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ALI and ARDS: Challenges and Advances

K Raghavendran¹ and LM Napolitano¹

K Raghavendran: kraghave@med.umich.edu; LM Napolitano: lenan@med.umich.edu

¹Department of Surgery, University of Michigan, Ann Arbor, MI

I. Introduction

The description of “acute respiratory distress” syndrome as a distinct entity was first reported by Ashbaugh and colleagues in 1967, defined as a clinical pattern including “severe dyspnea, tachypnea, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest x-ray¹”. In their initial report of 12 patients, 7 patients died, and the autopsy finding confirmed striking findings on lung microscopy including the presence of hyaline membranes, diffuse interstitial inflammation and interstitial and intra-alveolar edema and hemorrhage. Since the initial description of ARDS more than 40 years ago, the optimal definition of ALI/ARDS remains a controversial subject.

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are characterized by rapid-onset respiratory failure following a variety of direct and indirect insults to the parenchyma or vasculature of the lungs. The pulmonary pathology of ALI/ARDS can be divided conceptually into acute and fibroproliferative phases that have distinctive features but vary in detail depending on the etiology of injury. Mortality from ALI/ARDS is substantial, and current therapy primarily emphasizes lung protective mechanical ventilation and a restrictive fluid management strategy plus standard treatment of the initiating insult or underlying disease.

Although ALI/ARDS are “syndromes” caused by different injuries and conditions, the patho-biology of the lung injury and similar clinical picture makes a compelling case for us to study them as a single entity rather than characterize the individual risk factors as separate clinical entities. More importantly an array of potential specific targets for pharmacologic intervention can be applied to ALI/ARDS as a disease entity as a whole.

Clinical presentations consistent with ALI and ARDS can arise in patients of all ages from *direct* (pulmonary) or *indirect* (extrapulmonary) insults that induce pulmonary inflammation, damage the cells of the alveolar-capillary membrane, and lead to severe acute respiratory failure. Uniform diagnostic criteria are essential for meaningful clinical studies and therapeutic development for ALI/ARDS. The clinical entities of ALI and ARDS are syndromes defined by a relatively limited set of descriptive patho-physiologic clinical findings, and patients are included regardless of the specific etiology of acute pulmonary dysfunction.

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Although a working definition of ALI/ARDS that includes both pulmonary and extrapulmonary causes can have benefit in standardizing supportive intensive care, it can also complicate assessments of the efficacy of therapeutic interventions. For example, the lack of stratification of patients with ALI/ARDS by etiologic causes has the potential to confound data interpretation in therapeutic trials, since interventions that might benefit one cause of ALI/ARDS may have no benefit or may even be harmful in treating another etiology.

In the following discussion, the definitions that have been recently used for ALI/ARDS in various clinical studies of ALI/ARDS will be discussed individually.

II. Importance of defining ALI/ARDS

A precise definition of the syndrome of ARDS is necessary to facilitate research into the pathogenesis and standardize treatment modalities. There is broad recognition that ALI/ARDS have many predisposing risk factors and the definition merely represents a functional indicator of the severity of the lung injury. Should we be studying individual risk factors/disease that led to this syndrome –such as aspiration-induced lung injury, lung contusion, transfusion related acute lung injury (TRALI) or lung injury secondary to sepsis? There exist major differences in the pathogenesis of these individual insults especially when studied in animal model systems. However, there are major advantages of defining a syndrome like ALI/ARDS.

A standardized universal definition for ALI/ARDS has many benefits. Most importantly, it would allow comparison of the findings of various clinical trials in ALI/ARDS with a greater degree of certainty. For the clinician, a functional definition of ALI/ARDS allows early institution of standardized clinical care, i.e. certain therapeutic modalities that have been tested and proven to have benefits. For instance, early identification of patients with ALI/ARDS allows the early application of protective lung ventilation with lower tidal volumes based on predicted body weights².

