

Acute respiratory distress syndrome: new definition, current and future therapeutic options

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ABSTRACT

Since acute respiratory distress syndrome (ARDS) was first described in 1967 there has been large number of studies addressing its pathogenesis and therapies. Despite this intense research activity, there are very few effective therapies for ARDS other than the use of lung protection strategies. This lack of therapeutic modalities is not only related to the complex pathogenesis of this syndrome but also the insensitive and nonspecific diagnostic criteria to diagnose ARDS. This review article will summarize the key features of the new definition of ARDS, and provide a brief overview of innovative therapeutic options that are being assessed in the management of ARDS.

KEY WORDS

Acute respiratory distress syndrome (ARDS); pathogenesis; therapeutic options

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Introduction

Acute respiratory distress syndrome (ARDS) is a life threatening respiratory condition characterized by hypoxemia, and stiff lungs (1-4); without mechanical ventilation most patients would die. ARDS represents a stereotypic response to many different inciting insults and evolves through a number of different phases: alveolar capillary damage to lung resolution to a fibro-proliferative phase (3). The pulmonary epithelial and endothelial cellular damage is characterized by inflammation, apoptosis, necrosis and increased alveolar-capillary permeability, which lead to development of alveolar edema (3). Since its first description in 1967 (4), there have been a large number of studies addressing various clinical aspects of the syndrome (risk factors, epidemiology, treatment) as well as studies addressing its pathogenesis (underlying mechanisms, biomarkers, genetic predisposition). A search of PubMed using the search terms: "Acute Respiratory Distress Syndrome" yields >20,000 journal

articles. However, despite this intense research activity, there are very few effective therapies for ARDS other than the use of lung protection strategies. This lack of therapeutic modalities is certainly related to the complex, pathogenesis of this syndrome with multiple signaling pathways activated depending on the type of lung injury. In addition, the lack of sensitive and specific diagnostic criteria to diagnose ARDS has hampered progress. To partially address the latter concern a recent consensus group made a number of changes to the previous American-European Consensus Conference definition of ARDS (5,6).

In the present review article, we will summarize the key features of the new definition of ARDS, which has been recently proposed from a panel of experts. In addition, we will also provide a brief overview of innovative therapeutic options that are being assessed in the management of ARDS, including gene therapy, and the administration of mesenchymal stem cells.

Updated definition of ARDS

ARDS is a syndrome with multiple risk factors that trigger the acute onset of respiratory insufficiency. The pathogenic mechanisms vary depending on the inciting insult, but as demonstrated on autopsy findings, there are a number of common pathological pulmonary features (7), such as increased permeability as reflected by alveolar edema due to epithelial and endothelial cell damage, and neutrophil infiltration in the early phase of ARDS. Until recently, the most accepted

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definition of ARDS for use at the bedside or to conduct clinical trials (1,8) was the American-European Consensus Conference (AECC) definition, published in 1994 (9). ARDS was defined as: the acute onset of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 mmHg, and no evidence of left atrial hypertension or a pulmonary capillary pressure < 18 mmHg (if measured) to rule out cardiogenic edema. In addition, Acute Lung Injury (ALI), the less severe form of acute respiratory failure, was different from ARDS only for the degree of hypoxemia, in fact it was defined by a $200 < \text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg.

Over the past 18 years of practice, the diagnostic accuracy of the ARDS definition by AECC has been questioned. In a series of 138 ARDS patients, the definition had relatively low specificity (51%) when compared with autopsy findings demonstrating diffuse alveolar damage as assessed by two independent pathologists (10). The reliability of the chest radiographic criteria of ARDS has been demonstrated to be moderate, with substantial interobserver variability (11,12). In addition, the hypoxemia criterion (i.e. $\text{PaO}_2/\text{FiO}_2 < 200$ mmHg) can be markedly affected by the patient's ventilator settings, especially the PEEP level used (13). Finally, the wedge pressure can be difficult to interpret and if a patient with ARDS develops a high wedge pressure that should not preclude diagnosing that patient as having ARDS. Based on these concerns, the European Society of Intensive Care Medicine with endorsement from the American Thoracic Society and the Society of Critical Care Medicine convened an international expert panel to revise the ARDS definition (14); the panel met in 2011 in Berlin, and hence the new definition was coined the Berlin definition. The goal of developing the Berlin definition was to try and improve feasibility, reliability, face and predictive validity (14). Of interest, this definition was empirically evaluated for predictive validity for mortality compared with the AECC definition, using data derived from multi and single center clinical trials (14). There are a few key modifications (oxygenation, timing of acute onset, Chest X-ray, and wedge pressure criterion) in the Berlin definition as compared with the AECC definition.

