
	8. Edema after lung transplantation

EXTRACORPOREAL MEMBRANE OXYGENATION

The definition of extracorporeal membrane oxygenation (ECMO) is a life support device outside the body that has an external artificial circuit and functions to carry venous blood from the patient for gas exchange in an oxygenator so that the blood becomes rich in oxygen and carbon dioxide can be removed. The blood is put back into the body.[8] Extracorporeal membrane oxygenation is a method that is often used in extracorporeal life support (ECLS). The ECLS system is a temporary mechanical technology.[4]

Tools included in ECLS include extracorporeal CO_2 removal ($ECCO_2R$), cardiopulmonary bypass support (CPS), and ECMO. Extracorporeal CO_2 removal is used to remove the partial pressure of carbon dioxide in hypercapnia respiratory failure. Cardiopulmonary bypass support can be used to maintain oxygenation and perfusion but can only be used for a few hours due to the limited half-life of the membrane oxygenator.[4]

ECMO devices require vascular access, connecting tubes, blood pumps, and gas exchange devices. Vascular access can be divided into veins or veins-arterials, depending on the physiological needs that occur in the patient. In adult patients, ECMO is often used in severe, acute, and irreversible

cardiopulmonary heart failure cases. The principle of the ECMO device differs from the cardiopulmonary bypass (CPB) device in several ways. On the CPS device, the heart is stopped, and perfusion occurs at a very slow rate of 2 L/min, so anticoagulation with heparin prevents thrombus formation. The ECMO device does not require heparin due to the high blood flow of 4 L/minute. Besides that, the ECMO device can be used for up to several weeks, while the CPS is only for a few hours.[4]

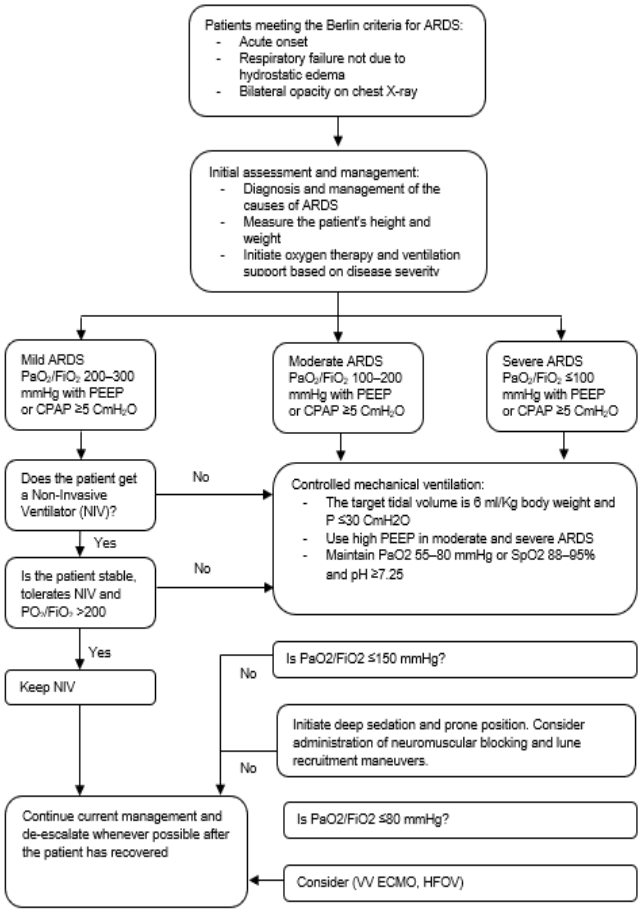


Figure 2. ARDS Management Algorithm[7]

The goal of ECMO is the successful gas exchange between oxygen and CO_2. Oxygen is exchanged through the membrane oxygenator which depends on the thickness of the blood layer, membrane material, FiO_2, and hemoglobin concentration. Excess volume and poor device flow can affect oxygen exchange thereby creating a ventilation-perfusion mismatch in the oxygenator device according to the natural processes of the lungs. CO_2 exchange, like the lungs, is affected by surface area, blood flow, and gas exchange rates. Gas exchange is measured in L/min gas flow through the oxygenator membrane. It's different with children. In adults the membrane oxygenator adds CO_2 to prevent excessive CO_2 loss and the development of respiratory alkalosis.[4]

The extracorporeal circuit has been assembled to meet the need for full gas exchange support, although certain patients only require CO2 removal. The circuit consists of:[9]

a) *Blood flow for heart support*. Using the venoarterial system, the selected circuit components can sustain a blood flow of 3 L/m2/min (neonates 100 ml/kg/min, children 80 ml/kg/min, adults 60 ml/kg/min). The target for measuring optimal systemic perfusion after installing the ECMO device is 70% venous saturation.

