Management, therapeutic options for ARDS, complications, and long-term outcomes after ARDS

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Abstract

Background: Management and therapeutic options for ARDS Although there have been huge advances in the overall management of patients with ARDS since Ashbaugh first described it in a Lancet publication in 1967, many controversial aspects concerning the pathogenesis, diagnosis, therapeutic options, and supportive measures for this condition still exist. The effectiveness of ARDS management strategies is influenced by several factors, including the underlying cause of ARDS (pulmonary or extrapulmonary), the stage of the disease (early or late), the patient's general health status, and the occurrence of complications such as multiple organ dysfunction syndrome (MODS), infection, and barotrauma. While these factors can impact treatment response, none of them can reliably predict patient outcomes or definitively distinguish responders from non-responders. Moreover, ARDS is a self-limiting disease, and the primary goal of treatment is to provide time for the lungs to heal naturally or for specific therapies to take effect

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Introduction

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Over the last decade, the management of acute respiratory distress syndrome (ARDS) has made considerable progress both regarding supportive and pharmacologic therapies. Lung protective mechanical ventilation is the cornerstone of ARDS management **(1).**

1. Standard supportive therapy:

Standard supportive therapy for ARDS is directed toward the identification and management of pulmonary and non-pulmonary organ dysfunction. General principles of the supportive care for ARDS patients with or without MODS include identifying and treating underlying causes of ARDS, avoiding secondary lung injuries such as aspiration, barotraumas, nosocomial infections, or oxygen toxicity, maintaining adequate oxygen delivery to end-organs by minimizing metabolic rate and optimizing cardiovascular function and body fluid balance, and nutritional support **(2)**

While respiratory failure alone is a rare cause of death in ARDS patients, mortality is more often attributed to the underlying condition or secondary complications such as sepsis. These patients demand meticulous supportive care, encompassing prophylaxis against deep vein thrombosis (DVT) and gastrointestinal (GIT) bleeding, nutritional support, prompt evaluation and treatment of nosocomial infections, and judicious use of sedatives and neuromuscular blockade **(3).**

A. Fluid and hemodynamic management:

The rationale for restricting fluids in patients with ALI and ARDS is to decrease pulmonary edema. Studies in animals with acute lung injury indicated that the degree of edema was reduced if left atrial pressure was lowered. A reasonable objective in managing ARDS patients is to maintain intravascular volume at the lowest level compatible with adequate systemic perfusion, as assessed by metabolic acid-base balance and renal function. This approach aims to balance the need for adequate fluid resuscitation to support organ function with the risk of fluid overload and worsening pulmonary edema. In patients with septic shock, where systemic perfusion may not be maintained despite optimal fluid resuscitation, vasopressors are indicated to restore end-organ perfusion and normalize oxygen delivery. A prospective, randomized, multicentered clinical trial evaluated the use of a liberal versus conservative fluid strategy (using diuretics to target a central venous pressure < 4 mmHg or pulmonary artery occlusion pressure < 8 mmHg) in patients with ALI. The fluid-conservative strategy resulted in a significant increase in ventilator-free days and a non-significant decrease in mortality by 3%. The same clinical trial found no additional benefit to the use of a pulmonary artery catheter rather than a central venous catheter in fluid management **(4)**.

B. Blood transfusion:

The optimal red cell transfusion strategy for critically ill patients with ARDS remains a subject of debate. While a seminal study suggested that a restrictive approach was as effective as a liberal approach in terms of mortality, concerns about the potential risks of transfusion, such as Transfusion-Related Acute Lung Injury (TRALI), have led to a more cautious approach. A more recent observational cohort study further highlighted the potential drawbacks of transfusion in ARDS patients, demonstrating an association between transfusion and increased mortality **(5).**

2. Non-invasive mechanical ventilation (NIV):

The benefits of non-invasive ventilation (NIV) in acute respiratory distress syndrome (ARDS) have long been debated. A recent well-designed found that compared to standard oxygen therapy, NIV in mild ARDS patients did not reduce the intubation rate. Potential advantages of NIV in the management of patients with ARDS are mainly related to the avoidance of complications linked to sedation, muscle paralysis, and ventilator-associated complications associated with endotracheal intubation and invasive mechanical ventilation (MV) **(5).**

Several concerns exist regarding the use of NIV in patients with ARDS. The subgroup of ARDS most likely to benefit from NIV remains unclear. Although some literature suggests that NIV may best be reserved for patients with mild ARDS (i.e., patients with a Pa_{O2}/Fi_{O2} ratio of 200–300 mm Hg), it is not always the case in practice **(2)**

Although some factors leading to NIV failure in patients with ARDS are better understood, relatively few patients have been studied to date. The impact of NIV on outcome in ARDS is therefore not well understood. In particular, concerns have been raised regarding the impact of prolonged NIV in the absence of respiratory status improvement, potentially delaying tracheal intubation and invasive MV **(6).**

