Acute Respiratory Distress Syndrome: Therapeutics, Pathobiology, and Prognosis

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Abstract

Acute respiratory distress syndrome (ARDS) is a critical syndrome consisting of acute respiratory failure, which is characterized by injury to the alveolar capillary barrier that leads to the influx of protein-rich fluid infiltrates into alveolar spaces and subsequent devastating lung fibrosis. This deadly respiratory condition can be caused by various pulmonary (e.g., pneumonia, aspiration) or non-pulmonary (e.g., sepsis, pancreatitis, trauma) injuries, leading to the development of nonhydrostatic pulmonary edema. Despite various seminal events in the understanding of molecular mechanisms underpinning the ARDS, the armamentarium of therapies aimed at the underlying pathology remains limited and highly ineffective. ARDS has an enormous mortality rate of approximately 40%. Till today, ARDS management remains mostly supportive with lung-protective mechanical ventilation. Here, we deduce the recent advances in the understanding of the biology of the disease, the diagnosis, and the treatment of ARDS. Moreover, this review also provides a historical background and highlights areas of future perspectives in therapeutics.

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7.1   Introduction

The syndrome of acute respiratory distress (ARDS) is a life-threatening condition that is characterized by intense lung inflammation, diffuse alveolar damage, progressive micro-atelectasis, increased pulmonary vascular permeability, increased lung weight, and loss of aerated tissue [1, 2]. ARDS was first described in 1967 by Ashbaugh et al. [3] in a case series of 12 patients who shared the common features of unusually persistent tachypnea and hypoxemia, opacification on chest radiographs, and poor lung compliance, despite different underlying causes [2–4].

Following the initial description of acute respiratory distress syndrome (ARDS) by Ashbaugh et al. in 1967, multiple definitions were proposed and used until the 1994 publication of the American-European Consensus Conference (AECC) definition. The AECC defined ARDS as the acute onset of hypoxemia (arterial partial pressure of oxygen to a fraction of inspired oxygen [PaO2/FIO2] 200 mmHg) with bilateral infiltrates on frontal chest radiographs, with no evidence of left atrial hypertension. A new overarching entity—acute lung injury (ALI)—was also described, using similar criteria but with less severe hypoxemia (PaO2/FIO2 300 mmHg) [5].

Initially, ARDS was described as an "adult" respiratory distress syndrome to differentiate it from infant respiratory distress syndrome. Presently, this has been changed to acute respiratory distress syndrome due to the fact that both adults and children develop ARDS. Lung development increases linearly with age and height until the adolescent growth spurt at 10 years in girls and 12 years in boys. Therefore, there are significant differences between adult and child ARDS pathophysiology due to remodeling, growth of the lung parenchyma, and progressive maturation of the immune system [5–10]. Until recently, the most widely accepted definition was that from the American European Consensus Conference (AECC) in 1994. The AECC defined ARDS as the acute onset of hypoxemia with bilateral infiltrates on a frontal chest radiograph, with no clinical evidence of left atrial hypertension (or pulmonary artery wedge pressure of greater than or equal to 18 mmHg when measured) and a P/F ratio of less than or equal to 200 mmHg. Acute lung injury (ALI) was also defined using the same criteria but with a P/F threshold of 300 mmHg; thus, ARDS was a subset of patients with ALI. Although this consensus definition better enabled comparative studies of epidemiology and mortality and enrollment in clinical trials, it was hampered by many limitations. Key among the limitations were the uncertainty of timing of the insult leading to ARDS, confusion surrounding the ALI category, ambiguity surrounding the use of P/F ratio relative to the application of PEEP, which may modify this ratio, marked inter-observer variation in the interpretation of chest radiography, and controversies in excluding volume overload or heart failure as the primary cause of respiratory failure. The current Berlin definition of ARDS addresses these limitations. It specifies an acute time frame for the development of ARDS (within 1 week of known clinical insult or new or worsening respiratory symptoms), stipulates minimum ventilator settings (PEEP of 5 cm H_2O or more), and clarifies chest radiography criteria as well as the adjudication of respiratory failure from volume overload or heart failure. Furthermore, the Berlin

definition removes the ALI term and classifies ARDS into three categories (mild, moderate, and severe) to facilitate prognostication [11, 12].

Despite nearly five decades of study into ARDS, there are still no specific therapies beyond low tidal mechanical ventilation to reduce the mechanical stress placed on the injured lung. However, even with the advent of protective ventilation ARDS, mortality has not significantly declined below 40% [12, 13].