b) *Blood flow and gas exchange for respiratory failure*. Using the venous-arterial system or veins. Pulmonary membrane apparatus and blood flow can maintain oxygen flow and remove CO_2 in proportion to the patient's normal metabolic rate (neonates 6 ml/kg/minute, children 4–5 ml/kg/minute/ and adults 3 ml/kg/minute). A normal metabolic rate can be achieved with a venous system of 120 ml/kg/min for neonates and 60–80 ml/kg/min for adults. Oxygen delivery is determined by blood flow, hemoglobin concentration, hemoglobin saturation, and gas content in the lung membranes. CO_2 discharge occurs when the circuit is set for total support. Circuits regulated for CO_2 excretion may use venous-arterial, venous, or arterial-venous access with a blood flow of up to 25% cardiac output (CO) sufficient to remove CO_2 produced by metabolism, ie, 3–6 ml/kg/min. CO_2 output is determined from blood flow, gas sweep rate, PCO_2, and gas content in the lung membranes.

c) *Circuit components*. The circuit consists of a blood pump, lung membrane, connecting tube, and additional equipment such as heaters, monitors, and alarms.

d) *The pump*. The pump used can maintain the patient's total blood flow. The pump consists of various systems depending on the specifications

(modified roller with pressure control, centrifugal pump, peristaltic pump). Extracorporeal Life Support Organization (ELSO) recommendations for suction pressure not to exceed -300 mmHg. An aspiration pressure of more than this value is used when venous occlusion occurs, and the adjustment is carried out by a servo-controlled sensor that has a sensor inside the pump. The outlet pressure does not exceed 400mmHg, and the pump must have a battery that lasts at least one hour. This is necessary when there is a loss of power. The pump and circuit shall have an alarm mechanism intended to prevent arterial-to-venous backflow when using the venous-arterial mode in the event of a power failure.

e) *Lung membranes*. Gas exchange across the lung membranes occurs in the perforated layers of the dense silicone rubber membrane. The rate of contact between the blood flow and the surface area of the membrane determines the oxygen-carrying capacity. When using a total support system, blood that is 75% desaturated can reach a full saturation of 95% per minute. In the venous mode, blood recirculation is possible when the incoming blood is above 75% saturation. In this condition, oxygen flow per unit of blood flow is reduced, and it is necessary to regulate high blood flow. Cannula readjustment and increased hematocrit levels are required to achieve the required oxygen

f) *Sweep gas.* At the time of removal of CO_2 blood flow is regulated as low as 500 ml/min/m2.

g) *Circuit*. Circuits must be sterile with an isotonic electrolyte fluid content referring to normal extracellular fluids, namely potassium levels of 4-5 meq/L. The liquid circulates through the reserve bag until the bubbles disappear. The circulation process can be accelerated by adding 100% CO2 before filling the liquid in the circuit.

h) *Heater.* Heaters are needed to maintain body and blood temperature at a certain level. The heater requires a container filled with water, and the heating machine will be passed by a hose from the circuit so that the temperature is maintained at $<40^0$C.

i) *Monitors*. The monitor is set to assess circuit function and has an alarm on an abnormal condition.

j) *Blood tube.* The length and diameter of the tube determine the resistance to the blood flow pressure. The selected hose can drain venous blood and avoid high pressure when the blood flows back into the body. Blood will flow through a 1-meter-long tube at a pressure of 100 mm Hg. The diameter of the hose is 3/16 inches is capable of flowing blood at a rate of 1.2 L/minute, ¼ inch is capable of flowing blood at a rate of 2.5 L/minute, 3/8 inches is capable of flowing blood at a rate of 5 L/minute and ½ inch is capable of flowing blood at a rate of 10 L/min.

The system in ECMO has two systems, namely the veins (V-V) and the veins-arteries (VA). The V-V system is used for respiratory failure, while the VA system is used for heart or combined heart-lung failure. The V-V ECMO system produces oxygenated return blood resulting in high oxygen content and low CO2 in the right atrium. Arterial oxygen partial pressure and hemoglobin oxygen saturation are determined by the mixing effect of oxygenated return blood from the ECMO circuit to the right heart and deoxygenated blood from the bronchial veins, coronary sinus, and vena cava. Measurable pulmonary recovery can be characterized by the improvement of mixed venous oxygenation or systemic oxygen saturation during weaning from ECMO, indicating the lungs' ability to exchange gases. The Venoarterial extracorporeal membrane oxygenation (V-A SECMO) system can support patients who have lost partial or total function of the heart and lungs due to the blood flow provided by the ECMO circuit.

