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Review

Update on management of acute respiratory distress syndrome

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Abstract: Acute respiratory distress syndrome (ARDS) is a frequent and life-threatening condition in intensive care units (ICUs). Management of ARDS remains challenging despite years of research. Morbidity and mortality are not only caused by the syndrome itself but can also be the result of ventilator-induced lung injury. In this article, an update on ARDS management including ventilator strategies, rescue therapies, pharmacological treatments, ICU supportive care, and rehabilitation is proposed. While lung protective ventilation remains the standard option for patients with ARDS, neuromuscular blockade and prone positioning are gaining support after successful trials. Helmet non-invasive ventilation and high-flow nasal cannula might be useful for mild-to-moderate ARDS. Extracorporeal membrane oxygenation and carbon dioxide removal are not recommended in standard practice although they might be useful in severe ARDS.

Keywords: acute respiratory distress syndrome; respiratory failure; lung protective strategies; mechanical ventilation; ECMO; prone ventilation; neuromuscular blockade; high flow nasal cannula

Abbreviations: CT = Computed Tomography; PEEP = Positive end-expiratory pressure; CPAP = Continuous Positive Airway Pressure; PaO_2 = Partial pressure of arterial oxygen; FiO_2 = Fraction of inspired oxygen; ARDS = Acute respiratory distress syndrome; HFNC = High flow nasal cannula; NIV = Non-invasive ventilation; ECMO = Extracorporeal membrane oxygenation; $ECCO_2R$ = Extracorporeal carbon dioxide removal; ICU = intensive care unit; 95% CI = 95% confidence interval; HR = Hazard ratio; HFOV = High frequency oscillation ventilation; APRV = Airway pressure release ventilation

1. Introduction

Acute respiratory distress syndrome (ARDS) describes an acute lung injury caused by inflammation and capillary leakage and resulting in diffuse pulmonary infiltrates and hypoxemia. Distinctive from pulmonary edema, which is caused by cardiac failure or fluid overload, ARDS is triggered by direct pulmonary insults or systemic inflammation (Table 1) [1]. It is a common disease entity in intensive care units (ICUs) and a recent worldwide observational study showed that ARDS accounted for 10.4% of ICU admissions [2]. The Berlin definition proposed in 2012 is the latest definition for ARDS and emphasizes on clinical features, radiological findings, the degree of hypoxemia, and the need to exclude alternative diagnoses including cardiac failure and fluid overload (Table 2) [3]. The severity of ARDS can be categorized by the degree of hypoxemia reflected by the PaO_2/FiO_2 ratio. Compared with the American-European Consensus Conference definition from 1994, the radiographic criteria in the Berlin definition are more explicitly defined although whether this translates to improved inter-observer variability is controversial [4,5,6]. Despite accumulating therapeutic options, the mortality of severe ARDS is still over 40% [2].

Table 1. Risk factors for acute respiratory distress syndrome [1].

Direct pulmonary injury	Indirect insults
Pneumonia	Extra-pulmonary sepsis
Aspiration	Transfusion-related acute lung injury
Drowning	Shock
Fat and amniotic fluid embolism	Severe pancreatitis
Thoracic contusions	
Pulmonary hemorrhage	
Inhalation injury	

Table 2. Berlin definition of acute respiratory distress syndrome [3].

Acute-onset, meaning within 1 week of known clinical insult or new or worsening respiratory symptoms
Bilateral opacities consistent with pulmonary edema must be present and may be detected on CT or chest radiography
Presence of hypoxemia defined by PaO_2/FiO_2 ratio < 300 mmHg at a minimum of 5 cm H_2O PEEP (or CPAP)
“Must not be fully explained by cardiac failure or fluid overload”, in the physician’s best estimation using available information—An objective assessment (e.g. echocardiogram) should be performed in the absence of ARDS risk factors such as trauma or sepsis

2. Ventilator strategies

2.1. Lung protective ventilation

It has been reported that nearly one in four patients requiring mechanical ventilation for indications other than acute lung injury or ARDS suffer from ventilator-induced lung injury (VILI) [7]. The incidence is likely to be higher in patients with ARDS but the exact figure varies across studies [8]. The concept of "baby lung" has come to light since the innovation of computed tomography (CT), which showed that the normally aerated and recruitable lung tissue in patients with ARDS measured at end-expiration was reduced to only 200–500 g, roughly equivalent to the normally aerated tissue of a healthy boy of 5–6 years [9]. These diseased lungs are susceptible to VILI [10]. Volutrauma is the result of high tidal volume, while barotrauma refers to lung injury caused by high airway pressure associated with high lung volume. Atelectrauma refers to lung injury due to the cyclic opening and closing of terminal lung units, which worsens regional lung strain and denatures the surfactant. Biotrauma is the translocation of pro-inflammatory mediators and bacterial products causing local endothelial injury and systemic organ dysfunction [10,11].