7.2   Epidemiology/Morbidity

Various studies have attempted to identify the incidence, outcomes, and population metrics of ARDS. But, the epidemiology of ARDS suffers from the lack of a true diagnostic test. Despite standardized definitions, most are hampered by inter-observer variability in ascertainment of cases, variations in validity of case definitions, geographic differences in availability of medical resources such as intensive care unit (ICU) beds, heterogeneity of risk factors among populations, and problems with determining mortality that can be directly attributed to ARDS, leading to inconsistencies of epidemiological measures [11].

The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) is the latest cross-sectional study that provides data on the epidemiology of ARDS. Globally, ARDS accounts for 10% of intensive care unit admissions, representing more than three million patients with ARDS annually [11, 14]. Of the 12,906 patients who received mechanical ventilation, 23.4% fulfilled the Berlin definition of ARDS [11].

ARDS affects approximately 200,000 patients each year in the United States, resulting in nearly 75,000 deaths annually, more than breast cancer or HIV infection [15, 16]. Mortality from ARDS remains high, ranging from 35% to 46%, with higher mortality being associated with greater degrees of lung injury severity at onset. Survivors may have substantial and persistent physical, neuropsychiatric, and neurocognitive morbidity that has been associated with significantly impaired quality of life, as long as 5 years after the patient has recovered from ARDS.

7.3   Cause/Symptoms

ARDS is characterized by impaired oxygenation and bilateral infiltrates on a chest radiograph. It is caused by various conditions like pneumonia, burns, sepsis, trauma, acute pancreatitis, aspiration, toxic inhalation transfusion, and cardiopulmonary bypass surgery (Table 7.1) [1, 5, 6]. The clinical hallmarks are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (i.e., edema, inflammation, hyaline membrane, or hemorrhage) [5].

A variety of clinical risk factors have been associated with the development of ARDS and fall into two broad categories: direct and indirect lung injury (Table 7.1).

Table 7.1 Direct and indirect etiological factors contributing to ARDS

S. No	Direct injury of the lung
1	Aspiration
2	Pneumonia
3	Inhalation injury
4	Drowning
5	Pulmonary contusion
S. No	Indirect injury of the lung
1	Sepsis
2	Trauma-induced injury/Shock
3	Severe burns
4	Pancreatitis
5	Cardiopulmonary bypass
6	Drug overdose
7	Head injury

Table 7.2 ARDS biomarkers [24]

Pathway	Biomarkers
Endothelial	Ang 1/2
	vWF
	VEGF
Epithelial	RAGE
	SP-D
	KGF
Coagulation and fibrinolysis	PAI-1
Inflammatory	IL-1Beta
	TNF-a
	IL-8
	IL-18
	IL-10
	sTNF-RI/II

The symptoms of ARDS are potentially underrecognized by clinicians. Early recognition and subsequent optimal treatment of patients with ARDS may be facilitated by usage of biomarkers. Several biomarkers have been examined with regard to their discriminatory ability for the diagnosis of ARDS (Table 7.2). Surfactant protein D (SP-D) has been proposed as such a candidate. Lung inflammation and injury affect the synthesis and secretion of SP-D from lung epithelial cells into the systematic circulation [17–19]. Infants and children are vulnerable to severe respiratory insult as compared to adults. Therefore, adult-based clinical definitions and parameters of ARDS are not applicable in pediatrics due to anatomic and physiologic differences. Pediatric acute lung injury consensus conference (PALICC), defined the first pediatric-focused characterization of ARDS. In pediatric ARDS, the oxygen index (OI) or oxygen saturation index defines the stratification of the severity of the disease based on the oxygen deficit [20–23].

7.4   Pathophysiology of ARDS

ARDS, a clinical syndrome of noncardiogenic pulmonary edema, is characterized by hypoxemia, radiographic infiltrates, decreased functional residual capacity, and decreased lung compliance [5, 23].

