What Is the Acute Respiratory Distress Syndrome?

Jesús Villar MD PhD

It has been known for decades that shock and sepsis can cause a syndrome of acute respiratory failure with characteristics of non-cardiogenic pulmonary edema. Over the years, this syndrome has been given a number of names, including congestive atelectasis, traumatic wet lung, and shock lung. In 1967 the modern counterpart to this syndrome was described and subsequently called the "acute respiratory distress syndrome" (ARDS). This syndrome results from lung injury and inflammation. As with inflammation elsewhere, ARDS is accompanied by many cellular and molecular processes, some of them specific to the syndrome, others perpetuating the syndrome, and others inactivating the by-products of inflammation. Since no specific clinical sign or diagnostic test has yet been described that identifies ARDS, its diagnosis is based on a constellation of clinical, hemodynamic, and oxygenation criteria. Current ARDS treatment is mainly supportive, since these patients frequently have coexisting conditions. Although in 1994 a new standard ARDS definition was accepted, that definition failed to standardize the measurement of the oxygenation defect and does not recognize different severities of pulmonary dysfunction. Based on current evidence there is a need for a better definition and classification system that could help us to identify ARDS patients who would be most responsive to supportive therapies and those unlikely to benefit because of the severity of their disease process. This paper examines our current understanding of ARDS and discusses why the current definition may not be the most appropriate for research and clinical practice. *Key words: acute respiratory distress syndrome; ARDS; acute lung injury; positive end-expiratory pressure; PEEP; lung inflammation; biomarker.* [Respir Care 2011;56(10):1539–1545. © 2011 Daedalus Enterprises]

Dr Villar is affiliated with Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain, and with the Research Unit, Multidisciplinary Organ Dysfunction Evaluation Research Network, Hospital Universitario Dr Negrin, Las Palmas de Gran Canaria, Spain, and with the Keenan Research Center, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada.

On behalf of the author, Robert M Kacmarek PhD RRT, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, presented a version of this paper at the 26th New Horizons Symposium, "ARDS Update," at the 56th International Respiratory Congress of the American Association for Respiratory Care, held December 6–9, 2010, in Las Vegas, Nevada.

This research was partly supported by grants PI10/0393, CB06/06/1088 from Instituto de Salud Carlos III, Spain. The author has disclosed no conflicts of interest.

This paper is dedicated to the memory of Thomas L Petty and Roger C Bone.

Correspondence: Jesús Villar MD PhD, Multidisciplinary Organ Dysfunction Evaluation Research Network, Hospital Universitario Dr Negrin Barranco de la Ballena, s/n 4th Floor, South Wing, 35010 Las Palmas de Gran Canaria, Canary Islands, Spain. E-mail: jesus.villar54@gmail.com.

DOI: 10.4187/respcare.01395

Introduction

In August 1967, Ashbaugh et al[1] published an article in the British journal *The Lancet* in which they described for the first time a syndrome that they termed the "acute respiratory distress syndrome" (ARDS). They studied a cohort of 272 patients who were receiving respiratory support, and in that cohort they identified 12 patients with a syndrome that was similar to the infant respiratory distress syndrome. The respiratory distress was defined as the presence of tachypnea, hypoxemia, decreased respiratory-system compliance, and bilateral pulmonary infiltrates on chest radiograph. Ashbaugh et al indicated that respiratory support consisted of oxygen therapy via nasal prongs or face mask (in 5 patients) and mechanical ventilation (in 7 patients). The mortality rate was 58%, and pathology examination found that the non-survivors' lungs were heavy, had atelectasis, interstitial and alveolar edema, and hyaline membranes. Since that time, the hallmarks of this syndrome have included:

- A risk factor for the development of ARDS (eg, sepsis, trauma, pancreatitis)
- Severe hypoxemia with a relatively high F_{IO_2}
- Decreased pulmonary compliance
- Bilateral pulmonary infiltrates
- No clinical evidence of cardiogenic pulmonary edema

Although this condition had been known for over a century and there were published data from the Second World War,[2,3] it was not until the landmark paper by Ashbaugh et al that interest in ARDS increased. In the subsequent 40 years, very few acronyms have received as much attention in critical care medicine.