Oxygenation

In the Berlin definition, there is no use of the term Acute Lung Injury (ALI). The committee felt that this term was used inappropriately in many contexts and hence was not helpful. In the Berlin definition, ARDS was classified as mild, moderate and severe according to the value of $\text{PaO}_2/\text{FiO}_2$ ratio (Table 1). Importantly, the $\text{PaO}_2/\text{FiO}_2$ ratio value is considered only with a CPAP or PEEP value of at least 5 cmH_2O .

Timing of acute onset

The timing of acute onset of respiratory failure to make diagnosis

of ARDS is clearly defined in Berlin definition. It defines the exposure to a known risk factor or worsening of the respiratory symptoms within one week. It is important to identify risk factors that explain the context of acute respiratory failure arising from (Table 2).

Chest X-ray

The chest radiograph is characterized by bilateral opacities involving at least 3 quadrants that are not fully explained by pleural effusions, atelectasis and nodules. In the absence of known risk factors, a cardiogenic origin of edema is to be excluded by objective evaluation of cardiac function with echocardiography. Consequently, the wedge pressure measurement was abandoned because ARDS may coexist with hydrostatic edema caused by fluid overload or cardiac failure (8).

The ARDS Berlin definition was empirically evaluated to test predictive validity for mortality (14) by using a large clinical database from multicenter and single center clinical trials that included 3,670 patients. The mortality rate was 27% for mild, 32% for moderate and 45% for severe ARDS. Moreover, the number of ventilator free days declined from mild to severe ARDS, and the more severe stages of ARDS were associated with a progressive increase in lung weight as evaluated by CT scan and shunt fraction.

Current therapies

Numerous clinical studies have been conducted in patients with ARDS, but great advances in the care of the patients are still lacking and supportive therapies remain the mainstay in the ARDS management.

Protective mechanical ventilation

There is a large body of evidence from experimental and clinical studies demonstrating that mechanical ventilation, particularly in the setting of lung injury, can exacerbate functional and structural alterations in the lung (15). It is noteworthy that mechanical ventilation not only perpetuates lung injury, but also contributes to both the morbidity and mortality of ARDS (2,16,17). The concept that the limitation of end inspiratory lung stretch may reduce mortality in ARDS patients, culminated in the NIH-sponsored multicenter study of patients with ARDS (1,18). In this trial, patients randomized to receive a lower tidal volume (V_t) [4-6 mL/kg predict body weight (PBW), and maintenance of plateau pressure between 25 and 30 cmH_2O] had a survival benefit. Mortality was reduced from 40% in the conventional arm to 31% in the low V_t arm (CI, 2.4-15.3% difference between groups) (1). The benefit in terms of mortality and ventilation free days did not appear to be related to the value

Table 1. ARDS Berlin definition.