A single-center randomized controlled trial in 1998 compared protective ventilation using a tidal volume of > 6 ml/kg of predicted body weight, with conventional ventilation of 12 ml/kg. The use of protective ventilation resulted in a significant reduction in 28-day mortality (38% vs. 71%, $p < 0.001$), a reduced rate of barotrauma, and shortened ventilator days [12]. In 2000, the ARDSnet multi-center randomized controlled trial compared ventilation with a lower tidal volume of 6 ml/kg of predicted body weight and a plateau pressure of < 30 cm H_2O, with the traditional ventilator strategy of a tidal volume of 12 ml/kg of predicted body weight and a plateau pressure of < 50 cm H_2O. The study was stopped after the fourth interim analysis as the lower tidal volume arm was associated with significantly lower mortality than the conventional ventilation arm (31% vs. 39.8%, $p = 0.007$) [13]. A recent systemic review demonstrated lower mortality with low tidal volume than with traditional tidal volume ventilation when combined with higher peak end-expiratory pressure (PEEP) (the open lung approach), but no significant difference with low tidal volume alone [14]. The clinical practice guidelines from the American Thoracic Society (ATS)/European Society of Intensive Care Medicine (ESICM)/Society of Critical Care Medicine (SCCM) strongly recommend ventilator strategies that limit tidal volume (4–8 ml/kg predicted body weight) and inspiratory pressure (plateau pressure < 30 cm H_2O) for adult patients with ARDS [15].

A major obstacle to low tidal volume ventilation is the drop in minute ventilation causing hypercapnia. Elevated carbon dioxide levels, although well tolerated in most patients, have been shown to be detrimental to the lungs at a cellular level [16] and to induce pulmonary vasoconstriction, leading to right ventricular failure [17,18]. Severe hypercapnia with $PaCO_2 \geq 50$ mmHg was also associated with increased ICU mortality in patients with ARDS [19]. With an increasing understanding of the harmful effects of hypercapnia, the use of extracorporeal carbon dioxide removal has been growing (see section 3.5 below) [20].

2.2. Positive end expiratory pressure

Adequate use of PEEP facilitates alveolar recruitment, reduces intrapulmonary shunt and arterial hypoxemia, counteracts alveolar collapse, and minimizes atelectrauma [21]. However, too much PEEP may result in alveolar over-distention and hemodynamic compromise from increased intrathoracic pressure and decreased venous return. Multiple randomized controlled trials including ALVEOLI, LOV, and EXPRESS failed to show a significant benefit of higher PEEP [22,23,24]. Although the use of a higher level of PEEP was shown to improve patients' oxygenation, no significant benefit to hospital mortality or rate of barotrauma was demonstrated [25]. The clinical practice guidelines from ATS/ESICM/SCCM conditionally suggest the use of higher rather than lower levels of PEEP in patients with moderate or severe ARDS [15].

Different methods to titrate the level of applied PEEP exist, for instance the PEEP-FiO_2 table, imaging studies such as computed tomography of the thorax and lung ultrasonography, and respiratory mechanics based on compliance, plateau pressure, and transpulmonary pressure. No single method has been shown to be superior to the others and the optimal level of PEEP remains uncertain [21]. There has been increasing interest in the use of esophageal pressure as a surrogate for pleural pressure for titrating PEEP. A single-center randomized controlled trial evaluated PEEP level set, with reference to esophageal pressure, to maintain a transpulmonary pressure greater than zero, and compared it to ventilation following ARDSnet protocols. There was improved oxygenation in the intervention group but no significant difference in mortality at 6 months [26]. Results from the ongoing EPVent2 trial might offer more insight into the use of esophageal pressure-guided mechanical ventilation [27].