Pathophysiology and Histopathology of ARDS

ARDS is caused by an insult to the alveolar-capillary membrane that results in increased permeability and subsequent interstitial and alveolar edema. The mechanisms by which a wide variety of insults can lead to this syndrome are not clear. Acute lung injury (ALI) includes injury to both the pulmonary capillary endothelium and the alveolar epithelium.[4] Independent of the clinical disorders associated with ARDS (Table 1), it is useful to think of the pathogenesis of ARDS as a result of 2 different pathways: a direct insult on lung cells, and an indirect insult as a result of an acute systemic inflammatory response. Despite our improved understanding of the role of cellular and humoral components of the inflammatory responses in the lung, we still do not understand the precise sequence of events leading to lung damage.

Table 1. Most Common Clinical Disorders Associated With the Development of the Acute Respiratory Distress Syndrome

Direct Lung Injury	Indirect Lung Injury
Common Causes	Common Causes
Pneumonia	Sepsis
Aspiration of gastric contents	Multiple trauma
Less common causes	Less common causes
Pulmonary contusion	Acute pancreatitis
Near-drowning	Drug overdose
Inhalation injury	Cardiopulmonary bypass
Fat emboli	Transfusion of blood products
Reperfusion pulmonary edema	

The typical histopathological features of ARDS are known as diffuse alveolar damage.[5] The early phase of ALI (exudative phase) is characterized by leakage of protein-rich edema fluid into the lung and inflammatory cellular alveolar infiltrates. During this phase a cytokine storm and an array of inflammatory mediators are released into the interstitium and alveolar space, perpetuating inflammation and promoting the development of atelectasis and structural damage to the lung architecture. In addition, damage to the alveolar-capillary barrier enhances the difficulty in removing the excess of extravascular lung fluid. Clinically, this initial phase is manifested as marked hypoxemia and reduced pulmonary compliance. Eventually these changes evolve to a fibroproliferative phase in which capillary thrombosis, lung fibrosis, and neovascularization take place. Most ARDS non-survivors die during this phase, despite aggressive ventilatory support with high F_{IO_2} and PEEP.

The Typical ARDS Patient

There is no typical ARDS patient. There are more than 50 recognized conditions associated with the development of this syndrome. The risk of developing ARDS depends on the predisposing clinical condition (ie, some events are more likely to progress to ARDS than others) but it also increases with the number of predisposing factors. Sepsis, bacterial pneumonia, multiple trauma, and aspiration pneumonia are the most common predisposing factors, accounting altogether for more than 70% of cases.[4] Overall mortality from ARDS has not decreased substantially since the publication of the 1967 report, and the current survival rate approximates 45% in all major epidemiological series.[6,7] Sepsis-related ARDS has a higher overall disease severity, poorer recovery from lung injury, and higher mortality than non-sepsis-related ARDS.[8] As part of the therapy for the underlying disease, patients with ARDS invariably require mechanical ventilation to decrease the work of breathing and to improve oxygen transport. An improvement in

oxygenation can be obtained in many ARDS patients by an increase in PEEP, a strategy that was originally suggested by Ashbaugh et al.[1]

Since it is difficult to measure changes in capillary and alveolar permeability at the bedside, diagnosis of ARDS is based on a combination of clinical, oxygenation, hemodynamic, and radiographic criteria. These criteria allow the inclusion of a highly heterogeneous group of critically ill patients, since various types of lung injury can lead to a similar pulmonary response.[4] Although there is a general agreement on the overall criteria on which to base a definition of ARDS (ie, severe hypoxemia, marked decreased of pulmonary compliance), the specific values of these variables and conditions of measurement vary greatly among clinicians and scientists. Thus, the original description of ARDS has proved to be incapable of identifying a uniform group of patients. Several of the patients in the original report would not be classified as ARDS today, since fluid overload was an important etiological factor in those patients. Some investigators have questioned whether ARDS is a distinct entity,[9] an issue addressed by one of the original authors of the 1967 article.[10] Others have suggested that ARDS should not be considered a separate syndrome, but should be seen as part of the multiple system organ dysfunction syndrome.[11]

Defining ARDS

From a clinical point of view, one can argue that a strict definition of ARDS may not be required, since current management for ARDS is supportive. However, from a therapeutic point of view, the need for a more precise definition is probably necessary, since the effects on outcome of certain ventilatory and adjunctive techniques could depend on the degree of lung severity.[12-14] In terms of prognosis, several investigators have examined whether various oxygenation and/or lung mechanics variables help predict outcome. In any case, there would certainly be some utility in having a standard definition so that data in the literature can easily be compared. From the perspective of ARDS research, there is a very strong argument for having a standard definition: it would help standardize experimental and clinical studies of ARDS natural history, incidence, pathophysiology, treatment, and outcomes. It also would help in the comparison of data among various clinical studies and centers. Thus, a precise definition is clearly important to accurate identification and quantification of various aspects of the underlying pathophysiology and to identify the best therapeutic approach.