The Berlin definition of acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging ^a	Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation ^b	
Mild	200 mmHg < PaO ₂ /FIO ₂ ≤ 300 mmHg with PEEP or CPAP ≥ 5 cmH ₂ O ^c
Moderate	100 mmHg < PaO ₂ /FIO ₂ ≤ 200 mmHg with PEEP ≥ 5 cmH ₂ O
Severe	PaO ₂ /FIO ₂ ≤ 100 mmHg with PEEP ≥ 5 cmH ₂ O

Abbreviations: CPAP, continuous positive airway pressure; F₁O₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; ^aChest radiograph or computed tomography scan; ^bIf altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO₂/FIO₂ (barometric pressure/760)]; ^cThis may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Table 2. Common risk factors for ARDS

Direct	Indirect
Pneumonia	Non-pulmonary sepsis
Aspiration of gastric contents	Major trauma
Inhalational injury	Pancreatitis
Pulmonary contusion	Severe burns
Pulmonary vasculitis	Non-cardiogenic shock
Drowning	Drug overdose
	Multiple transfusions or transfusion associated acute lung injury (TRALI)

of the lung compliance at baseline or to the underlying risk factor for ARDS (19). Of note, the survival benefit was associated with a reduction of plasma IL-6 concentration, supporting the hypothesis that a lung protective strategy limits the spill over into the systemic circulation of inflammatory mediators, which in turn may induce multiple system organ failure (17).

In addition to lung over-distention, cyclic opening and closing of small airways and alveolar units (so called atelectrauma) can also lead to lung injury (20,21). Several clinical trials have been conducted in ARDS patients to examine the effects of an “open lung” approach in which the application of recruitment maneuvers and higher levels of PEEP may limit atelectrauma. In two randomized studies, Amato and colleagues, and Villar and colleagues examined the effect of a composite strategy that minimized tidal volume, adopted lung recruitment maneuvers, and applied a level of PEEP above the closing pressure of the lung (22,23). Although the intervention arms decreased mortality, the studies were criticized due to relatively small sample sizes and relatively high mortality in the control arms. The ARDS Network performed a second large clinical trial comparing lower vs. higher levels of PEEP (the ALVEOLI study) (24).

The trial was stopped early for futility, showing a trend to worse outcome in the higher PEEP arm, although there was an imbalance in patient characteristics at baseline favoring the control arm; the mean age of the higher PEEP arm was higher (54±17 vs. 49±17, P<0.05), the mean PaO₂/FiO₂ was lower (151±67 vs. 165±77, P<0.05), and there was a trend to higher APACHE III scores, at baseline.

Similar results were obtained in the Canadian Lung Open Ventilation (LOV) (25) clinical trial. The PEEP values were slightly higher compared to those of the previous ALVEOLI study. The conventional arm received levels of PEEP similar to the ARMA study. The study enrolled 985 patients and it failed to demonstrate any difference in mortality in the two groups (36.4% and 40.4% in the treatment and control groups respectively). The use of rescue therapies and death from refractory hypoxemia were less in the LOV - higher PEEP group. A French multi-centre randomized control trial (EXPRESS study) (26) addressed the superiority of an open lung approach in which PEEP was titrated to the highest value possible keeping P_{plat} <28-30 cmH₂O. In the control arm, PEEP was set between 5 and 9 cmH₂O. In both groups V_t was <6 mL/kg PBW. Patient treated according

to the open lung approach had significantly more ventilator free days and organ failure free days; however, hospital, 28-day and 60-day mortality were not different between the study groups, patients. Of note, patients who now would be considered to have moderate to severe lung injury ($P/F < 200$) tended to have lower 28-day mortality in the higher PEEP group compared to patients treated with lower PEEP.

A recent meta-analysis that incorporated trials (from 1996 to January 2010) comparing higher vs. lower levels of PEEP concluded that there is no difference in mortality applying lower vs. higher levels of PEEP in patients with mild ARDS. However, in the subgroup of patients with severe ARDS, as defined by a $PaO_2/FiO_2 < 200$, there was a benefit from higher levels of PEEP (27).

Non conventional therapies in severe ARDS

Historically prone positioning, high frequency oscillatory ventilation and extracorporeal membrane oxygenation have been proposed as non-conventional therapies for life-threatening refractory hypoxemia in severe ARDS patients (28). Although all these strategies have demonstrated to improve oxygenation, their impact on mortality is controversial. In fact, two recent RCT have questioned the safety of HFOV (29,30), where promising results come from a French study in which mortality was significantly lower in patients treated with extended period of prone position (28).