The most common pathophysiology of ARDS are the following:

1. *Disruption of pulmonary endothelial and alveolar epithelial integrity*
2. *Alveolar Epithelial injury and dysfunction*
3. *Disruption of Lung endothelial homeostasis*
4. *Inflammatory dysfunction*
5. *Surfactant dysfunction*
6. *Coagulation and fibrinolysis dysfunction*

7.4.1   Disruption of Pulmonary Endothelial and Alveolar Epithelial Integrity

Alveolar epithelial cells (AECs) collaboratively form a tight barrier between atmosphere and fluid-filled tissue to enable normal gas exchange. The tight junctions of AECs provide intercellular sealing and are integral to the maintenance of the AEC barrier integrity [25]. The alveolar epithelium is coated with a thin layer of alveolar wall liquid, which is necessary for dispersion of surfactant, transfer of gases, and host defense against inhaled pathogens. Integrity of this barrier is critical for gas exchange, and separation of the aqueous and gaseous compartments. Disruption and failure of reconstitution of the AEC barrier result in catastrophic consequences, leading to alveolar flooding with protein-rich edema fluid and subsequent devastating fibrotic scarring. Cytokines (interleukin-1 [IL-1], IL-8, tumor necrosis factor-a [TNF-a]) and lipid mediators (leukotriene B4) are attracted to alveoli and, in response to these proinflammatory mediators, neutrophils are recruited into the pulmonary interstitium and alveoli. The presence of protein, fibrinogen, and fibrin degradation products in the alveolar fluid results in surfactant degradation [6, 21, 22, 25].

7.4.2   Alveolar Epithelial Injury and Dysfunction

The alveolar wall is lined by two types of AECs: type I and type II AECs. The flat type I AECs and capillary endothelial cells constitute the blood–air barrier that facilitates efficient gas exchange. The cuboidal type II AECs secrete a surfactant that is believed to contribute to the lowering of alveolar surface tension. Apart from this, it is also responsible for the removal of excess alveolar fluid through sodium-dependent intracellular transport. Type II AECs proliferate and differentiate to Type I cells after injury.

Decreased alveolar fluid clearance is associated with severity and worse clinical outcomes and increased mortality in ARDS. Direct alveolar epithelial injury and indirect alveolar capillary injury (Table 7.1) cause barrier breakdown and inability of the alveolar epithelium to remove excess alveolar fluid. Surfactant protein D (SP-D), a marker of alveolar epithelial injury, has been proposed as a potentially useful biomarker for diagnosis of ARDS in a few studies [17] (Fig. 7.1).

7.4.3 Disruption of Lung Endothelial Homeostasis

Dysregulated endothelial activation and the resultant loss of homoeostatic mechanisms are aspects of ARDS pathobiology [6, 26]. Pulmonary endothelium is a dynamic, metabolically active organ that modulates several key regulatory functions including leucocyte diapedesis, intravascular coagulation, vasomotor tone, and solute and fluid trafficking via regulation of barrier permeability. Reactive oxygen species (ROS) and reactive nitrogen species production by activated cells saturate local antioxidants and contribute to tissue injury directly via downregulation of VE-cadherin, upregulation of neutrophil adhesion molecule expression, and release of neutrophil chemotactic factors. Endothelial-specific proteins, such as von Willebrand factor and angiotensin-converting enzyme activity, correlate with ARDS mortality. Moreover, activated endothelial cells also assume a procoagulant phenotype by increasing the expression of platelet adhesion molecules, intra-alveolar and intravascular fibrin deposition, and release of activators of the extrinsic coagulation cascade [1, 26–28].

7.4.4 Inflammatory Dysfunction

Several studies have demonstrated evidence for dysregulation of inflammatory pathways in ARDS and their association with outcome. There is a strong correlation between mortality and upregulated levels of proinflammatory (IL-6, IL-8, IL-18, MIP-1b, TNF-a) and anti-inflammatory cytokines (IL-1RA, IL-10, and TNF-R2). These cytokines were associated with ARDS illness severity, including the P/F ratio, OI, pediatric risk of mortality score (PRISM-3), ICU morbidity, and biochemical evidence of endothelial injury, including elevated plasma angiopoietin 2 and soluble thrombomodulin [4, 6, 29].