A good example of the problems inherent to a definition for ARDS is the wide disparity in the literature on the incidence of ARDS. The most common figure cited for the incidence of ARDS is 75 cases per 100,000 population per year. This is based on an American Lung Program Task Force of the National Heart and Lung Institute in 1972, which was an internal report that suggested that were about 150,000 cases per year of ARDS in the United States, a value similar to the number of all new cases of cancer. In 1988, Webster and colleagues, in England, estimated an incidence of 4.5 cases per 100,000 population,[15] and in 1989, Villar et al, in Spain,[16] calculated the incidence at 3.5 cases per 100,000. In an attempt to overcome some of these problems, Murray et al[17] proposed an expanded definition of ARDS, which takes into account various pathophysiological features of the syndrome. The definition uses a "lung injury score" to characterize the acute pulmonary damage, by considering 4 components: chest radiograph, degree of hypoxemia (P_{aO_2}/F_{IO_2}), PEEP, and (when available) respiratory-system compliance (Table 2). The lung injury score is obtained by dividing the total score by the number of components that were used. A score of 0 indicates no lung injury, a score of 1–2.5 indicates mild to moderate lung injury, and a score $>$ 2.5 indicates severe lung injury or ARDS. However, the lung injury score is not specific for ARDS and has not been validated, since it is not clear whether patients with identical lung injury scores have similar degrees of lung injury.[18] Furthermore, a patient with a major component of cardiogenic edema

Table 2. Lung Injury Scoring System

Domain	Score*
Chest Radiograph Infiltrates (no. of quadrants)	
None	0
1	1
2	2
3	3
4	4
Hypoxemia (P_{aO_2}/F_{IO_2} (mm Hg)	
$\geq$ 300	0
225–299	1
175–224	2
100–174	3
$<$ 100	4
PEEP (cm H_2O)	
$\leq$ 5	0
6–8	1
9–11	2
12–14	3
$\geq$ 15	4
Lung Compliance (if measured) (mL/cm H_2O)	
$\geq$ 80	0
60–79	1
40–49	2
20–39	3
$\leq$ 19	4

* To obtain the final score, add the scores from the 4 domains and divide that sum by the number of domains used. No lung injury = 0. Mild to moderate lung injury = 0.1–2.5. Severe lung injury (acute respiratory distress syndrome [ARDS]) = $>$ 2.5.

Table 3. American-European Consensus Definitions for Acute Lung Injury and Acute Respiratory Distress Syndrome

Acute onset
Severe hypoxemia ($P_{aO_2}/F_{IO_2} < 300$ mm Hg for acute lung injury (ALI), or ≤ 200 mm Hg for acute respiratory distress syndrome (ARDS)
Diffuse bilateral pulmonary infiltrates on frontal chest radiograph
Absence of left-atrial hypertension (or pulmonary-artery wedge pressure < 18 mm Hg if measured)

may be misidentified as having ARDS, and a postoperative patient with moderate atelectasis and mild fluid overload may fulfill the lung injury score criteria of ARDS.

Given that severe hypoxemia is the hallmark of ARDS, it should be crucial to assess the severity of ARDS, for predicting the development and evolution in any given patient, and for assessing the response to treatment. In order to better characterize the severity of lung damage, in 1994 an American-European Consensus Conference on ARDS[19] defined ALI and ARDS as follows:

- Acute and sudden onset of severe respiratory distress
- Bilateral infiltrates on frontal chest radiograph
- Absence of left-atrial hypertension (pulmonary capillary wedge pressure $<$ 18 mm Hg or no clinical signs of left-ventricular failure)
- Severe hypoxemia (assessed via P_{aO_2}/F_{IO_2})