The prone positioning exploits gravity and re-positioning of the heart in the thorax to recruit the lung and to improve ventilation perfusion matching. Despite improving arterial oxygenation (31,32), prone position failed to show a significant improvement in mortality (32). In a subsequent study, prone ventilation was associated with a decrease in (37.8% vs. 46.1%) 28-day mortality in the subgroup of patients with severe hypoxemia, but given the small numbers, definitive conclusions cannot be drawn regarding the effect on mortality in this subgroup (32). However, pending results from a recent French study seem to clearly demonstrate a lower mortality in patients with severe ARDS who were treated with longer period of prone position.

In theory, high frequency oscillatory ventilation (HFOV) encapsulates the main principles of lung protection: it delivers extremely small tidal volumes around a relatively high mean airway pressure, at high respiratory frequencies (3-15 Hz), with the goal of avoiding tidal overstretch and recruitment/derecruitment (33,34). Despite the strong physiological rationale and preliminary human studies (35,36) showing improvement in oxygenation two recent large clinical trials (29,30) of HFOV in patients with moderate/severe ARDS failed to show any improvement in survival and have questioned safety of HFOV. Both trials compared HFOV to a lung protective strategy that employed low tidal volume and higher PEEP levels

to fully recruit the lung. In the OSCAR study 398 patients were randomized to HFO and 397 patients to a conventional lung protective strategy. There was no difference in mortality between the two groups (HFOV 42% vs. conventional ventilation 41%). In the OSCILLATE study, an excess mortality was reported in the HFOV arm and the trial was stopped early after enrolling 548 patients instead of planned 1,200 patients. In-hospital mortality was 47% in the HFO group compared to 35% in the control group (relative risk of death with HFO, 1.33; 95% confidence interval, 1.09 to 1.64; $P=0.005$). In addition, 11% of patients in the conventional arm crossed over to HFOV arm for refractory hypoxemia and despite this the death rates due to refractory hypoxemia were not different between groups. Possible factors that might explain this excess mortality in the HFOV arm are a greater use of sedation, neuromuscular blocker use, and longer and higher rates of vasoactive drugs. In light of these considerations, the results of these two studies preclude the routine use of this strategy in patients with ARDS (37).

In patients with severe hypoxemic and/or hypercapnic respiratory failure, extracorporeal lung support (ECLS) techniques, including extracorporeal membrane oxygenation (ECMO), have been considered to be possible rescue therapies. The aim of this strategy is to overcome severe hypoxemia and respiratory acidosis while keeping the lung completely at rest. Despite earlier negative trials (38,39), the CESAR study suggested the benefit of ECLS in patients with severe ARDS. In this RCT, 180 patients were randomized to receive veno-venous ECMO (after transfer to a specialized center) or conventional mechanical ventilation (in regional centres). The former group had a better 6 months survival than the latter one, but critics argue that the ECMO patients received a best practice treatment in specialized centers, while the control group treatment was left to the discretion of physicians in multiple non-specialized hospitals (40). Currently there is a French-led international multicenter randomized trial evaluating the impact of early veno-venous ECMO treatment in patients with ARDS, in terms of morbidity and mortality in the first 30, 60 and 90 days. The results are expected around January 2014.

ARDS therapies other than mechanical ventilation

Over the last decade, several non-ventilatory treatments have been investigated to further improve the outcome of ARDS patients. In particular, we will focus on the role of conservative fluid strategy and the putative role of neuromuscular blocking agents (8,41).

In ARDS patients, alveolar edema formation caused by increased vascular permeability may be worsened by higher hydrostatic pressure as a consequence of fluid overload. Of note, positive fluid balance, higher values of central venous and capillary wedge pressures are independent risk factors for

mortality in critical ill patients. To examine whether a more fluid-conservative strategy would impact outcomes, ARDSnet sponsored a RCT to evaluate the effects of fluid therapy strategy aimed to limit the net fluid balance in ARDS patients without shock and renal failure requiring replacement therapy (8). Mortality at 60 days was not different between the two study groups. However, patients randomized to fluid restriction had more mechanical ventilation free days and a lower ICU length of stay compared to those patients randomized to liberal fluid intake. The two study groups were different in terms of cumulative fluid balance; in particular the liberal fluid group had positive fluid balance of 7 liters in one week with 1 L of net fluid gain each day (8).