Additionally, a standardized definition including ALI and ARDS can assist with outcome prognostication and is of help especially while discussing the care of the patient with families. For the researcher, it helps to capture a larger patient population for potential recruitment into large clinical studies, as proven by multiple clinical trials conducted under the auspices of the ARDS network^{2,3}. Moreover, it offers a common language of communication between the basic and clinical researcher where therapeutic modalities can be constantly tested in the laboratory and brought to the clinical arena.

Additionally, to the public and health care administrators, the many epidemiologic studies reporting on the incidence and outcomes of ALI/ARDS in specific countries and populations helps determine the amount of ever shrinking health care-dollars that can be ascribed to this disease and its societal impact⁴⁻⁷. Finally, it has to be understood that while combining both ALI and ARDS as one entity offers advantages, the results of the clinical studies with testing of therapeutic modalities have to be carefully interpreted, as many specific discrete disease entities have been examined as one.

III. Definitions of ALI/ARDS

A. The American-European Consensus Conference (AECC) definition

The American-European Consensus Conference (AECC) on ARDS in 1994 defined ALI as respiratory failure of acute onset with a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 300 mmHg (regardless of the level of positive end expiratory pressure, PEEP), bilateral infiltrates on frontal chest radiograph, and a pulmonary capillary wedge pressure ≤ 18 mmHg (if measured) or no evidence of left

atrial hypertension⁸. ARDS was defined identically except for a lower limiting value of <200 mmHg for PaO₂/FiO₂ (Table 1)⁸.

The AECC definition of ALI/ARDS is in common use and simple to apply, but also has serious deficiencies in discrimination. There is often not a good correlation between these broad clinical definitions and diffuse alveolar damage (DAD), which is widely considered to be a major characteristic histological feature of ALI/ARDS⁹. The AECC definitions also do not take into consideration variables such as the mode of ventilation and the level of PEEP, which can significantly influence oxygenation. Additionally with the publication of studies that have shown that routine use of Swan-Ganz catheters can be associated with higher complications, the PCOP component of the definition is not commonly measured^{10, 11}. That places a significant emphasis on chest x-ray interpretation where there is a significant lack of inter-observer reliability. However the AECC definition particularly with the ARDS component has proven predictability. For instance patients with ARDS per this definition have higher mortality compared to patients without^{12, 13}.

The AECC definition of ALI/ARDS has been used in all of the ARDS Network clinical trials (www.ardsnet.org). The important question to consider - Does the ARMA ARDS Network trial (lower [6 ml/kg] vs. traditional [12 ml/kg] tidal volumes) with its finding of improved survival (31% vs. 39% mortality) for lower tidal volumes using this ALI/ARDS definition lend increased credibility to this definition²?

B. Murray Lung Injury Score

In 1988, Murray and colleagues proposed an expanded definition of ARDS, taking into account various pathophysiological features of the clinical syndrome. The Murray scoring system includes 4 criteria for the development of ALI/ARDS: a "scoring" of hypoxemia, a "scoring" of respiratory system compliance, chest radiographic findings, and level of positive end-expiratory pressure. Each criterion receives a score from 0 to 4 according to the severity of the condition. The final score is obtained by dividing the collective score by the number of components that were used. A score of zero indicates no lung injury, a score of 1 – 2.5 indicates mild to moderate lung injury, and a final score of more than 2.5 indicates the presence of ARDS (Table 2).

The AECC definition of ALI/ARDS is frequently supplemented by lung injury or critical care scores like the Murray score¹⁴. The major advantage of this scoring system is that it takes into consideration the amount of PEEP and pulmonary compliance, a sensitive indicator of lung injury. Recent studies like the CESAR trial¹⁵ (conventional ventilator support versus extracorporeal membrane oxygenation for severe ARDS) incorporated this scoring system as entry criteria for their study, and only patients with a Lung Injury Score > 3 were considered for the trial. The main disadvantage to the Murray score, especially in the conduct of large clinical studies, is that pulmonary compliance is not routinely measured. A significant deficiency of the Murray score is that cardiogenic pulmonary edema is not excluded.