According to these guidelines, ALI exists when P_{aO_2}/F_{IO_2} is $\leq$ 300 mm Hg regardless of the PEEP or F_{IO_2} level, and ARDS exists when P_{aO_2}/F_{IO_2} is $\leq$ 200 mm Hg regardless of PEEP or F_{IO_2} level (Table 3). Although that definition formalized the criteria for ARDS diagnosis and is simple to apply in the clinical setting, it has been challenged in several studies.[20-23] For example, all patients included in published papers start off with terrible oxygenation and there is little room for stratifying and separating the patients if there is no further re-evaluation of the hypoxemia. In a secondary analysis of 56 patients who met the American-European Consensus Conference criteria for ARDS, Villar et al[20] found that P_{aO_2} response to PEEP allowed the separation of patients into 2 groups with different severities and outcomes. In that cohort, a patient could fit the ARDS criteria when the P_{aO_2} was measured with zero PEEP, but not when measured at a PEEP of 5 or 10 cm H_2O. These findings illustrate the major problems in trying to compare the findings from various clinical trials of ventilation strategies,[24-29] since patients with very different levels of lung dysfunction and disease may have been enrolled. Furthermore, none of those studies[24-29] used the same ARDS definition nor evaluated the same ventilation approach. Diversity in ARDS definitions is apparent in a large number of studies[16,20,24-33] (Table 4).

In a retrospective analysis of 74 patients with ARDS who entered into the placebo arm of a pharmacologic study,[33] the investigators found that P_{aO_2}/F_{IO_2} was identical at baseline in patients who died and in those who survived their ARDS. However, over the subsequent few days there was a separation in the oxygenation status of the survivors and non-survivors. One can argue that the increasing difference in oxygenation in all of the studies as ARDS progressed is not surprising, since one would expect that the sicker patients would develop worse hypoxemia or would certainly not quickly improve their hypoxemia. In 1999, Villar et al[20] proposed the need for different guidelines, based on a specific, standard method of evaluating oxygenation status: a proposal that has been advocated by other authors.[20,21] In order to determine the impact of various PEEP and F_{IO_2} levels on the classification of patients meeting the American-European Consensus Conference definition for ARDS, Villar et al[23] evaluated the impact of standard ventilation settings applied on the day the patients met American-European Consensus Conference ARDS criteria and 24 hours later. They studied 170 patients and found that only 58% of them fulfilled ARDS criteria when evaluated on PEEP of $\geq$ 10 cm H_2O and F_{IO_2} of $\geq$ 0.5 at 24 hours. The ICU mortality of those patients was 46%. By contrast, 32% of patients were classified as having ALI, and their mortality was 20%. In addition, 10% of patients had a $P_{aO_2}/F_{IO_2} > 300$ mm Hg and were simply categorized as having acute respiratory failure; their ICU mortality was 6%. That study demonstrated the large variability in the severity of lung damage in patients who meet the American-European Consensus Conference definition of ARDS and the strong correlation between oxygenation impairment at 24 hours after ARDS onset and ICU outcome.

Biochemical Diagnosis of ARDS

In patients with acute coronary syndromes, the working diagnosis is based on the presence of acute chest pain accompanied by an abnormal electrocardiogram and the biomarker troponin. Troponin is the biomarker for detection of heart injury and the basis for risk stratification and therapeutic interventions in patients with coronary artery disease. By contrast, there is a lack of a pathognomonic laboratory or clinical feature in ARDS patients. There are no data that link a particular P_{aO_2}/F_{IO_2} to predictable structural changes in the alveolar-capillary membrane, most likely because ARDS represents a common pathway of diverse events and disease entities. Also, current guidelines for ARDS management do not follow a strict stratification, as seen in patients with coronary artery diseases. Villar et al[34] postulated that stratification of respiratory and ventilatory variables at the onset of ARDS could help identify and select (for clinical trials) patients with differ-

Table 4. Definitions of the Acute Respiratory Distress Syndrome in Several Published Reports