In patients with severe ARDS as defined by $\text{PaO}_2/\text{FiO}_2 < 150$, 48 hrs administration of non depolarizing neuromuscular blocking agent (NMBA) cisatracurium has been shown to improve oxygenation, and adjusted 90-day survival, as well as decreasing duration of mechanical ventilation and barotrauma, without increasing muscle weakness (41). Moreover, NMBAs have been shown to reduce levels of both pulmonary and systemic pro-inflammatory mediators (42). However, given the potential side effects of these medications in terms of critical illness neuromyopathy (CINM), its use should be limited to severe hypoxemic patients for a brief period.

Inhaled nitric oxide for its pulmonary vasodilator effects has been proposed to treat refractory hypoxemia reestablishing an adequate ventilation perfusion matching. Both recent randomized clinical trials (43,44) and robust meta-analyses (45,46) indicate that inhaled nitric oxide improves oxygenation over a 24 hour period of treatment. However, no benefit has been demonstrated on mortality. In addition, detrimental effects on kidney function have been documented thus limiting its cautious use to patients with severe ARDS and pulmonary hypertension.

Future non-ventilatory therapeutic options

In the last decade many molecular mechanisms have been discovered which greatly increase our understanding of ARDS pathogenesis. However, none of these new advances have been translated into effective therapies to improve outcome of ARDS patients. New therapeutic opportunities may come from gene and mesenchymal stem cells therapies. In the next sections of this review we will summarize the new findings of gene and mesenchymal stem cell therapies in animal models; these approaches hold promise in the treatment of ARDS.

Gene therapy for ALI/ARDS

Epithelial damage after lung injury is characterized by apoptosis and necrosis of type I and II alveolar cells. Epithelial damage dramatically contributes to alveolar edema formation, which is

associated with increased permeability; airspace infiltration by neutrophils amplifies and sustains the lung injury. After the acute exudative phase, alveolar edema clearance and proliferation and differentiation of type I into type II alveolar epithelial cells lead to resolution of lung injury. Abnormal tissue repair, depending on the severity of tissue damage, leads to extracellular matrix deposition and fibrosis.

In the acute exudative phase alveolar flooding associated with an impaired alveolar fluid clearance is the main determinant of ventilation perfusion mismatch and subsequent hypoxia in ARDS patients. This has led to extensive research to reestablish alveolar fluid clearance and keep the lung dry. The driving force for fluid reabsorption is based on the active transport of Na^+ from the alveolar space into the interstitial space. The Na^+ , K^+ transporting adenosine - 5'- triphosphate (Na^+/K^+ -ATPase) together with others ion transporters such as epithelial Na^+ channel (ENaC), the cystic fibrosis transmembrane conductance regulator (CFTR) create an osmotic gradient which reabsorbs fluid from the alveolar spaces.

Based on these physiological mechanisms, recent clinical trials have tested beta agonist administration as pharmacological intervention in patients with ARDS. In fact, several *in vitro* and animal studies have previously shown that beta agonist as salbutamol activate β -2 receptors on alveolar type-1 and type-2 cells, which increase intracellular cyclic adenosine monophosphate (cAMP), leading mainly to increased AFC. In 2011 the ARDS-net sponsored the ALTA study in which 282 patients with acute lung injury, as defined by PaO_2 and FiO_2 ratio of 300 or less, were randomized to receive aerosolized salbutamol (at dose of 5 mg) or placebo every 4 hours for up to 10 days (47). Unfortunately, the trial was stopped earlier because the primary end point, ventilator free days (VFDs), had crossed predefined futility boundaries. More recently, a large multicenter RCT, performed across 46 ICUs in the United Kingdom, showed that intravenous salbutamol is even hazardous for patients with early and severe ARDS (48). In fact, patients treated with salbutamol at dose of 15 $\mu\text{g}/\text{kg}$ ideal bodyweight/h had higher mortality at 28 days and lower ventilator and organ failure free days. The reason of these unfavorable outcomes seems to be related to higher rates of side effects as tachycardia, arrhythmias, and lactic acidosis in the interventional arm.