When alveolar macrophages are activated, they recruit neutrophils and circulating macrophages to the alveoli. Neutrophils communicate between the vessel wall and platelets, which results in endothelial injury and releases neutrophil extracellular traps, which may also cause damage to the lung [30, 31].
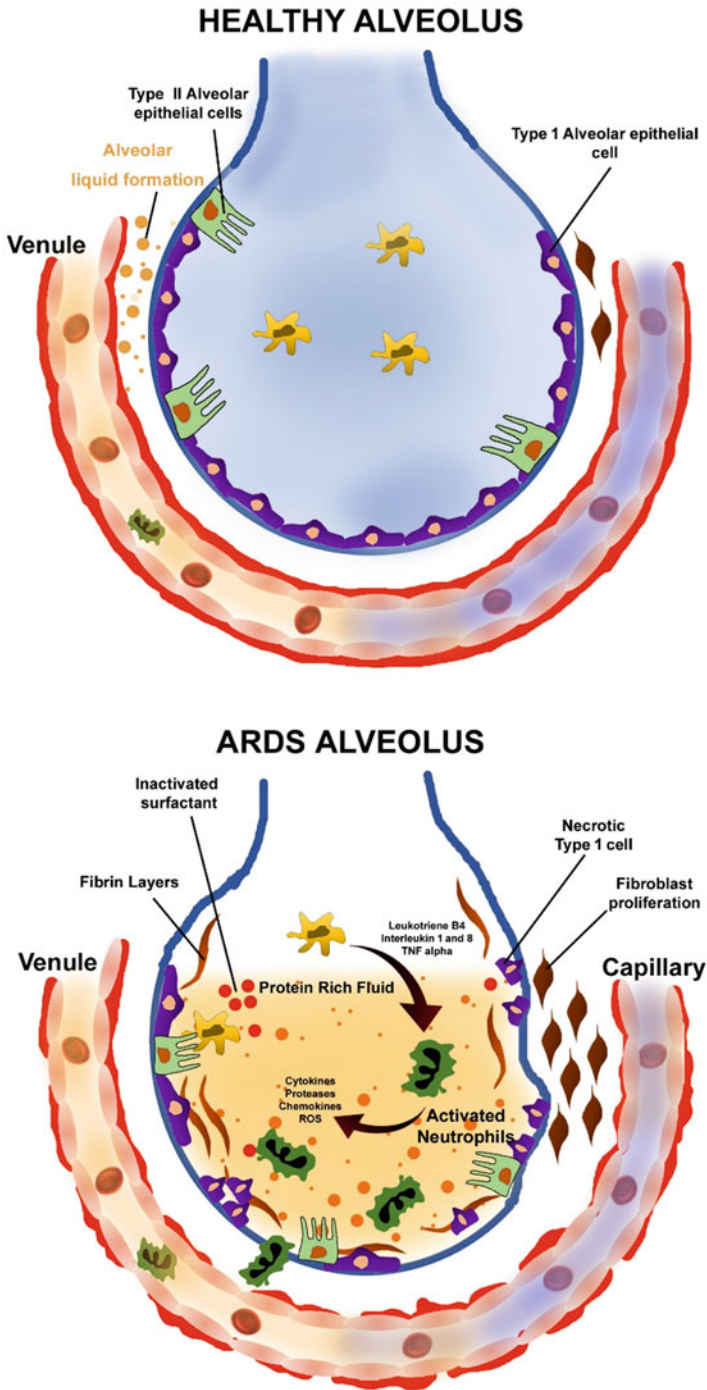
HEALTHY ALVEOLUS

Type II Alveolar epithelial cells

Alveolar liquid formation

Type 1 Alveolar epithelial cell

Venule

ARDS ALVEOLUS

Inactivated surfactant

Necrotic Type 1 cell

Fibrin Layers

Fibroblast proliferation

Leukotriene B4
Interleukin 1 and 8
TNF alpha

Venule

Protein Rich Fluid

Capillary

Cytokines
Proteases
Chemokines
ROS

Activated Neutrophils

Fig. 7.1 Schematic representation of healthy alveolus and pathophysiology in ARDS: In the healthy alveolus (**Top**), the alveolar epithelium and capillary endothelium are intact, which

7.5   Current Therapies for ARDS

Despite decades of research, treatment options for ARDS are limited. Supportive care with mechanical ventilation remains the mainstay of management [32]. Most advances in ARDS therapeutics have been through changes in mechanical ventilation methods, culminating in a 2017 International Clinical Practice Guideline for mechanical ventilation on adults with ARDS [14, 15, 24, 32]. The guidelines address six interventions:

1. *low tidal volume and inspiratory pressure ventilation*
2. *prone positioning*
3. *high-frequency oscillatory ventilation*
4. *higher versus lower positive end-expiratory pressure*
5. *lung recruitment maneuvers and*
6. *extracorporeal membrane oxygenation*

Most of the current treatment is supportive and palliative, with no current disease-modifying therapies available [24].