C. Delphi consensus panel definition

An alternative definition of ARDS by a consensus panel of senior investigators using the Delphi method includes PEEP restrictions (≥ 10) in defining hypoxemia (P/F ratio of <200), radiographic criteria for air space disease in two or more quadrants, and requires either quantitative pulmonary compliance abnormalities (static compliance of < 50 cm H₂O pressure with tidal volume of 8 ml/Kg) or the presence of a predisposing condition (direct/indirect cause of lung injury)¹⁶. Additionally, they emphasized the non-cardiogenic origin of the pulmonary dysfunction by either pulmonary artery catheter or cardiac

echocardiography evaluation. The authors acknowledged that signs of left atrial hypertension can coexist in patients with ARDS. However, the same authors reported that although the Delphi definition is more specific than the AECC criteria it is less sensitive when they chose autopsy findings of diffuse alveolar damage as the gold standards for the diagnosis of ARDS¹⁷.

D. Oxygenation Index (OI) and P/F ratio

Oxygenation Index¹⁸ (OI) is the most widely used system to quantify the degree of lung injury and hypoxemia in pediatric critical care. OI specifically takes into account mean airway pressure (MAP), an important determinant of oxygenation. OI is defined as the product of $MAP \times FiO_2 \times 100 / PaO_2$. OI has been associated with outcome in both adults and children with ALI/ARDS. The original study in 2005 reported on the ability of OI to predict the duration of mechanical ventilation but not survival¹⁸. Since then many adult studies have examined the efficacy of OI as a predictor of both duration of mechanical ventilation and mortality^{19–21}. In comparison, measurement of PaO_2 / FiO_2 (P/F ratio) as a predictor of mortality in ALI/ARDS is uncertain. Although there are little differences in outcome based on P/F ratio early in the course of ARDS, it is likely that persistently lower P/F ratios are associated with higher mortality²². A summary of the pros/cons of the definitions is listed in Table 3.

IV. Accuracy of Current ALI/ARDS Definitions

The diagnostic accuracy of the ALI/ARDS definitions currently in use has been critically examined. A comparison of the AECC definition to autopsy findings of diffuse alveolar damage in a series of 382 patients found the sensitivity (75%) and specificity (84%) to be only moderate¹². Interestingly, the AECC definition was more accurate for patients with extrapulmonary risk factors than for patients with pulmonary risk factors. The AECC definition has performed poorly in limited reliability testing^{23, 24}. Furthermore, there is only moderate agreement between the AECC and the Murray Lung Injury Score (LIS) definitions²⁵.

A study of 183 ICU patients who underwent autopsy after being mechanically ventilated compared the diagnostic accuracy of three clinical ARDS definitions (AECC, Murray Lung Injury Score, and Delphi). Sensitivity and specificity were as follows: AECC 0.83; 0.51, Murray LIS 0.74; 0.77, Delphi 0.69, 0.82. Specificity was significantly higher for both the Murray LIS and the Delphi definition than for the AECC definition, but sensitivity was not significantly different. It should be noted that none of the data for the Murray LIS require subjective interpretation, whereas this is not true for the other ARDS definitions.

V. Is the severity of hypoxemia important?

The traditional thinking with ARDS is that it is the multi-organ dysfunction and not hypoxemia that is responsible for mortality. This was based on a number of ARDS network trials where hypoxia was well tolerated (up to saturations of 88%)² and improvements in oxygenation did not translate into a survival advantage. A detailed discussion of such studies is provided in a number of manuscripts outlined in this edition and beyond the scope of discussion here.

It is important to point out that some studies after the adoption of lung protective strategies have suggested a strong correlation between the severity of hypoxemia and ICU or hospital mortality (see Table 4). In light of this, it is recommended that in future clinical trials of ARDS, severity of hypoxemia should be considered upon patient enrollment into the study, and that outcomes should be assessed based on severity of hypoxemia.