Based on the negative results of these large RCTs, gene therapy approaches to restore and potentiate the Na^+ movement across the alveolar epithelial barrier could be promising strategies to overcome the problem of systemic side effects of beta 2 receptors agonists. Transfer of $\alpha 2$ subunit or $\beta 1$ subunit of Na^+/K^+ ATPase has been demonstrated to increase the expression of Na^+/K^+ ATPase on alveolar epithelial cells and to improve alveolar fluid clearance (49,50). In a mouse model of LPS induced lung injury, plasmid transfer of genes encoding the $\alpha 1$ and $\beta 1$ subunits of the Na^+/K^+ -ATPase were delivered to

the lungs of mice using transthoracic electroporation. Delivery of plasmids expressing Na⁺, K⁺-ATPase subunits protected the lung from subsequent injury and partially reversed existing lung injury as demonstrated by a reduction of wet-to-dry ratios, bronco-alveolar lavage protein levels and an improvement of alveolar fluid clearance, and respiratory mechanics (51). Moreover, Adir and colleagues showed that overexpression of $\alpha 2$ or $\beta 1$ subunit of Na⁺/K⁺ ATPase significantly improved alveolar fluid clearance (AFC) not only in normal lungs but also in those exposed to ventilator induced lung injury (50,52). Seven days before the beginning of mechanical ventilation, rats were treated with adenovirus that expressed $\alpha 2$ or $\beta 1$ subunit of Na-K-ATPase. This gene therapy approach prevented the 50% reduction of AFC caused by VILI (50). Beta-adrenergic agonists improve Na⁺ transport mediated by Na⁺/K⁺ ATPase increasing the intracellular levels of cAMP. The adenovirus-induced overexpression of beta 2 adrenergic receptor gene greatly improved AFC increasing the expression of both ENaC and Na⁺/K⁺ ATPase (53).

A number of studies have demonstrated the role of growth factors in increasing AFC. In a mouse model of hyperoxia and oleic acid induced acute lung injury, liposome transfer of gene encoding keratinocyte growth factor attenuated lung injury likely increasing the proliferation of alveolar epithelial cells (54,55).

Lung injury in ARDS is characterized by a pro-inflammatory increase in vascular permeability and neutrophil infiltration, which sustain alveolar edema and damage to alveolar barrier. Several studies have focused on the role of gene therapy in modulating the pro-inflammatory response in the lung. Lung gene transfer encoding for IL10 has been shown to reduce the release of inflammatory cytokines in an *ex vivo* model of donor lungs before transplantation. Ten lungs of brain death patients, who did not match the criteria for transplantation, received 12 hour of normothermic *ex vivo* lung perfusion with or without the intra-tracheal delivery of adenoviral vector encoding human interleukin-10 (AdhIL-10). The lungs treated with this gene therapy approach demonstrated better graft function with improvement in oxygenation, pulmonary vascular resistance, and an increase in anti-inflammatory cytokines release (56). Moreover, in IL-10 knock out mice, chronically infected with *Pseudomonas Aeruginosa*, the adeno virus transfer of gene encoding for IL-10 produced a significant anti-inflammatory effect. Treated animals showed a reduction of IL-1 β , TNF α and macrophage inhibitory protein (MIP)-1 α release into the airway spaces. Moreover, this gene transfer mitigated neutrophil lung infiltration (57). Similar anti-inflammatory effects have been found with the delivery of genes encoding anti-inflammatory cytokines such as interferon protein 10 (IP-10) (58), IL 12 (59) and transforming growth factor beta-1 (TGF- $\beta 1$) (60).