2.3. Open lung approach/lung recruitment

Some clinicians advocate the open lung approach which involves lung recruitment and a decremental PEEP trial. The pilot multi-center OLA trial, published in 2016, performed lung recruitment maneuvers using pressure-controlled ventilation to peak pressures of 50–60 cm H_2O and PEEP of 35–45 cm H_2O. The decremental PEEP trial was performed with 2 cm H_2O steps until the PEEP corresponded to the maximum compliance (tidal volume/ by peak pressure—PEEP). The OLA trial reported improved oxygenation but no significant differences in mortality or ventilator-free days [28]. In 2017 however, the international multi-center ART trial was the first to demonstrate higher all-cause mortality in patients with moderate to severe ARDS who underwent lung recruitment (using staircase recruitment maneuvers and PEEP titrated according to the optimal static compliance) than in those with low PEEP [29]. Although it remains unclear whether there might be a certain subgroup of patients with ARDS that would benefit from an open lung approach, the current evidence to support routine use of such an approach is weak. The current clinical practice guidelines conditionally suggest the use of recruitment maneuvers in adult patients with ARDS [15]. Careful patient selection is justified. The use of lung imaging is emerging [30] and the LIVE trial by Jabaudon describing personalized ventilation strategies tailored to CT-scan lung morphologies is currently ongoing [31].

2.4. *Driving pressure*

Driving pressure is defined as the difference between the plateau pressure (Ppl) and PEEP while the static compliance of the respiratory system (C_{RS}) refers to the relationship between the tidal volume (Vt) and driving pressure:

$$\Delta P = Ppl - PEEP$$

$$C_{RS} = \frac{Vt}{(Ppl - PEEP)}$$

In turn, driving pressure reflects the Vt adjusted for the C_{RS} [32]:

$$\Delta P = \frac{Vt}{C_{RS}}$$

In 2015, Amato et al. published a meta-analysis of data from nine randomized controlled trials showing that, among the ventilation variables examined, driving pressure was best correlated with survival. A decrease in driving pressure is associated with lower 60-day mortality [33]. Although the association between driving pressure and clinical outcome has been well validated in multiple trials [34–37], there has been no trial utilizing driving pressure as the target during ventilator setting [32]. Further prospective studies are required to establish the value of driving pressure in patients with ARDS.

2.5. *Other modes of invasive ventilation*

High frequency oscillation ventilation (HFOV) maintains lung inflation at a constant and elevated mean airway pressure, using a piston to cycle the ventilation at a rate of several hundred cycles per minute and an extremely small tidal volume (1–4 ml/kg) to minimize atelectrauma. The OSCILLATE trial in 2013 randomized 548 patients with new-onset, moderate-to-severe ARDS to either HFOV or a low tidal volume, high PEEP-controlled ventilation strategy. However, the study was terminated prematurely in view of increased in-hospital mortality in the HFOV group (47% vs. 35% in the control) [38]. The OSCAR trial, published in the same year and comparing HFOV to usual care, showed no difference in mortality at 1 month [39]. The negative outcome in the OSCILLATE trial could be related to hemodynamic instability due to the increased vasopressor requirements of the elevated mean airway pressure in HFOV. Based on these large-scale randomized controlled trials, HFOV is not recommended routinely in patients with ARDS.

Airway pressure release ventilation (APRV) is the alternation between a sustained high, and a transient low, airway pressure during mandatory or spontaneous breath over the respiratory cycle. It is a pressure-controlled mode where the high and low pressures are specified by the clinicians and the inspiration to expiration ratio is reversed to encourage recruitment and oxygenation [40]. The high mean airway pressure prevents alveolar collapse and atelectrauma and spontaneous breathing is allowed throughout the respiratory cycle [41]. There is evidence from a single-center randomized controlled trial that APRV is associated with shorter durations of mechanical ventilation, improved oxygenation, reduced sedation requirements, and shorter ICU stays. However, no significant

differences in mortality, incidence of pneumothorax, or length of hospital stay were found [42]. Further studies are required to determine whether APRV should be incorporated into standard practice.