Finally, the Berlin definition of ARDS does not specify whether patients with ARDS managed with NIV should be all classified as having “mild” ARDS or whether the Pa_{O2}/Fi_{O2} ratio severity stratification is more appropriate **(7).**

Of concern is the finding that NIV use seems to be associated with increased ICU mortality. After adjusting for potential confounders, a patient treated with NIV at ARDS onset seemed to have a 30% increased risk of dying in the ICU compared with a similar patient treated with invasive MV **(2)**

3. High flow nasal cannula (HFNC):

HFNC has emerged as a novel approach that has shown promising results in counteracting the potential drawbacks of conventional oxygenation therapies. HFNC delivers high-flow oxygen, which provides several advantages over traditional oxygen delivery methods. HFNC can deliver higher levels of oxygenation, improve ventilation and mucociliary clearance, and provide greater patient comfort and tolerance. HFNC delivers heated and humidified oxygen at a high flow of 50-60 L/min via a wide-bore nasal cannula. The utilization of a high flow of oxygen facilitates the observation of enhanced inspiratory flow amplifications in individuals suffering from hypoxemia, thereby minimizing the dilution of oxygen and ensuring the delivery of an inspired oxygen fraction (FiO_2) that closely approximates the predetermined FiO_2 value **(8).**

Within the context of ARDS, the collective findings of the reviewed studies support the use of HFNC as an effective treatment modality. The etiologies of ARDS varied across the studies, suggesting that HFNC may be beneficial for a wide range of underlying conditions that lead to ARDS. Overall, the evidence presented in this systematic review indicates that HFNC can be considered a viable treatment option for ARDS, including COVID-19-related ARDS**.** High-flow nasal cannula (HFNC) has emerged as a promising treatment option for patients with acute respiratory distress syndrome (ARDS). Its noninvasive nature, ability to deliver high-flow oxygen, and favorable outcomes demonstrated in recent studies make it an appealing alternative to conventional oxygen therapy methods. More research is needed to refine its implementation, identify the optimal patient selection criteria, and compare its efficacy to other interventions for ARDS management **(9).**

Sedation, analgesia, and neuromuscular blockade in mechanically ventilated patients:

Most critically ill, patients need sedation and/or analgesia to achieve patient comfort, facilitate ventilation, and permit sleep. Occasionally, patients require paralytic drugs to control ventilator dysynchrony and reduce oxygen demand. Because of the short- and long-term paralytic risks associated with such treatment, usage of these agents should be limited to the briefest period possible, and patients should be monitored closely to minimize the depth of paralysis induced **(1).**

4. **Mechanical ventilation**

In acute respiratory distress syndrome (ARDS), impaired gas exchange due to intrapulmonary shunt and ventilation-perfusion mismatch leads to severe hypoxemia that can be life-threatening. Additionally, increased alveolar dead space and reduced respiratory system compliance contribute to a high work of breathing, potentially leading to ventilatory failure with hypercapnia and respiratory acidosis. Mechanical ventilation remains the primary supportive therapy for ARDS. By stabilizing respiration, mechanical ventilation facilitates the management of the underlying cause of ARDS (e.g., infection) and allows the natural healing processes to occur **(10).**

Ten golden rules to set the ventilator in patients with ARDS. VT, tidal volume; PBW, predicted body weight; IBW, ideal body weight; Pplat, plateau pressure; ΔP, driving pressure; RR, respiratory rate; PEEP, positive end-expiratory pressure; MP, mechanical power; ECCO2R, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation; PaO2, arterial partial pressure of oxygen; FiO2, the fraction of inspired oxygen; NMBAs, neuromuscular blocking agents; RMs, recruitment maneuvers. Acute Respiratory Distress Syndrome Network compared a traditional tidal volume (12 ml per kilogram of predicted body weight) with a lower tidal volume (6 ml per kilogram of predicted body weight) in 861 patients. In this study, the in-hospital mortality rate was 39.8 percent in the group treated with traditional tidal volumes and

31 percent in the group treated with lower tidal volumes. Thus, mortality was reduced in the group treated with lower tidal volumes, a finding of major importance**.** Conventional mechanical ventilation guided by normal values of gas exchange, with high tidal volumes (10-15 ml/kg body weight), a low frequency to avoid dead space ventilation, tolerance of high inspiratory pressures, and restricted use of PEEP was applied over several decades resulting in a mortality rate of 50-70%. This was challenged by a couple of small studies that used smaller tidal volumes and lower inspiratory plateau pressure to achieve a higher survival rate **(11).**

1-Mode of ventilation:

Volume-cycled ventilation modes, such as volume-assist control (VAC) and intermittent mandatory ventilation (IMV), are commonly employed in the treatment of ARDS patients. However, pressure-cycled ventilation modes, such as pressure-controlled ventilation (PCV) and pressure support ventilation (PSV), have demonstrated similar efficacy in providing ventilatory support. Regardless of the ventilator mode employed, the changes in transmural alveolar pressure and volume during inspiration are directly proportional to the pressure-volume characteristics of the lungs. Consequently, for a given tidal volume, there is no inherent advantage or disadvantage of pressure-controlled versus volume-cycled modes in terms of the risk of barotrauma or ventilator-induced lung injury. While some have proposed that the rapid inspiratory airflow associated with pressure-controlled ventilation modes might enhance gas exchange, available evidence suggests that there is no significant difference in PaO2 or PaCO2 levels between ARDS patients receiving volume-cycled versus pressure-controlled ventilation when tidal volume, end-expiratory alveolar pressure, and the inspiratory-to-expiratory duration ratio (I: E) are kept constant. However, some patients may find pressure-support ventilation to be more comfortable, particularly those with substantial respiratory efforts. Nevertheless, volume-cycled ventilation modes offer greater control over tidal volume, a critical factor in preventing ventilator-associated lung injury **(12).**

2-Inspiratory time:

Prolonging inspiratory time with an elevated I:E ratio is a commonly employed strategy for lung recruitment in ARDS patients. This approach elevates mean airway pressure, but shortening expiratory time can lead to hyperinflation and increased intrinsic PEEP (PEEPi). When ventilation is pressure-limited, PEEPi levels can be manipulated to further enhance lung recruitment. However, in volume-controlled ventilation modes without pressure limitation, excessive PEEPi levels can cause lung overdistension and hemodynamic compromise. While there is a lack of definitive clinical outcome studies specifically addressing inspiratory time or PEEPi levels, it is common practice during pressure-controlled ventilation to increase the I: E ratio to 1:1 or 2:1 (inverse ratio ventilation) with meticulous monitoring of PEEPi and hemodynamic **(13).**

3-Protective ventilatory strategies:

A-Low tidal volume:

Historically, patients with ARDS were ventilated with tidal volumes of 10-15 ml/kg. Due to concerns about acute lung injury (ALI) and ARDS, a landmark study examined the effect of reducing tidal volumes to 4-6 ml/kg lean body weight and setting inspiratory Plateau Pressure (PPlat) at a maximum of 30 cm of water, in a heterogeneous population with this condition. The study showed that the lower tidal volume group had improved survival as the mortality rate was 31% versus 40% . Interestingly, they found that low tidal volume ventilation was beneficial in patients whose lungs were less compliant, but patients with more compliant lungs tolerated low tidal volumes poorly, suggesting that a proportion of patients may be better managed with tidal volumes > 6 ml/kg. Other investigators have suggested that using levels of PPlat described in the ARDS Net study may be a better target than tidal volume for lung protective ventilation as some patients will reach this level before a tidal volume of 6 ml/kg is achieved **(14).**

Ventilation with small tidal volumes and limited airway pressures can reduce ventilator-associated lung injury from overdistention. However, small tidal volume ventilation may cause complications from acute respiratory acidosis. Thus, achieving the beneficial effect of this approach requires some compromise of traditional objectives concerning gas exchange and acid-base balance **(15).**

Current evidence strongly supports a low tidal volume, pressure-limited strategy for lung-protective ventilation in ARDS. While the precise target tidal volume remains a subject of debate, a value of 6 ml/kg lean body weight is recommended until more definitive data become available. This approach has been shown to reduce the risk of ventilator-induced lung injury and improve clinical outcomes in ARDS patients **(1).**

Open lung strategy:

the open lung approach (OLA) to ventilation involves increasing the level of Positive End Expiratory Pressure (PEEP) in combination with protective lung ventilation **(16).**

- protective lung ventilation with low tidal volumes (4-8 mL/kg PBW) and limited plateau pressures (Pplat <30 cmH20) is now widely considered the standard of care in acute respiratory distress syndrome (ARDS).
- **Lachmann's (17)** study entitled "Open up the Lung and Keep the Lung Open" explained his lung protective guidelines

There are three steps to open the lung:

1. A critical opening pressure must be overcome during inspiration.
2. This opening pressure must be maintained for a sufficiently long period.
3. During expiration, no critical time that would allow closure of lung units should pass, by using intrinsic PEEP or applying sufficiently high PEEP levels which prevent alveolar collapse.

Current evidence and clinical guidelines have shown that a lung-protective strategy including low tidal volume (< 6–8 ml/kg of predicted body weight), plateau (< 28–30 cmH2O) and driving pressure (< 14 cmH2O), and prone position for at least 12–16 h per day may alleviate VILI and improve clinical outcome **(18).**

When a lung is "open", it is characterized by optimal gas exchange and a low rate of intrapulmonary shunting. At the same time, airway pressures are minimal, ensuring the required gas exchange and hemodynamic side effects are thus minimized. All alveoli are almost equally expanded, minimizing shear forces and reducing any further damage or progression of lung injury. An open lung corresponds with the normal state of a healthy lung **(18).**

B-High PEEP and alveolar recruitment:

Ashbaugh first noticed that PEEP had beneficial therapeutic effects in ARDS in 1967. PEEP improves gas exchange and pulmonary function in several ways. It increases the functional residual capacity, thereby recruiting collapsed alveoli, improving oxygenation, and increasing lung compliance. By keeping alveoli open throughout the respiratory cycle, shear forces are reduced, therefore limiting ALI. It also redistributes extravascular lung water and improves ventilation-perfusion matching. Detrimental effects of PEEP also occur including reducing cardiac output and cerebral perfusion and over-distension of areas of less affected lung (Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (Writing Group for the Alveolar Recruitment for Acute. It is a commonly held view among intensivists that ongoing alveolar recruitment, to avoid atelectasis and atelectotrauma, is beneficial in patients with ALI. This view is based on the results of experimental studies that demonstrated reduced pulmonary edema and atelectotrauma once the lungs are fully recruited at end-expiration. As atelectotrauma may cause local and systemic

inflammation, bacterial translocation, and gross barotrauma, ongoing alveolar recruitment should be of clinical benefit **(16).**

Some authors recommend the lowest level (5-10 cm H_2O) of PEEP to be used to support oxygenation and maintain FiO_2 at or below 0.6. A recent meta-analysis, which included data from ALVEOLI, LOVS, and EXPRESS clinical trials, revealed that higher levels of PEEP were associated with improved survival and oxygenation among patients with moderate to severe ARDS. The distinction between atelectasis and atelectotrauma has significant implications for understanding the pathophysiology of acute respiratory distress syndrome (ARDS). Atelectotrauma, the mechanical stress and inflammation caused by repetitive alveolar collapse and reopening, is considered a more potent driver of lung injury than atelectasis itself. Experimental studies have demonstrated that atelectotrauma induces greater activation of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), macrophage inflammatory protein-2 (MIP-2), and interleukin-6 (IL-6), compared to atelectasis alone. These findings suggest that atelectotrauma plays a crucial role in the pathogenesis of ARDS and may serve as a therapeutic target **(19).**

Four large randomized clinical trials (**ART**, **ALVEOLI**, **ExPress**, and **LOV** trials) enrolling 3264 patients have compared higher PEEP (approximately 15 cmH2O) with lower PEEP (approximately 8 cmH2O or 13 cmH2O in the ART trial), and all failed to improve survival with higher PEEP, even if a trial suggested a survival benefit in sicker patients. Interestingly, the ART trial reported higher mortality in the presence of high PEEP levels **(20).**

Permissive hypercapnia:

Permissive hypercapnia occurring as a result of lowering tidal volumes and minute ventilation is safe. While permissive hypercapnia is tolerated in the majority of ARDS patients, those with pre-existing metabolic acidosis may require treatment to prevent worsening acidosis, so the use of both increased respiratory rates (up to 35 breaths/minute) and bicarbonate infusions in such patients **(21).**

B-Prone positioning ventilation:

Prone positioning has been known for decades to improve oxygenation in animals with acute lung injury and most patients with ARDS. The mechanisms of this improvement include a more uniform pleural-pressure gradient, a smaller volume of lung compressed by the heart, and more uniform and better-matched ventilation and perfusion. Prone positioning has an established niche as an intervention to improve gas exchange in patients with severe hypoxemia refractory to standard ventilatory manipulations. Prone positioning has been proposed as a beneficial maneuver in ARDS. The basic rationale behind the strategy is to recruit areas of previously collapsed lungs, allowing more homogeneous ventilation, therefore preventing over-distension and ALI. However, a prone-positioned patient generates several problems such as potential endotracheal tube displacement, abnormal pressure areas, difficulty in providing adequate Cardiopulmonary Resuscitation (CPR), and difficulty in feeding **(22).**

The favorable effect of the prone position on oxygenation has been confirmed in a recent trial, which also demonstrated that pronation with PEEP-optimization may reduce VILI. Changes in patient positioning can have a dramatic effect on oxygenation and ventilation in severe ARDS. Changing the patient position to a prone position can improve the distribution of perfusion to ventilated lung regions, decreasing intrapulmonary shunt and improving oxygenation.While some studies have observed sustained improvements in oxygenation upon returning to the supine position, the optimal duration of prone positioning remains unclear. One study involving trauma patients with ARDS demonstrated impressive and persistent oxygenation improvement with repeated cycles of prone positioning (20 hours prone and 4 hours supine).

Others advocate for continuing prone ventilation as long as it remains effective before initiating weaning, with position changes limited to those necessary for routine nursing care **(13).**

Other modalities of ventilation:

1-High-Frequency Ventilation (HFV): High-frequency ventilation allows effective recruitment of atelectasis while delivering minimal tidal volumes at rates exceeding the normal respiratory rate. HFV is considered in the setting of failing conventional ventilation in patients with acute lung injury**.** High-frequency ventilation is considered in the setting of failing conventional ventilation in patients with acute lung injury. Patients with uncorrected hypotension should be adequately volume-resuscitated and stabilized on vasopressors before the initiation of HFV. Also, cardiac conditions with passive pulmonary blood flow dependency "without using a pump" are a relative contraindication **(23).**

Types of HFV:

Currently, there are three different methods to deliver this type of ventilation:

I-High-frequency positive pressure ventilation((HFPPV)): uses a conventional ventilator at higher-than-normal respiratory rates (60-100 breaths/minute). This strategy is rarely used because of mechanical inefficiencies of the ventilator **(24).**

II-High-Frequency Jet Ventilation (HFJV) uses a device that injects

a jet of air through a small diameter tube near the endotracheal tube. This jet of air draws gas into the lungs and directs it toward the bronchi. High-frequency jet ventilation uses a high-pressure gas jet delivered at a high frequency of 1-10 Hz (60-600 breaths/minute). Other gas in the ventilator circuit is entrained producing a tidal volume (VT) of 2-5 ml/kg that can be adjusted by altering the inspiratory time and/or driving pressure. Exhalation in HFJV is passive. Its use requires sedation and, in most cases, neuromuscular paralysis. HFJV has been associated with the development of necrotizing tracheobronchitis and endotracheal tube mucus inspissation. These complications can be avoided with proper gas humidification **(25).**

III- High- Frequency Oscillatory Ventilation (HFOV):

High-frequency oscillatory ventilation was first conceived as a potential ventilatory strategy after it was noted that panting dogs take breaths smaller than their dead space, but still maintain oxygenation. The mechanism of this observation is still unknown but it is thought that the high frequency of panting increases turbulence and thus mixing and diffusion of oxygen. This principle is utilized in HFOV and has had some success as a ventilatory strategy in ARDS. High-frequency oscillatory ventilation differs from HFV in several important aspects. Respiratory rate 3-20 Hz (180-1200 breaths/minute) and tidal volume (1-3 ml/kg) are generated by the excursion of an oscillator within a ventilator circuit similar to that used for CPAP and are varied by altering the frequency, I: E ratio and oscillator amplitude. The use of an oscillator to generate tidal volume results in active expiration. Mean airway pressure is adjusted by altering the fresh gas flow into the circuit or the expiratory pressure valve. Oxygenation is controlled by altering mean airway pressure or FiO2 **(26).**

In summary, based on the available data, high-frequency oscillation might reduce mortality in patients with ARDS compared with conventional ventilation and is unlikely to cause harm. It improves the PaO2/FiO2 ratio by increasing the mean airway pressure but not the oxygenation index. Clinicians who currently use or are considering high-frequency oscillation to treat ARDS can be reassured by these results. Completion of ongoing multicentre randomized controlled trials will provide more definitive data on mortality and safety for this intervention **(24).**

2- Airway pressure release ventilation (APRV):

Airway pressure release ventilation (APRV) is a ventilatory modality that alternates between high and low airway pressures, allowing for spontaneous breathing. This novel approach has shown promise in improving oxygenation and shortening ICU stay in patients with ARDS. Studies suggest that APRV reduces VILI and improves lung function and inflammation compared with other ventilation modes **(20).**

Airway pressure release ventilation is a pressure-targeted, time-cycled mode of ventilation that is similar to conventional Pressure-Controlled Ventilation (PCV). In addition, APRV allows spontaneous breathing during inflation by pressure release mechanism leading to more comfortable ventilation. Persisting spontaneous breathing during ventilatory support has been shown to improve the distribution of ventilation to dependent lung areas as well as gas exchange, mediated presumably by spontaneous diaphragmatic contraction apposing compressed alveoli. Improved gas exchange has been observed during spontaneous breathing with APRV as compared with controlled mechanical ventilation in patients with ARDS **(27).**

3-Pressure-Controlled Inversed Ratio Ventilation (PC-IRV): The exact mechanisms by which PC-IRV leads to improved gas exchange in ARDS are not clear but potential advantages are that a longer period of the respiratory cycle is spent at PPLAT, promoting a more homogeneous ventilation pattern, and peak airway pressures are reduced. It is also thought that a benefit may be provided by the shortened expiratory time in PC-IRV, which increases intrinsic PEEP, allowing alveolar compartments that expire slowly to remain open. However, this may also produce dynamic hyperinflation, barotrauma, and hypotension, which is undesirable. This mode of ventilation has successfully improved oxygenation when used in ARDS but its role continues as a rescue therapy **(28).**

Extracorporeal gas exchange:

Extracorporeal Membrane Oxygenation (ECMO) is when venous blood is removed via a cannula in the inferior vena cava or right atrium, passed through a heart/lung machine, and is returned to either the right atrium (venovenous bypass) or aorta (veno-arterial bypass). In venovenous bypass, pulmonary and systemic hemodynamics are maintained by the patient's cardiovascular function. Veno-arterial bypass allows systemic hemodynamic support as well as gas exchange. ECMO may have the ability to support lung protective ventilation and maintain low ΔP because a recent meta-analysis including more than 500 patients showed that ΔP during the first 3 days in ECMO had an independent association with in-hospital mortality **(20).**