First Author	Year	Criteria
Montgomery[30]	1985	$P_{aO_2}/F_{IO_2} < 150$ mm Hg Pulmonary capillary pressure < 18 mm Hg
Villar[16]	1989	$P_{aO_2} \leq 75$ mm Hg on $F_{IO_2} \geq 0.5$ Pulmonary capillary pressure < 18 mm Hg
Bone[33]	1989	$P_{aO_2}/F_{IO_2} \leq 150$ mm Hg (with zero PEEP) or $P_{aO_2}/F_{IO_2} \leq 250$ mm Hg with PEEP Pulmonary capillary pressure ≤ 18 mm Hg
Amato[24]	1998	Lung injury score ≥ 2.5 Pulmonary capillary pressure < 16 mm Hg
Stewart[25]	1998	$P_{aO_2}/F_{IO_2} < 250$ mm Hg on PEEP of 5 cm H_2O
Brochard[26]	1998	Lung injury score > 2.5
Villar[20]	1999	$P_{aO_2}/F_{IO_2} \leq 150$ mm Hg on PEEP of ≥ 5 cm H_2O
ARDS Network[27]	2000	American-European consensus definitions
Gattinoni[31]	2001	$P_{aO_2}/F_{IO_2} \leq 200$ mm Hg on PEEP ≥ 5 cm H_2O Pulmonary capillary pressure ≤ 18 mm Hg
Villar[32]	2006	$P_{aO_2}/F_{IO_2} \leq 200$ mm Hg on PEEP ≥ 5 cm H_2O and $F_{IO_2} \geq 0.5$
Meade[28]	2008	$P_{aO_2}/F_{IO_2} < 250$ mm Hg
Mercat[29]	2008	$P_{aO_2}/F_{IO_2} \leq 200$ mm Hg Pulmonary capillary pressure ≤ 18 mm Hg

ent risks of death. They evaluated data from 220 patients included in 2 multicenter trials of ARDS patients ventilated with a lung-protective strategy. Using demographic, pulmonary, and ventilatory data collected at ARDS onset, they derived and validated a simple prediction model based on a stratification of variable values into low, intermediate, and high tertiles. They found that tertile distribution for age, plateau airway pressure, and P_{aO_2}/F_{IO_2} at ARDS onset identified subgroups with markedly different mortalities.

Identifying the molecular mechanisms responsible for ARDS is the most important obstacle to the successful diagnosis and treatment of ARDS patients. When comparing the management of acute chest pain to the management of ARDS, the former is based on an emergency medical model of awareness of a life-threatening condition and the importance of adherence to predefined decision algorithms. No comparable awareness and emergency decision algorithms are evident for the care of ARDS patients. It is plausible that a new definition based on specific biochemical criteria of lung inflammation, rather than on clinical parameters, is likely to provide us with a better stratification and identification of a more homogeneous population of patients with ALI and ARDS.[34-38] Thus, stratification of ARDS patients should be linked to 2 measures of severity: one that specifically quantifies the severity of ALI/ARDS, and another that quantifies the overall physiologic response along with comorbidities and premorbid health. Adding objectives measures, such as levels of biological markers, could facilitate recognition of ALI/ARDS. The use of simple thresholds for the diagnosis of disease processes of increasing prevalence in the general population is common. This is the case for the use of blood sugar for diabetes and hemoglobin for anemia. It appears improbable in the case of ARDS that a biomarker alone will resolve this issue. Instead, a clinical prediction model[34] or a combination of such a prediction model with a biomarker would provide a better definition of ALI/ARDS (Table 5).

An appropriate biomarker for early identification, diagnosis or severity of lung injury should provide information for appropriate stratification of patients at risk for ARDS, at ALI/ARDS onset and during the evolution of the disease process. Ideally, such a biomarker should be:

- 100% sensitive
- 100% specific
- Easy to measure in blood, exhaled air, or other biological sample
- Affected by treatment
- Cost-effective

There have been recent efforts to identify biological markers in pulmonary edema fluid and in blood from patients with and without ARDS.[35,37,39-41] It is postulated that, due to increased permeability of the alveolar-capillary barrier, these proteins leak into the circulation. Donnelly et al[35] found that patients at risk for ARDS who had more interleukin-8 in bronchoalveolar lavage fluid subsequently progressed to ARDS. In 180 patients with severe sepsis, Villar et al[39] found a direct correlation between lipopolysaccharide-binding protein level and severity of lung injury, which suggests that serial lipopolysaccharide-binding protein may be a clinically useful biomarker for identifying patients at risk for the worst outcomes and with

Table 5. Comparison of the Current American-European Consensus Conference Definition of Acute Respiratory Distress Syndrome and the Proposed New Definition