7.5.1   Management-Based Therapy for ARDS

A standard therapy for ARDS is mainly based and reliant on management of pulmonary dysfunction; however, the identification involves non-pulmonary organ dysfunction also.

7.5.1.1 Treatment of the Inciting Clinical Disorder
ARDS is an outcome of several disease processes, which mainly include trauma, ischemia reperfusion, pneumonia, multiple transfusions, sepsis, and aspiration of gastric contents [33, 34]. Several of these have a direct treatment based on

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Fig. 7.1 (continued) maintains the air-filled, fluid-free alveoli. The alveolar wall liquid formation is required for gas exchange, which is the medium for dispersal of the surfactant and alveolar macrophages, thereby maintaining alveolar stability and host defenses. (**Bottom**) In contrast, the alveolar space in ARDS looks highly disturbed with severe flooding with solutes and large molecules such as albumin. This fluid accumulation is due to the loss of epithelial and endothelial barrier integrity, leading to severe pulmonary edema. The endothelium of pulmonary micro-vessels gets activated; there is high influx of proinflammatory mediators. This leads to the recruitment of leukocytes into the pulmonary interstitium and alveoli. There are also high amounts of fibrin deposition due to increased concentration of fibrinogen and fibrin degradation products in the edema fluid. Depletion of surfactant leads to increase in surface tension and loss of alveolar shape and integrity. There is also fibroblast proliferation, ROS generation, and NET (neutrophil extracellular traps) in the diseased alveoli

antibiotics/antimicrobials, which however needs a careful examination for the type of pathogen involved in inciting the disease such as bacteria (Mycoplasma or Legionella) or fungi (Pneumocystis carinii). Sometimes ALI/ARDS is incited by extrapulmonary infections, e.g., urinary tract, pulmonary infection, or biliary tract infection, which hence warrants a thorough clinical examination. The clinical treatment should take the clinical history of the patient into account. In some situations, like transfusions or gastric aspirations, stopping the recurrence is the optimal treatment method along with good supportive care [33–36].

7.5.1.2 Mechanical Ventilation

ARDS generates an alveolar dead space, an impaired pulmonary compliance. The required amount of breathing is too high a work for the voluntary pulmonary system, which may lead to a ventilatory failure pulmonary acidosis and hypercapnia [37]. Overall, there is a huge respiratory burden, which demands an extra support to be functional. In such situations, mechanical ventilation serves as a backbone to respiration and hence is an essential supplementary care. Mechanical ventilation not only acts as a mainstay of supportive care but also provides sufficient time for natural healing and drug treatments [36, 38].

7.5.1.3 Effective Oxygenation (PEEP and FIO2)

An ARDS patient needs effective oxygenation at the start of mechanical ventilation, which is a high priority measure. During mechanical ventilation, positive end-expiratory pressure (PEEP) and fraction of inspired oxygen (FiO2) provide effective oxygenation and support arterial oxygenation and hence are crucial. PEEP and FiO2 are associated with serious limitations, which can be avoided by keeping the FiO2/PEEP index in check. For human subjects, FiO2 <50% is considered safe [39–42]. PEEP improves arterial oxygenation and decreases intrapulmonary shunt. It keeps a check on FiO2 while allowing adequate arterial oxygenation [43, 44].

7.5.1.4 Vasodilators

ARDS patients are known to have modest pulmonary arterial hypertension, which has been demonstrated to progress with the progression of disease. The rise is a multifactorial process and can make the disease severe by affecting the vascular bed and hypoxic vasoconstriction or sometimes cardiac dysfunction. Several studies have attempted to reduce the pulmonary hypertension to evaluate its effect on progression of ARDS. There are reports of using hydralazine in animal models, which has proven effective though [36, 45]. Continuous infusion of prostaglandin E1 has proven effective in clinical cases also [46]. Nitric oxide (NO) is an effective endogenous vasodilator. Encouraged from promised results obtained in animal models, clinicians attempted to use gaseous NO to treat pulmonary hypertension in ARDS patients; however, mild and transient success in clinical cases of ARDS was noted [47–51].