Mechanical complications include oxygenator failure, tubing/ circuit disruption, pump or heat exchanger malfunction, and problems associated with cannula placement or removal. Patient-related medical problems are bleeding, neurological complications, additional organ failure (eg renal, cardiovascular, liver), barotrauma, infection, and metabolic disorders. Widely accepted exclusion criteria are as follows: contraindication of ECMO to anticoagulation, irreversible damage to the central nervous system, severe chronic pulmonary disease, extremely poor prognosis due to underlying disease (e.g., terminal cancer), immunosuppression, multiple organ failure and left ventricular failure. ECMO has proven mortality benefits in neonatal ARDS. In adults, a single prospective randomized study failed to show a survival advantage over conventional support **(29).**

Extracorporeal carbon dioxide Removal (ECCO2R) It has been suggested that extracorporeal carbon dioxide removal (ECCO2R) can manage both hypoxemic and hypercapnic respiratory failure. ECCO2R uses a blood flow of around 0.5–1.5 L/min, allowing the removal of low-flow CO2 and pH control while avoiding the invasiveness of ECMO. Some studies have suggested that ECCO2R is able to decrease VILI and maintain oxygenation. High-flow VV-ECMO makes it more difficult to optimize oxygenation and

CO2 removal given the higher flows adopted (2–4 L/min). A prospective, randomized trial compared important clinical outcomes in 40 patients with severe ARDS who received either conventional mechanical ventilation or Low-Frequency Positive-Pressure Ventilation (LFPPV) with ECCo2R. There was no significant difference in mortality between the two treatment groups. Perhaps the beneficial effects from LFPPV were counteracted by complications from ECCO2R, such as bleeding with increased transfusion requirements. These findings suggest that the improved mortality in the earlier, uncontrolled trials was not from LFPPV with ECCO2R, but instead from improvements in other aspects of critical care **(30).**

Liquid ventilation: For 350 million years, fish have breathed liquid through gills. Mammals evolved lungs to breathe air. Rarely, circumstances can occur when a mammal needs to "turn back the clock" to breathe through a special liquid medium. This is particularly true if surface tension at the air-liquid interface of the lung is increased, as in acute lung injury. In this condition, surface tension increases because the pulmonary surfactant system is damaged, causing alveolar collapse, atelectasis, increased right-to-left shunt, and hypoxemia. The aims of treatment are: to offset increased forces causing lung collapse by applying mechanical ventilation with PEEP, to decrease alveolar surface tension with exogenous surfactant, and lastly to eliminate the air-liquid interface by filling the lung with a fluid in which both oxygen and carbon dioxide are highly soluble to serve as a respiratory medium **(31).**

There are two types of liquid ventilation: Total liquid ventilation requires a liquid ventilator-gas exchange device to oxygenate the liquid, deliver the tidal volume, and remove carbon dioxide. The other type is Partial Liquid Ventilation (PLV), in which the lungs are filled approximately to functional residual capacity. Gas ventilation is then continued with a conventional ventilator **(32).**

Perfluorocarbons (PFCs) as a respiratory medium:

The PFCs are organic compounds in which all hydrogen atoms have been replaced by halogens, usually fluoride. PFCs are stable, inert compounds, and have low intermolecular forces, so the surface tension of these liquids is remarkably low, and their elimination from the body is almost entirely by exhalation in the unchanged form **(31).**

They are immiscible with both hydrophobic and aqueous solutions. Of great interest is that at atmospheric pressure and body temperature, PFCs dissolve large amounts of gases, in particular oxygen and carbon dioxide. The ideal PFC for liquid ventilation should have a high solubility for oxygen and carbon dioxide to maintain gas exchange, and a greater density than body fluids so that it descends to the dependent regions of the lungs, where most atelectasis occurs, and re-opens them (an effect termed liquid PEEP) and a low surface tension to compensate for deficient surfactant and improve lung compliance. PFCs have anti-inflammatory properties in the alveolar space. The anti-inflammatory effects of liquid ventilation in acute lung injury are from the inhibition of neutrophil and macrophage function and the dilution of inflammatory debris in the airways **(31).**

Pharmacological management of ARDS:

1-Exogenous surfactant therapy:

Surfactants act by reducing alveolar surface tension, thus preventing alveolar collapse and limiting pulmonary edema. Surfactants also have anti-inflammatory and antimicrobial properties. Findings on the impact of surfactants on mortality in ARDS have been conflicting over years, and a recent meta-analysis concluded no significant improvement of mortality and gas exchange. In addition to the absence of effect, surfactants may cause hypoxemia and hypotension **(33).**

2-Inhaled vasodilators:

Most ARDS patients have mild-to-moderate pulmonary arterial hypertension. A progressive rise in pulmonary vascular resistance has been observed in patients who die from ALI. The cause of pulmonary

arterial hypertension is multifactorial, and may include hypoxic vasoconstriction, destruction and/or obstruction of the pulmonary vascular bed, and high levels of PEEP. In some patients, pulmonary arterial hypertension can lead to cardiac dysfunction from right ventricular overload, lowering pulmonary arterial pressure with pulmonary vasodilators improve the management of ARDS **(34).**