2.6. Non-invasive ventilation

The benefits of non-invasive ventilation (NIV) have been well validated in hypercapnic respiratory failure and cardiogenic pulmonary edema. However, NIV use was found to be associated with increased ICU mortality in severe ARDS [43] with concerns of incomplete control over respiratory drive and delayed intubation in the event of NIV failure. Whether NIV use is a predictor of poor prognosis or just a marker of severity warrants further investigation. The role of NIV in ARDS was debatable until the recent introduction of helmet NIV. In a single-center randomized controlled trial including 83 patients, patients receiving NIV by helmet showed a significantly lower intubation rate than patients receiving NIV by face mask (18.2% vs. 61.5%, 95% CI for absolute difference −62.4% to −24.3%), and also showed a reduced length of ICU stay and lower hospital mortality as secondary outcomes. The helmet NIV group was able to deliver a higher PEEP (8 vs. 5 cm H_2O in the face mask group), which might be related to a reduction in air leakage and better patient tolerance [44]. Larger trials are required to inspect the general stability of the results outside this single-center study.

2.7. High flow nasal cannula

The use of a high-flow nasal cannula (HFNC) for oxygenation has gained increasing interest in different areas of clinical practice, including the management of acute hypoxemic respiratory failure. It consists of a flow meter, an air-oxygen blender, a heated inspiratory circuit, an active humidifier, and a designated nasal cannula. With a total flow of up to 60 L/min from the air-oxygen blender, HFNC permits a high (0.21–1.0) inspiratory fraction of oxygen. The heated and humidified gas flow reduces upper airway dryness and is potentially protective of the mucociliary function of the airways [45]. The continuous high flow of gas creates a low level of positive pharyngeal pressure during expiration (up to 3–5 cm H_2O with the mouth closed) and draws carbon dioxide out of the upper airways [46,47]. The multi-center FLORALI trial comparing HFNC to oxygen delivery through non-rebreathing masks or NIV in acute hypoxemic respiratory failure did not show a significant difference in intubation rates. However, HFNC was shown to increase ventilator-free days and 90-day mortality as secondary outcomes, and decrease the rate of intubation in a subgroup with PaO_2/FiO_2 ratios < 200 in post-hoc analysis [48]. While HFNC was shown to be an alternative to NIV to reduce intubation rate, close monitoring of patients on HFNC is mandatory to prevent delayed intubation and adverse clinical outcomes [49,50]. Further research regarding the role of HFNC specific to ARDS management is much anticipated.

3. Adjunctive measures in refractory ARDS

3.1. Neuromuscular blockade

Neuromuscular blockade is often combined with heavy sedation to facilitate lung protective strategies, minimize patient-ventilator asynchrony, and potentially lower oxygen consumption [51]. The ACURASYS trial demonstrated that in early-onset ARDS (less than 48 hours after endotracheal mechanical ventilation), the use of cisatracurium infusion for 48 hours improved 90-day mortality (HR 0.68, 95% CI 0.48–0.98) without increasing the risk of ICU-acquired weakness [35]. The application of neuromuscular blockade should be balanced against its potential complications including ICU-acquired weakness, venous thromboembolism, pressure ulcers, and awareness.

3.2. Pulmonary vasodilators

Common pulmonary vasodilators include inhaled nitric oxide and prostaglandins which selectively vasodilate pulmonary vessels in well-ventilated lung units without significant changes in mean arterial pressure or cardiac output [52]. Specifically, inhaled nitric oxide increases cyclic guanosine monophosphate in the cytosol, resulting in vasodilatation. A dose-response relationship has been demonstrated. It reduces ventilation-perfusion mismatch and, at a higher dose, improves pulmonary hypertension [53]. It is minimally toxic but carries the risk of methemoglobin formation at a dose of over 40 ppm [54]. A recent systemic review showed that inhaled nitric oxide improved oxygenation but the effect was not sustained for 48 or 72 hours, and there was no significant mortality benefit [55]. The inhaled prostaglandins alprostadil (prostaglandin E_1) and epoprostenol (prostaglandin I_2) exhibit pulmonary vasodilatory effects through cyclic adenosine monophosphate and anti-platelet properties. Similar to inhaled nitric oxide, inhaled prostaglandin was shown to improve only oxygenation, with no effect on mortality. There was also a significant increase in the rate of hypotension with prostaglandin use [56].

Despite the multiple potential benefits of β-agonist use shown in pre-clinical trials, including bronchodilation, anti-inflammatory action, and enhanced alveolar fluid clearance two subsequent randomized controlled trials did not demonstrate significant benefits [57]. The ALTA study using nebulized salbutamol and the BALTI-2 study, using intravenous salbutamol, were both terminated prematurely due to clinical futility [58,59]. Therefore, the current data do not support the routine use of inhaled pulmonary vasodilators and β-agonist in ARDS.