7.5.1.5 Infection Management in ARDS

Uncontrolled infection is a prominent feature associated with ALI/ARDS. Often, lung infection becomes a causal factor for development of ALI/ARDS [51]. However, infection may occur as an outcome of ARDS development, though reports of non-pulmonary sepsis are also known to cause ARDS. There is a high amount of risk associated with development of pneumonia and catheter-related sepsis also known as nosocomial infections in patients receiving ventilation, which is an area of investigation that is being highly investigated for quite some time [36, 52, 53]. Administration of antibiotics/antimicrobials does not help always. Therefore, infections are managed by frequent washing of hands by medical personnel, nonstop suction of subglottic secretions to avoid their aspiration, and the usage of new endotracheal tubes to avoid making of a bacterial biofilm. Almost all the management strategies for nosocomial pneumonia in ARDS are contentious. One of the important aspects that adds to this is the ambiguity in the diagnosis itself. There is a significant overlap between ARDS diagnosis and clinical data obtained from pneumonia, as the immune cell infiltration is highly similar in both pathologies [54, 55].

7.5.2 Drawbacks of the Current Pharmacological Treatment

Despite several decades of investigation into potential treatment strategies, use of lung-protective ventilation remains the only proven therapy to decrease mortality in ARDS [2]. In patients with ARDS, recruitment maneuvers improve oxygenation, but this is a temporary approach that does not improve mortality. Clinical trials of β2-agonists, statins, surfactants, and keratinocyte growth factor (KGF) have been disappointing. In addition, monoclonal antibodies (anti-TNF) and TNFR fusion protein have also been unconvincing. Glucocorticoids may improve oxygenation and airway pressures in established ARDS, but have failed to demonstrate a role in preventive therapy. In patients with pneumonia, steroids may improve radiological appearances, but again does not improve mortality [24, 56]. Trials conducted on established ARDS investigated different doses and duration of treatment, preventing generalization of the results. However, analysis suggests that if steroids are started 14 days or more after the diagnosis of ARDS, they can be harmful. The combination of inhaled β2-agonists and glucocorticoid administered early in patients at risk of ARDS has recently shown to prevent development of ARDS and improve oxygenation but its effect on mortality has not been demonstrated [24].

Despite intense investigation, no specific pharmacological treatment for ARDS has been shown to affect the mortality, even though preclinical trials in animal models have looked promising. Therefore, targeting a single pathogenetic pathway is not unlikely to be advantageous due to the complexity of the mechanisms involved [24].

7.6   Future Directions in Therapeutics and Perspectives

No pharmacologic treatments aimed at the underlying pathology have been shown to be effective, and management remains supportive with lung-protective mechanical ventilation. Guidelines on mechanical ventilation in patients with acute respiratory distress syndrome can assist clinicians in delivering evidence-based interventions that may lead to improved outcomes [15].

Even after 50 years of study, ARDS still looks like a threatening enemy to defeat. Studies on ARDS incidence consistently show that the disease is not rare, albeit often not recognized by clinicians. ARDS is undertreated and basic ventilator strategies are not yet standardly optimized, despite major advances in the management of mechanical ventilation and non-ventilatory strategies, aimed at preventing the VILI. Although mortality associated with ARDS is decreasing in clinical trials, it remains unchanged at approximately 40% in major observational studies. Various factors contribute to the mortality associated with ARDS. They include patient age and illness severity, country-level socioeconomic status, ventilator management, and ICU organizational method. This suggests the need of a commonly accepted therapeutic strategy for ARDS, which should be the prerogative of all the countries including the less-developed ones [57, 58]. Molecular mechanisms identifying the susceptibility of injury and aberrant activation of alveolar epithelial cells and pulmonary endothelial cells would be pivotal in moving toward the positive outcomes of these intractable diseases.

The characterization of the ARDS sub-phenotype by blood biomarkers may help clinicians to select patients who may benefit from specific therapeutic strategies and ultimately tailor the treatment of our single patient. In fact, it has been proved that a high PEEP strategy in ARDS patients affected the major outcome only in the hyperinflammatory sub-phenotype. Moreover, the restrictive fluid strategy was beneficial in the same selected ARDS patients. More studies are needed to further explore the benefits of different therapies based on a particular ARDS biomarker profile [24, 59]. To further reduce mortality, the therapy of ARDS should possibly take genetic difference among patients and the origin of ARDS into account, such as the primary or the secondary ARDS.

In the future, by understanding the role of biomarkers in the pathophysiology of ARDS and lung injury, it is hoped that this will provide rational therapeutic targets and ultimately improve clinical care.

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