Complications from ECMO can be complications during cannulation or while on ECMO support. Complications can occur as bleeding, stroke, limb ischemia, thrombosis and infection. Research shows complications occur in 1:50 patients using ECMO, with bleeding and infection as the most common complications. Bleeding complications occur during cannulation or are caused by using anticoagulation while using ECMO. The V-A system

requires more aggressive anticoagulation because of the high risk of arterial thrombosis. Other complications, such as hemolysis, pulmonary edema, and leg ischemia, can be prevented by changing the cannula placement regularly.[10]

Table 3. Indications and contraindications[4]

Indications	Contraindications
1. Murray score ≥3	1. Irreversible heart and lung disease
2. Severe hypercapnia with a pH <7.2	2. Age >65 years
3. PaO_2:FiO_2 <50-100mmHg	3. Malignant disease
4. *Alveolar-arterial oxygen gradient* >600 mmHg without cardiogenic pulmonary edema	4. A serious brain injury
5. *Transpulmonary shunts >30%*	5. Mechanical ventilation >5–10 days
	6. Multiple traumas with high risk of bleeding

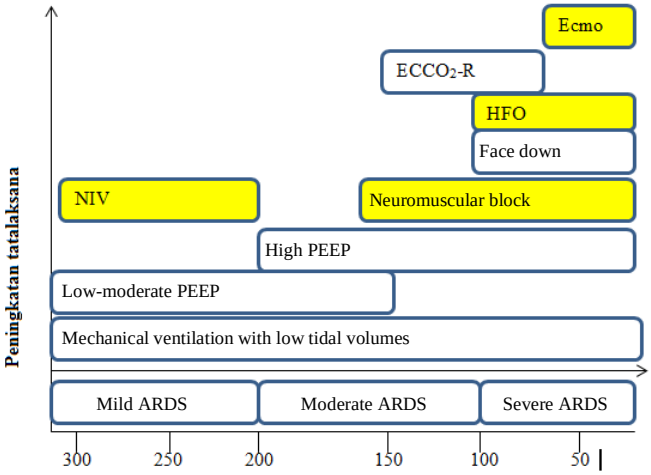
Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome

The main indications for using ECMO are acute respiratory failure caused by a reversible process such as ARDS and as support before lung transplantation. Using a ventilator with positive pressure ventilation can cause VILI, oxidative stress, and lung injury, souse of ECMO can rest the lungs and is more protective than the ventilator. At the time of the H1N1 pandemic, the incidence of ARDS greatly increased, and patients treated with ECMO achieved a high survival rate of 79%. The multicenter conventional ventilatory support versus extracorporeal membrane oxygenation (CESAR) study using the RCT method compared ECMO with conventional therapy in patients with severe ARDS. The results of this study stated that the mortality rate was not significantly different, and the use of a single ECMO could not improve the outcome of patients with severe ARDS.[10]

The ongoing *extracorporeal membrane oxygenation for severe acute respiratory distress syndrome* (EOLIA) study evaluates early use of ECMO 3 hours before mechanical ventilation can improve the outcome of patients with ARDS.[10]

The Ministry of Labor's study of 49 ARDS patients with a median PaO_2/FiO_2 of 69, the median number of days on a ventilator before two days of ECMO cannulation and a median use of ECMO for 311 hours showed that 38 patients (78%) were successfully decannulated and survived. This study shows that the use of ECMO in combination with mechanical ventilation can increase the survival rate of patients with ARDS.[11] The American Thoracic Society (ATS) guidelines for the management of ARDS recommend setting mechanical ventilation using a low tidal volume of 4–8 ml/kgBB/breath, using inspiratory pressure lowest, namely the target <30 cmH_2O for severe ARDS patients (PaO_2/FiO_2 <100), prone position for at least 12 hours/day, not using HFOV and recommending the use of ECMO.[12]

Based on epidemiological data, ECMO can be considered a treatment for patients with hypoxemic-type respiratory failure. Data from Germany show the use of ECMO in respiratory failure starting in 2007, with a frequency of 2.4 cases per 100,000 population. The duration of ECMO use for ARDS patients varies. The CESAR study with a median of 9 days, and research in Korea showed a median of 7.4 days, and patients could be weaned. The study by Seiler et al. reported an average of 8 days of ECMO use before patients required mechanical ventilation. ECMO international registration data shows that as many as 22% of patients use ECMO with a duration of up to 14 days.[13]



Figuew 3. ARDS Management Algorithm implementing the Berlin criteria[14]

Figure 3 shows the treatment strategy according to the Berlin criteria, namely mild ARDS using NIV if it fails to use mechanical ventilation with low tidal volumes and low-moderate PEEP, for

moderate-grade ARDS using mechanical ventilation with low tidal volumes. Still, PEEP is set high and can even use additional neuromuscular block anesthesia at an advanced stage, namely severe ARDS using mechanical ventilation with low tidal volume using high PEEP added prone position (prone) is recommended using Extra Corporeal CO_2 Removal ($ECCO_2$-R). Still, if not available ECMO can be used.[14]

CONCLUSION

Giving oxygen therapy should be based on indications and the patient's oxygen needs. Acute respiratory distress syndrome can be caused by various conditions that cause diffusion disorders so that oxygenation to the tissues is reduced. The use of ECMO, together with mechanical ventilation, can be beneficial for ARDS patients and ~~can~~ increase patient survival. Appropriate management of hypoxemia and management of the causes of ARDS will reduce patient mortality.

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CONFLICT OF INTEREST

None.

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