Nitric Oxide (NO) and prostacyclin:

Inhaled nitric oxide (iNO), prostaglandins, and prostacyclins have been tested in patients with ARDS, providing different results. Guidelines suggest the use of iNO in the case of severe hypoxemia in severe ARDS despite the use of other rescue maneuvers (e.g., prone positioning), possibly as a bridge therapy to ECMO. Despite the confirmed benefits in improving oxygenation, there is no conclusive evidence on mortality outcome. Similar to nitric oxide, prostaglandins and prostacyclins have vasodilatory properties. A recent trial confirmed there were no improvements in oxygenation or clear benefits on outcomes using treprostinil**.** Aerosolized prostacyclin showed similar efficacy to iNO on pulmonary vasodilation and improvement of oxygenation **(35).**

β-Agonists:

β-agonist drugs are known for their bronchodilator effects and have been proposed as a therapeutic option for ARDS due to their potential anti-inflammatory properties and ability to promote alveolar fluid clearance. While β-agonists have demonstrated the ability to improve oxygenation in ARDS patients, evidence supporting their impact on overall patient outcomes remains limited. The BALTI-2 trial, which compared salbutamol to placebo, failed to show any improvement in patient outcomes. Currently, no further clinical trials are underway to investigate the use of β-agonists in ARDS. Identifying specific patient populations that may benefit from airway clearance therapies could be a potential strategy for evaluating the true efficacy of β-agonists in future clinical trials. **(20).**

Nebulized Heparin:

Nebulized heparin demonstrated efficacy in dissolving thrombi and mitigating alveolar fibrin deposition, which can contribute to hypoxemia and impaired alveolar capillary permeability. A phase 3 trial investigating the effects of nebulized unfractionated heparin (25,000 IU every 6 hours until day 10) versus placebo revealed no improvement in daily physical activities but did show a reduced progression of lung injury. An ongoing trial (NCT03465085) is comparing the efficacy of nebulized heparin (10,000 IU every 4 hours) to streptokinase (250,000 IU every 4 hours) and placebo on gas exchange in 15 of 25 participants. No further trials are currently scheduled **(36).**

3-Antioxidant therapy:

Patients with ARDS experience oxidative stress from neutrophil activation and from high levels of inspired oxygen. Works by Quinlan et and Matthay indicated that patients who do not survive ARDS sustain much greater levels of oxidative molecular damage, suggesting that their antioxidant defense mechanisms are weakened. N-Acetylcysteine (NAC) and procysteine, oxygen free-radical scavengers and precursors for glutathione, were efficacious in some experimental studies. A recent study investigated the effects of NAC treatment (IV NAC in 150 mg/kg at the first day followed by 50 mg/kg/day for three days) on 27 ICU patients with ARDS considering the glutathione-S-transferase genetic variations, as an important enzyme contributing in oxidative stress pathways. The results indicated that NAC improved oxygenation (increase in PaO2/FiO2) and decreased mortality rate in treated patients compared to control group, Evaluation of glutathione-S-transferase (GST M1, P1 and T1), in these patients have showed an association between GST M1, null, and GST M1 and T1 double null polymorphisms with increased mortality in control group, suggesting antioxidant therapy critical for this group of patients **(37).**

A recent study on high-dose antioxidant protocol (ascorbic acid 1000 mg q8h, α-tocopherol 1000 IU q8h, and selenium 200 mcg qd for 7-day course) demonstrated pulmonary benefits like reduction in acute lung injury and ventilator-induced pneumonias during the period of high-dose antioxidant supplementation for critically ill trauma patients **(38).**

4-Anti-inflammatory therapy:

A-Corticosteroid therapy:

The inflammatory cascade that contributes to the progression of ARDS has led to the use of anti-inflammatory drugs, particularly corticosteroids. Corticosteroids appear to be effective in halting the harmful sequence of immunological events associated with ARDS and preventing fibrosis due to their ability to suppress cell-mediated immunity and reduce cytokine release and activation **(39)**

The use of corticosteroids in the treatment of ARDS has been the subject of great controversy and debate. Corticosteroid therapy in ARDS has been studied with regard to:

1) Preventilation of ARDS in high-risk patients

2) Early treatment with high-dose, short-term therapy, and Prolonged therapy with low-dose, in unresolved cases based on pharmacological efficacy of methylprednisolone in ARDS **(39)**

In trials of short term, high dose steroid therapy (for example, methylprednisolone 30 mg/kg 6 hourly for 24 hours) failed to show an improvement in mortality of patients at risk of or with early ARDS associated with sepsis, aspiration, and trauma. Current evidence does not support a role for Corticosteroids in the management of ARDS in either the early or late stages of the disease. More research is required to establish the role of steroids in specific subgroups of patients with severe sepsis and early ARDS who have relative adrenal insufficiency and patients with late ARDS 7-14 days after the onset of disease. A recent meta-analysis from eight RCTs supported the use of corticosteroids for mortality benefits (relative risk, 0.71; 95% CI, 0.54–0.92). However, corticosteroids cannot be considered as standard of care in patients with ARDS, and the heterogeneity in responses among patients with ARDS is a possible reason for the uncertain response to this treatment **(20).**