3.3. Prone ventilation

In a supine position, there is a pleural pressure gradient across the ventral and dorsal part of the lungs, contributed by the weight of the heart, ventral part of lungs, and abdominal viscera and by the asymmetric expansion of the lungs conformed by the chest wall [60–62]. The gravitational component is augmented by the pulmonary edema in ARDS [63]. While the pulmonary blood flow to the dorsal part of lung remains relatively unchanged, prone ventilation reduces the pleural pressure gradient from non-dependent to dependent regions and decreases ventilation-perfusion mismatch, leading to improved oxygenation [64]. More homogenous lung ventilation reduces regional shear forces and lowers the risk of ventilator-induced lung injury [65,66]. In the PROSEVA trial published in 2013, prone ventilation (performed for at least 16 hours per day for up to 28 days until a significant improvement in oxygenation was seen, the PaO_2/FiO_2 ratio worsened by 20%, or

complications arose requiring immediate interruption, for example non-scheduled extubation) was compared with conventional ventilation in a supine position in the control group. The 28-day mortality was significantly lower in the prone ventilation group (HR 0.39, 95% CI 0.25–0.63) with no significant increase in adverse effect [36]. Meta-analysis revealed no difference in overall mortality but a lower mortality in the subgroup receiving more than 12 hours of prone ventilation per day and in patients with moderate to severe ARDS (RR 0.74, CI 0.56–0.99) [67]. As prone ventilation is labor-intensive and carries the risk of inadvertent extubation, tube dislodgement or obstruction, pressure sores, and difficult patient monitoring, an established protocol and well-trained medical staff would be crucial for its successful application.

3.4. Extracorporeal membrane oxygenation

The use of extracorporeal membrane oxygenation (ECMO) has been growing steadily since the H1N1 pandemic and the CESAR trial in 2009 [68]. Venovenous ECMO offers respiratory support by establishing an extracorporeal circuit and taking over the gaseous exchange from the native lungs. It draws deoxygenated blood from a venous access cannula, pumps it through an oxygenator, and has a gas blender to adjust the sweep gas flow rate for carbon dioxide removal. The oxygenated blood is then returned to patient's venous system through a return cannula. Theoretically, by replacing the gaseous exchange function, ECMO allows the diseased lungs to rest although this has not yet been proven in an animal study [69]. In the CESAR trial, 180 patients were randomized to either ECMO or conventional ventilation management in which a lung protective strategy was not mandatory. There was an increase in survival at 6 months without disability in the ECMO arm and the study supported the referral of patients with severe ARDS to an ECMO-based center. The optimal mechanical ventilation strategies during ECMO remain under investigation. Higher PEEP levels during the first 3 days on ECMO were independently associated with decreases in mortality [70] while another study showed that driving pressure during ECMO was the only ventilator parameter associated with in-hospital mortality [71]. With lung protective strategies being widely adopted, the use of ECMO in addition to low tidal volume ventilation failed to demonstrate a mortality benefit [72]. Besides, ECMO-related complications such as cannulation injury, bleeding associated with anticoagulation, thrombotic complications, and nosocomial infections have been well documented [73,74]. ECMO is also technically challenging, labor-intensive, and resource demanding [75]. Given the limited positive evidence in the era of low tidal volume ventilation, the risk of catastrophic complications, and economic considerations, ECMO remains a salvage therapy in patients with refractory ARDS.

3.5. Extracorporeal carbon dioxide removal

Extracorporeal carbon dioxide removal ($ECCO_2R$) takes advantage of the high diffusibility of carbon dioxide and is effective in removing up to 50% of the carbon dioxide produced. The rate of carbon dioxide removal is largely limited by the rate of blood flow [76,77]. $ECCO_2R$ is analogous to ECMO except for its lower extracorporeal blood flow (250–1000 ml/min) and sweep gas flow. The setup of $ECCO_2R$ is less invasive than that of ECMO, using a smaller cannula for a lower blood

flow. Arteriovenous devices are pumpless systems utilizing the patient's own arteriovenous blood pressure gradient while venovenous devices are pump-driven, require lower blood flow with smaller cannulas, and minimize the risk of limb ischemia by avoiding arterial cannulation. The Xtravent study demonstrated the feasibility of an "ultra-protective" ventilation strategy with a tidal volume of 3 ml/kg with the use of $ECCO_2R$, but no significant differences in mortality or ventilator-free days were reported [78]. A systemic review showed no significant difference in mortality but a trend towards an increase of ventilator-free days with the use of $ECCO_2R$ in severe ARDS [79]. Data from ongoing large-scale trials would be valuable for considering the use of $ECCO_2R$ in routine practice.