	American-European Consensus Conference Definition	Proposed New Definition
Clinical condition	Not included in the definition	A known predisposing clinical condition
Onset	Acute	Acute
Chest radiograph	Diffuse bilateral pulmonary infiltrates on frontal chest radiograph	Bilateral pulmonary infiltrates consistent with permeability pulmonary edema
Need for endotracheal intubation and mechanical ventilation	No	Yes
Severe hypoxemia	$P_{aO_2}/F_{IO_2} \leq 200$ mm Hg, independent of F_{IO_2} or PEEP level	P_{aO_2}/F_{IO_2} ratio ≤ 200 mm Hg on $F_{IO_2} \geq 0.5$ and PEEP ≥ 10 cm H_2O (at ARDS onset and reassessed 12–24 h after onset)
Absence of heart failure	Absence of left-atrial hypertension (or pulmonary-artery wedge pressure < 18 mm Hg if measured)	Exclusion of left-ventricular failure as a cause of ARDS (although ARDS and left-atrial hypertension can coexist) by a pulmonary capillary pressure ≤ 18 mm Hg, or no clinical signs of left-ventricular failure
Biochemical diagnostic	Not included in the definition	Ideally, plasma levels of specific biomarkers of lung injury above specified threshold values

the highest probability of developing sepsis-induced ARDS. Ware et al[41] analyzed a combination of 8 biological markers that reflect endothelial and epithelial pulmonary injury, inflammation, and coagulation in 549 patients in the ARDS Network trial of low versus high PEEP, and, although they found that a combination of biomarkers and clinical predictors was superior to clinical predictors or biomarkers alone for predicting mortality or stratifying ALI/ARDS patients, the sensitivity and specificity for ARDS was low. Finally, Determann et al[42] measured plasma Clara cell protein (CC16) in 22 patients with pneumonia and 15 controls, and found that plasma CC16 was 3 times higher in the patients with ALI/ARDS than in the patients without ALI/ARDS. A CC16 level of ≥ 18 ng/mL was diagnostic for ALI/ARDS with a sensitivity of 80% and a specificity of 92%. Furthermore, plasma CC16 was elevated 24–48 hours before ALI/ARDS was diagnosed, which suggests that CC16 may predict the development of ALI/ARDS.

Summary

The current ARDS definition was established almost 2 decades ago. Based on recent evidence, there is a need for a new definition that better characterizes ARDS. In addition to an appropriate clinical setting and radiographic infiltrates consistent with non-cardiogenic pulmonary edema, we need to measure the oxygenation defect (P_{aO_2}/F_{IO_2}) under standard ventilator settings (specific F_{IO_2} and PEEP). In addition, it would be very useful to incorporate into the new definition specific biomarkers of lung injury.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2(7511):319-323.
2. Burford TH, Burbank B. Traumatic wet lung: observations on certain physiologic fundamentals in thoracic trauma. J Thorac Surg 1945; 14:415-420.
3. Nash G, Blennerhasset JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 1967;276(7):368-374.
4. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342(18):1334-1349.
5. Tomashefski JF Jr. Pulmonary pathology of acute respiratory distress syndrome. Clin Chest Med 2000;21(3):435-466.
6. Villar J, Slutsky AS. Is the outcome from acute respiratory distress syndrome improving? Curr Opin Crit Care 1996;2:79-87.
7. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, et al. Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. Am J Respir Crit Care Med 2009;179(3):220-227.
8. Sheu CC, Gong MN, Zhai R, Chen F, Bajwa EK, Clardy PF, et al. Clinical characteristics and outcomes of sepsis-related vs non-sepsis-related acute respiratory distress syndrome. Chest 2010;138(3):559-567.
9. Murray J. The adult respiratory distress syndrome (may it rest in peace). Am Rev Respir Dis 1975;111(6):716-718.
10. Petty TL. The adult respiratory distress syndrome (confessions of a lumper). Am Rev Respir Dis 1975;111(6):713-715.
11. Kreuzfelder E, Joka T, Keinecke HO, Obertacke U, Schmit-Neuerburg KP, Nakhosteen JA, et al. Adult respiratory distress syndrome as a specific manifestation of a general permeability defect in trauma patients. Am Rev Respir Dis 1988;137(1):95-99.
12. Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med 2010;36(4):585-599.
13. Gattinoni L, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophys-