Heme oxygenases (HO) are essential enzymes, which degrade heme into carbon monoxide (CO), biliverdin and free iron.

Due to its anti-inflammatory, anti-apoptotic and, as recently described, anti-viral properties the inducible HO isoform HO-1 is an important molecule which has been used in different genetic approaches to mitigate acute lung injury (61-63). Gene transfer of HO-1 provided lung protection against hyperoxia, influenza virus pneumonia and endotoxin mediated lung injury (61-63).

Mesenchymal stem cells

Mesenchymal stem cells (MSC) are multipotent stromal cells that can differentiate into a variety of cells types including osteoblasts, chondrocytes, adipocytes, *etc.* These cells can be isolated not only from bone marrow but also from fat, umbilical cord blood, placental tissue, skeletal muscle, and tendons. The International Society of Cellular Therapy published the criteria to identify MSCs: (I) adherence to plastic surfaces; (II) expression of CD105, CD73, CD90, without expressing CD45, CD34, CD14, CD11b, CD79 α , CD19 and human leukocyte antigen (HLA) II; and (III) the ability to differentiate into osteoblast, adipocytes, and chondroblasts *in vitro*.

MSCs have several properties that make them promising as a therapeutic approach in ARDS. MSCs differentiating into several cell types have regenerative properties and may repair damaged tissues. In addition, they can release many molecules, which contribute to immunomodulatory and anti-inflammatory effect. Moreover, MSCs lacking the HLA II molecules may escape the immune response after allogenic or xenogenic transplantation and may be used as carriers for gene therapy.

Recent findings describe a therapeutic role of MSCs in animal models of ARDS and sepsis. MSCs may attenuate the local and systemic inflammatory response in different mouse models of sepsis, predominantly through their paracrine immune-modulatory effect, despite their limited engraftment and differentiation in alveolar epithelial cells (64). Mei and colleagues demonstrated the immune modulatory effect of MSCs in a mouse model of LPS associated acute lung injury. The systemic administration of MSCs 30 minutes after LPS injection was associated with reduction in total cell and neutrophil counts in bronco-alveolar lavage (BAL) fluid as well as in pro-inflammatory cytokines in both BAL fluid and lung parenchyma homogenate. Of interest, the authors showed the role of MSC as carriers for the vasculo-protective gene angiopoietin 1 (ANGPT1). Mice treated with MSCs transfected with ANGPT1 had complete restoration of lung vascular permeability (65). Moreover, these results were expanded in a mouse model of sepsis in which the MSC therapy not only attenuated the systemic inflammatory response and organ dysfunction, but also improved bacterial clearance and survival through the enhancement of phagocytic activity (66). Thus, MSCs seem to be potent immunomodulators; they may interact with circulating and tissue monocytes and macrophages and reprogram them to

enhance an anti-inflammatory response.

Nemeth and colleagues demonstrated that monocytes and macrophages treated with MSCs produced large amount of the anti-inflammatory cytokine IL 10; in contrast, plasma concentrations of TNF α and IL 6 were reduced. The temporal reprogramming of monocytes induced by MSCs seems to be in part related to the production of prostaglandin E₂ (PGE₂) by MSCs. PGE₂ acting on the EP2 and EP4 macrophage receptors stimulate the production of IL 10 (67).

Conclusions

ARDS still represents a deadly form of respiratory failure with long term consequences in patient survivors and indeed, their families (68,69). Supportive therapies represent the mainstay of treatment of ARDS, whereas the limitation of end end-inspiratory lung stretch has been clearly demonstrated to reduce the ARDS associated mortality. Adoption of the new definition may be useful to better classify patients according to severity and prognosis. Lacking of effective therapies relies on the complex pathogenesis of the syndrome characterized by different overlapping signaling pathways Gene therapy and mesenchymal stem cells may be promising novel therapeutic strategies aimed at modulate key pathophysiological mechanisms of ARDS.

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