4. Pharmacotherapy

There has been much enthusiasm for pharmacological treatments to combat the inflammatory response of ARDS [80,81]. Steroids target the fibroproliferative phase of ARDS by decreasing collagen deposition. Evidence to support steroid use in ARDS is contradictory. No effect on the prevention of ARDS in septic shock patients was found, nor any mortality benefit in early ARDS [82]. In contrast, a meta-analysis by Meduri et al. showed that prolonged glucocorticoid steroid treatment accelerated ARDS resolution and improved hospital mortality [83] although the study was criticized for substantial heterogeneity and publication bias. Ketoconazole is a synthetic anti-fungal agent with potential anti-inflammatory effects through the inhibition of 5-lipoxygenase. A large multi-center study did not show significant improvements in terms of mortality, ventilator-free days, or lung function with the use of ketoconazole [84]. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and dampen pulmonary and systemic inflammation. Meta-analysis did not demonstrate any benefits of statins in reducing mortality, ventilator-free days, or length of ICU stay in patients with ARDS [85]. The results of studies on the use of surfactant and immuno-modulation nutrition using fish oil were also disappointing [86,87]. The current evidence to support pharmacotherapy for ARDS is therefore insufficient.

5. Supportive care

In addition to specific treatments for underlying causes and organ support to maintain oxygenation and ventilation, supportive care is equally important in the management of patients with ARDS. Heavy sedation has been associated with increased ventilator days, prolonged ICU and hospital stay, and increased mortality [88] and thus light sedation strategies should be protocolized. Although ARDS is, by definition, not related to fluid overload, a restrictive fluid management strategy in acute lung injury was associated with shorter ventilator days [89] and extravascular lung water was shown to be an independent prognostic factor in patients with ARDS [90]. Overalimentation with excessive caloric provision correlates with increased carbon dioxide production and nutritional support therapy should therefore be individualized [91]. Comparable to management of other critically ill patients, normoglycemia with a blood glucose level of < 10 mmol/L (180 mg/dL) [92], the use of stress ulcer prophylaxis, and pressure sore prevention are recommended.

6. Rehabilitation

Critical care rehabilitation, though often neglected amidst busy clinical chores, plays a major role in the long-term functional outcome in ARDS survivors. There was higher morbidity, such as poor quality of life and functional impairment, in patients who did not receive rehabilitation [93]. Early mobilization and rehabilitation of patients after respiratory failure has proven to be feasible and safe in ICU [94]. A single-center randomized controlled trial studied the effect of standardized rehabilitation programs with patients receiving daily therapy of a passive range of motion, physical therapy, and progressive resistance, and compared the results to a control group who received weekend therapy only when ordered by the caring team. Although the standardized rehabilitation program failed to demonstrate an improvement in length of hospital stay or ventilator days, there was an improvement in physical and functional performance at 6 months [95]. With a growing number of ARDS survivors thanks to the advances in management, the demand for critical care rehabilitation is expanding.

7. Future directions

7.1. Personalized medicine

The concept of personalized ARDS medicine has been growing. ARDS is a heterogenous syndrome with different subphenotypes and endophenotypes [96]. The subphenotypes represent particular patient groups within the heterogenous population of patients with ARDS who share common observable clinical features, radiological characteristics or outcome [97]. Calfee et al. identified two subphenotypes of patients with ARDS in their latent class modelling of data from the ARMA trial and the ALVEOLI trial [13,22,80]. One subphenotype was characterized by more severe inflammation, shock, metabolic acidosis, and higher mortality, with a differential response to higher versus lower PEEP strategy [80]. Famous et al. also identified two subphenotypes of patients with ARDS that responded differently to conservative versus liberal fluid management [81]. The accumulating evidence suggests that the management of ARDS, from ventilator strategies and pharmacotherapy to fluid management, should be targeting the appropriate subphenotype. A deeper understanding of these ARDS subphenotypes is essential to bring personalized ARDS medicine to patients.