Phospholipase inhibitors:

The positive effects of secretory phospholipase A2 inhibition in animal models of sepsis and lung injury led to preliminary trials of two concentrations of a selective inhibitor of group IIa secretory, phospholipase A2, namely LY315920Na and S-5920, infused for 7 days "in patients presenting within 36 hours with severe sepsis. In the phase II study, the treatment group showed a non-significant reduction in the development of ARDS and time spent on the ventilator. The principal mortality benefit occurred in patients who received the drug within 18 hours of their first organ failure. Prospective trials are required to confirm that early administration of LY315920Na/S-5920 protects lung function and improves mortality in patients with severe sepsis **(40).**

Prostaglandin E1 (PGE1):

Intravenous PGE1 causes both pulmonary and systemic vasodilation and, in some critically ill patients, increases cardiac output and oxygen delivery. Although the effect on the pulmonary circulation is usually small, vasodilation is more marked under hypoxic conditions, and the nebulised drug improves ventilation-perfusion matching. PGE1 also inhibits platelet aggregation and neutrophil adhesion. The initial trial of PGE1 showed improved survival in trauma patients with respiratory failure. The dose of PGE1 was limited by side effects, particularly systemic hypotension, fever, diarrhea, thrombocytopenia and arrhythmia **(41).**

Thromboxane and 5-lipoxygenase inhibitors:

Thromboxane and leukotrienes are in part responsible for the pulmonary hypertension and hypoxemia of ARDS. Pulmonary vascular smooth muscle cells, endothelial cells, platelets, and neutrophils all release TXA2 on stimulation. TXA2 can initiate microvascular thrombosis consisting of neutrophil and platelet aggregates that are responsible for perfusion abnormalities and recurrent ischaemia-reperfusion injury to the lung. The vasoconstrictive effect of TXA2 similarly contributes to impaired gas exchange **(42).**

Other therapy for ARDS:

Recombinant human-activated protein C: Most recently, alterations in coagulation and fibrinolysis in the pathogenesis of ALI and ARDS have been examined, particularly related to alveolar fibrin deposition. Increased local tissue factor-mediated thrombin generation and depression of local fibrinolysis related to increased plasminogen activator inhibitors have been reported. Recent studies have documented that intravenous infusion and inhalation of aerosolized recombinant human-activated protein C attenuated ovine lipopolysaccharide-induced lung injury by preventing a decline in the volume of aerated lung tissue and improving oxygenation **(43).**

Keratinocyte Growth Factor and Granulocyte-Macrophage Colony Stimulating Factor Keratinocyte growth factor (KGF):

a product of fibroblasts and T cells, inhibits apoptosis and has mitogenic effects. Two trials evaluated the effects of KFG but found no efficacy in reducing leukocyte infiltration or inflammation. In the KARE trial, KFG did not improve gas exchange and clinical outcome, and mortality was even higher than expected, suggesting potential harm. Granulocyte-macrophage colony stimulating factor (GM-CSF) showed promising results in the preclinical setting, stimulating the maturation of alveolar epithelial cells. However, no benefits were confirmed in clinical trials on ventilator-free days and mortality. There is currently a trial comparing GM-CSF with placebo that is investigating bronchoalveolar lavage fluids of patients with ARDS **(20).**

Stem-cell therapy:

Stem cells could be a potential therapy for ARDS, promoting lung repair and attenuating the inflammatory response. However, the mechanisms involving the anti-inflammatory and antifibrogenic effects of stem cells must be better elucidated, limiting their immediate clinical use in ARDS. Several experimental sutides have evaluated the effect of stem cells in ALI. These models showed the presence of donor stem cells in the lungs, including epithelial cells types I and II, endothelial cells, fibroblasts and interstitial monocytes. Stem cells are recruited to the lung due to the inflammatory process triggered by lung injury. In this context, studies have shown that the use of Mesenchymal Stem Cells (MSCs) in Lipopolysaccharide (LPS)-induced ALI yielded a marked decrease in mortality and systemic inflammatory response, by suppressing the production of proinflammatory cytokines and stimulating the release of anti-inflammatory cytokines **(43).**

Recently, **Araujo et al. (44)** reported that bone marrow mononuclear cell therapy was effective at inhibiting fibrogenesis independent of the etiology of lung injury (pulmonary or extrapulmonary ALI), but its ability to attenuate inflammatory responses varied according to the cause of ALI.

Certainly, more studies are necessary to determine which cells are the source of the soluble factors and to elucidate the effects of the interaction between lung injury and the consequent recruitment of stem cells, with subsequent differentiation into lung cells. In summary, endogenous and exogenous stem cells have reduced lung injury and its consequent fibrotic process, diminished systemic and pulmonary inflammation and produced more appropriate tissue repair through differentiation into various lung cells **(45)**

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