iologic review and individual patient meta-analysis. Minerva Anestesiol 2010;76(6):448-454.
14. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, 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(9):865-873.
15. Webster NR, Cohen AT, Nunn JF. Adult respiratory distress syndrome: how many cases in the U.K.? Anaesthesia 1988;43(11):923-926.
16. Villar J, Slutsky AS. The incidence of the adult respiratory distress syndrome. Am Rev Respir Dis 1989;140(3):814-816.
17. Murray JE, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988;138(3):720-723.
18. Meade MO, Guyatt GH, Cook RJ, Groll R, Kachura JR, Wigg M, et al. Agreement between alternative classifications of acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163(2):490-493.
19. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Am J Respir Crit Care Med 1994;149(3 Pt 1):818-824.
20. Villar J, Pérez-Méndez L, Kacmarek RM. Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. Intensive Care Med 1999; 25(9):930-935.
21. Ferguson ND, Kacmarek RM, Chiche JD, Singh JM, Hallett DC, Mehta S, Stewart TE. Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial. Intensive Care Med 2004;30(6):1111-1116.
22. Ferguson ND, Davis AM, Slutsky AS, Stewart TE. Development of a clinical definition for acute respiratory distress syndrome using the Delphi technique. J Crit Care 2005;20(2):147-154.
23. Villar J, Pérez-Méndez L, López J, Belda J, Blanco J, Saralegui I, et al; HELP Network. An early PEEP/F_{IO_2} trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2007;176(8):795-804.
24. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338(6):347-354.
25. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, et al. An evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med 1998;338(6):355-361.
26. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondéjar E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 1998;158(6):1831-1838.
27. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301-1308.
28. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al; Lung Open Ventilation Study Investigators. 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(6):637-645.
29. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al; Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome. JAMA 2008;299(6):646-655.
30. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985;132(3):485-489.
31. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al. Prone-Supine Study Group Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001;345(8):568-573.
32. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A. 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(5): 1311-1318.
33. Bone RC, Maunder R, Slotman G, Silverman H, Hyers TM, Kerstein MD, Ursprung JJ. An early test of survival in patients with the adult respiratory distress syndrome. The P_{aO_2}/F_{IO_2} ratio and its differential response to conventional therapy. Chest 1989;96(4):849-851.
34. Villar J, Pérez-Méndez L, Basaldúa S, Blanco J, Aguilar G, Toral D, et al; the HELP network. A risk tertiles model for predicting mortality in patients with acute respiratory distress syndrom: age, plateau pressure and P_{aO_2}/F_{IO_2} at ARDS onset predict outcome. Respir Care 2011;56(4):420-428.
35. Donnelly SC, Strieter RM, Kunkel SL, Walz A, Robertson CR, Carter DC, et al. Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. Lancet 1993;341(8846): 643-647.
36. Abraham E. Toward new definitions of acute respiratory distress syndrome. Crit Care Med 1999;27(2):237-238.
37. Pugin J, Verghese G, Widmer MC, Matthay MA. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 1999;27(2):304-312.
38. Schuster DP. The search for "objective" criteria of ARDS. Intensive Care Med 2007;33(3):400-402.
39. Villar J, Pérez-Méndez L, Espinosa E, Flores C, Blanco J, Muriel A, et al. GRECIA and GEN-SEP Groups. Serum lipopolysaccharide binding protein levels predict severity of lung injury and mortality in patients with severe sepsis. PLoS One 2009;4(8):e6818.
40. Wang Z, Chen F, Zhai r, Su L, Lin X, Thompson T, Christiani DC. Plasma neutrophil elastase and elastin imbalance is associated with acute respiratory distress syndrome (ARDS) development. PLoS One 2009;4(2):e4380.
41. Ware LB, Koyama T, Billheimer DD, Wu W, Bernard GR, Thompson BT, et al; NHLBI ARDS Clinical Trials Network. Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. Chest 2010;137(2):288-296.
42. Determann RM, Millo JL, Waddy S, Lutter R, Garrard CS, Schultz MJ. Plasma CC16 levels are associated with development of ALI/ARDS in patients with ventilator-associated pneumonia: a retrospective observational study. BMC Pulm Med 2009;9:49.