REVIEW ARTICLE

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 PaO_2/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 < PaO_2/FiO_2 ≤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. PaO_2/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 PaO_2/FiO_2 ratio (Table 1). Importantly, the PaO_2/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 arised 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 (Vt) [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 Vt 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_2O[c]
Moderate	100 mmHg < PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cmH_2O
Severe	PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

Abbreviations: CPAP, continuous positive airway pressure; F_IO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; [a]Chest radiograph or computed tomography scan; [b]If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2_(barometric pressure/760)]; [c]This 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 PaO_2/FiO_2 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 Pplat <28-30 cmH_2O. In the control arm, PEEP was set between 5 and 9 cmH_2O. In both groups Vt 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 be 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 PaO_2/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 neuromyophathy (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 μg/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 α2 subunit or β1 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 α1 and β1 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 α2 or β1 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 α2 or β1 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-1β, TNFα and macrophage inhibitory protein (MIP)-1α 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-β1) (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, CD79α, 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 trough 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 TNFα and IL 6 were reduced. The temporal reprogramming of monocytes induced by MSCs seems to be in part related to the production of prostaglandin E_2 (PGE_2) by MSCs. PGE_2 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 pathophysiologic mechanisms of ARDS.

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References

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301-8.
2. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 1999;282:54-61.
3. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-49.
4. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. Lancet 1967;2:319-23.
5. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
6. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med 1994;20:225-32.
7. Esteban A, Fernández-Segoviano P, Frutos-Vivar F, et al. Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. Ann Intern Med 2004;141:440-5.
8. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
9. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
10. Ferguson ND, Frutos-Vivar F, Esteban A, et al. Acute respiratory distress syndrome: underrecognition by clinicians and diagnostic accuracy of three clinical definitions. Crit Care Med 2005;33:2228-34.
11. Meade MO, Cook RJ, Guyatt GH, et al. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. Am J Respir Crit Care Med 2000;161:85-90.
12. Rubenfeld GD, Caldwell E, Granton J, et al. Interobserver variability in applying a radiographic definition for ARDS. Chest 1999;116:1347-53.
13. Villar J, Pérez-Méndez L, López J, et al. An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2007;176:795-804.
14. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
15. Dos Santos CC, Slutsky AS. Invited review: mechanisms of ventilator-induced lung injury: a perspective. J Appl Physiol 2000;89:1645-55.
16. Ranieri VM, Giunta F, Suter PM, et al. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000;284:43-4.
17. Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 2005;33:1-6; discussion 230-2.
18. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 2009;302:1872-9.
19. Eisner MD, Thompson T, Hudson LD, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;164:231-6.
20. Caironi P, Cressoni M, Chiumello D, et al. Lung opening and closing during ventilation of acute respiratory distress syndrome. Am J Respir Crit Care Med 2010;181:578-86.
21. Muscedere JG, Mullen JB, Gan K, et al. Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 1994;149:1327-34.
22. Villar J, Kacmarek RM, Pérez-Méndez L, et al. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med 2006;34:1311-8.
23. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338:347-54.
24. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive

end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327-36.
25. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:637-45.
26. Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:646-55.
27. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010;303:865-73.
28. Pipeling MR, Fan E. Therapies for refractory hypoxemia in acute respiratory distress syndrome. JAMA 2010;304:2521-7.
29. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013;368:806-13.
30. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013;368:795-805.
31. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001;345:568-73.
32. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA 2009;302:1977-84.
33. Chan KP, Stewart TE, Mehta S. High-frequency oscillatory ventilation for adult patients with ARDS. Chest 2007;131:1907-16.
34. Fessler HE, Derdak S, Ferguson ND, et al. A protocol for high-frequency oscillatory ventilation in adults: results from a roundtable discussion. Crit Care Med 2007;35:1649-54.
35. Mehta S, Lapinsky SE, Hallett DC, et al. Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome. Crit Care Med 2001;29:1360-9.
36. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166:801-8.
37. Malhotra A, Drazen JM. High-frequency oscillatory ventilation on shaky ground. N Engl J Med 2013;368:863-5.
38. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979;242:2193-6.
39. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295-305.
40. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351-63.
41. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
42. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006;34:2749-57.
43. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004;291:1603-9.
44. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26:15-23.
45. Afshari A, Brok J, Møller AM, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Cochrane Database Syst Rev 2010;(7):CD002787.
46. Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. BMJ 2007;334:779.
47. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Matthay MA, Brower RG, et al. Randomized, placebo-controlled clinical trial of an aerosolized β_2-agonist for treatment of acute lung injury. Am J Respir Crit Care Med 2011;184:561-8.
48. Gao Smith F, Perkins GD, Gates S, et al. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. Lancet 2012;379:229-35.
49. Factor P, Saldias F, Ridge K, et al. Augmentation of lung liquid clearance via adenovirus-mediated transfer of a Na,K-ATPase beta1 subunit gene. J Clin Invest 1998;102:1421-30.
50. Adir Y, Welch LC, Dumasius V, et al. Overexpression of the Na-K-ATPase alpha2-subunit improves lung liquid clearance during ventilation-induced lung injury. Am J Physiol Lung Cell Mol Physiol 2008;294:L1233-7.
51. Mutlu GM, Machado-Aranda D, Norton JE, et al. Electroporation-mediated gene transfer of the Na+,K+ -ATPase rescues endotoxin-induced lung injury. Am J Respir Crit Care Med 2007;176:582-90.
52. Squadrone V, Coha M, Cerutti E, et al. Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. JAMA 2005;293:589-95.
53. Dumasius V, Sznajder JI, Azzam ZS, et al. beta(2)-adrenergic receptor overexpression increases alveolar fluid clearance and responsiveness to endogenous catecholamines in rats. Circ Res 2001;89:907-14.
54. Baba Y, Yazawa T, Kanegae Y, et al. Keratinocyte growth factor gene transduction ameliorates acute lung injury and mortality in mice. Hum Gene Ther 2007;18:130-41.
55. Ulrich K, Stern M, Goddard ME, et al. Keratinocyte growth factor therapy in murine oleic acid-induced acute lung injury. Am J Physiol Lung Cell Mol Physiol 2005;288:L1179-92.
56. Cypel M, Liu M, Rubacha M, et al. Functional repair of human donor lungs by IL-10 gene therapy. Sci Transl Med 2009;1:4ra9.
57. Buff SM, Yu H, McCall JN, et al. IL-10 delivery by AAV5 vector attenuates inflammation in mice with Pseudomonas pneumonia. Gene Ther 2010;17:567-76.
58. McAllister F, Ruan S, Steele C, et al. CXCR3 and IFN protein-10 in

Pneumocystis pneumonia. J Immunol 2006;177:1846-54.
59. Ruan S, McKinley L, Zheng M, et al. Interleukin-12 and host defense against murine Pneumocystis pneumonia. Infect Immun 2008;76:2130-7.
60. Mora BN, Boasquevisque CH, Boglione M, et al. Transforming growth factor-beta1 gene transfer ameliorates acute lung allograft rejection. J Thorac Cardiovasc Surg 2000;119:913-20.
61. Otterbein LE, Kolls JK, Mantell LL, et al. Exogenous administration of heme oxygenase-1 by gene transfer provides protection against hyperoxia-induced lung injury. J Clin Invest 1999;103:1047-54.
62. Hashiba T, Suzuki M, Nagashima Y, et al. Adenovirus-mediated transfer of heme oxygenase-1 cDNA attenuates severe lung injury induced by the influenza virus in mice. Gene Ther 2001;8:1499-507.
63. Inoue S, Suzuki M, Nagashima Y, et al. Transfer of heme oxygenase 1 cDNA by a replication-deficient adenovirus enhances interleukin 10 production from alveolar macrophages that attenuates lipopolysaccharide-induced acute lung injury in mice. Hum Gene Ther 2001;12:967-79.
64. Gupta N, Su X, Popov B, et al. Intrapulmonary delivery of bone marrow-derived mesenchymal stem cells improves survival and attenuates endotoxin-induced acute lung injury in mice. J Immunol 2007;179:1855-63.
65. Mei SH, McCarter SD, Deng Y, et al. Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. PLoS Med 2007;4:e269.
66. Mei SH, Haitsma JJ, Dos Santos CC, et al. Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. Am J Respir Crit Care Med 2010;182:1047-57.
67. Németh K, Leelahavanichkul A, Yuen PS, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med 2009;15:42-9.
68. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348:683-93.
69. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364:1293-304.

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