7.2. Cell-based therapy

Allogenic human mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue, and umbilical cord tissue have become a potential new treatment for ARDS in recent years. MSCs are multipotent cells which secrete paracrine factors and transfer mitochondria into injured cells. The anti-inflammatory and anti-microbial properties focus on the pathology in the lungs of patients with ARDS. There were no significant adverse effects in phase 1 trials while the phase 2 trials are ongoing [98,99]. Larger-scale trials are needed to translate the benefits of cell-based therapy from bench to bedside.

8. Conclusion

ARDS is a common clinical condition with significant heterogeneity and its management remains challenging and controversial. To date, studies demonstrating efficacy are largely due to reduced harm from ventilator-associated lung injury. Based on the available evidence, effective ARDS management (summarized in Figure 1) relies on the prevention of ventilator-induced lung injuries with low tidal volume ventilation, the possible application of an open lung approach, the use of adjunctive therapies such as neuromuscular blockade, and of rescue therapies including prone positioning, ECMO and $ECCO_2R$. Supportive care must not be forgotten and should be offered in continuum with early rehabilitation. Future research on personalized medicine and cell-based therapy is ongoing. High-quality and large-scale trials are needed to offer more insights into the management of patients with ARDS.

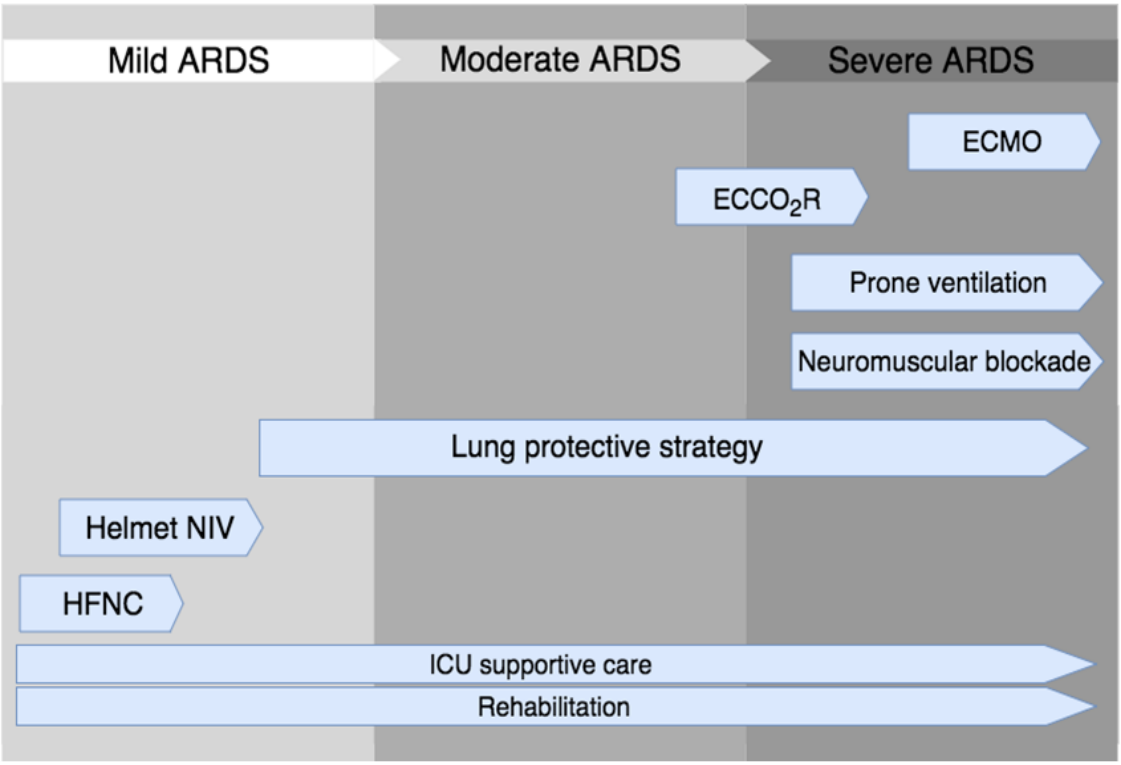

Figure 1. Key components in management of acute respiratory distress syndrome, according to disease severity. ARDS severity is defined by PaO_2/FiO_2 ratio at a minimum PEEP of 5 cm H_2O. Mild ARDS: PaO_2/FiO_2 = 200–300; Moderate ARDS: PaO_2/FiO_2 = 100–200; Severe ARDS: $PaO_2/FiO_2 < 100$.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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