What could be the reasons for these observations? One can speculate on the following possibilities. In patients with severe hypoxia, there is perhaps increased incidence of hyperoxia-induced lung injury from increased requirements of FiO₂ to maintain saturations of 88%. Hyperoxia has been implicated as a factor responsible for increased lung injury in many animal models by the generation of reactive oxygen species, increased apoptosis and necrosis^{26–29}.

Secondly it is important to consider the patho-physiological disturbances linking ARDS with multi-organ dysfunction. Is the multi-organ dysfunction as a result of ALI/ARDS or is the ALI/ARDS a result of multi-organ dysfunction? Are these two separate entities? These questions need to be fully explored in additional studies through basic and clinical research.

V. Is it time to change the definition of ALI/ARDS?

Over the past few years many different study groups have raised doubts about the validity of the current ALI/ARDS definitions and have recommended a change^{30, 31}. We feel strongly that it is time to change the definition after 17 years of the predominant use of the AECC definition for ALI/ARDS. Based on available data with various validity studies it is suggested that the new definition should be standardized as follows: **a.** Risk factors-Direct (Pulmonary) or Indirect (Extra-pulmonary), as most experimental data suggest that these two entities have distinct pathogenic mechanisms; **b.** Calculation of P/F ratios with specific and standard ventilator settings (PEEP and MAP); **c.** Exclude heart failure objectively (use of cardiac echocardiogram); and **d.** Only include patients with P/F ratio with standard ventilator settings of less than 200.

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Table 1

The American-European Consensus Conference (AECC) Definition of ALI and ARDS developed in 1994

ALI Criteria	Timing: Acute onset Oxygenation: $\text{PaO}_2/\text{FiO}_2 \leq 300$ mm Hg (regardless of positive end-expiratory pressure [PEEP] level) Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph Pulmonary artery wedge: ≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension
ARDS Criteria	Same as ALI except: Oxygenation: $\text{PaO}_2/\text{FiO}_2 \leq 200$ mm Hg (regardless of positive end-expiratory pressure [PEEP] level)

Table 2

The Murray Lung Injury Score.

The lung injury score (Murray score) ¹⁴		
<u>1. Chest roentgenogram score</u>		
No alveolar consolidation		0
Alveolar consolidation confined to 1 quadrant		1
Alveolar consolidation confined to 2 quadrant		2
Alveolar consolidation confined to 3 quadrant		3
Alveolar consolidation in all 4 quadrant		4
<u>2. Hypoxemia score</u>		
PaO ₂ /FiO ₂	>300	0
PaO ₂ /FiO ₂	225–299	1
PaO ₂ /FiO ₂	175–224	2
PaO ₂ /FiO ₂	100–174	3
PaO ₂ /FiO ₂	≤ 100	4
<u>3. PEEP score (when ventilated)</u>		
PEEP	≤ 5 cm H ₂ O	0
PEEP	6–8 cm H ₂ O	1
PEEP	9–11 cm H ₂ O	2
PEEP	12–14 cm H ₂ O	3
PEEP	> 15 cm H ₂ O	4
<u>4. Respiratory system compliance score (when available)</u>		
Compliance	>80 ml/cmH ₂ O	0
Compliance	60–79 ml/cmH ₂ O	1
Compliance	40–59 ml/cmH ₂ O	2
Compliance	20–39 ml/cmH ₂ O	3
Compliance	< 19 ml/cmH ₂ O	4

The final score is calculated by the addition of the component parts.

Score 0= no lung injury; 1–2.5 = mild to moderate lung injury

>2.5= severe lung injury

Table 3

Comparative analyses of commonly used definitions for ALI/ARDS

Definition	Pros	Cons
AECC⁸	Simple and easy to use Differentiates ALI and ARDS Prognostic capability based on ARMA study?	Acute onset-not defined PAOP often not measured PEEP/Compliance/MAP not taken into consideration Risk factors not emphasized
Murray score¹⁴	Takes PEEP/Compliance into consideration Differentiates mild to moderate from severe lung injury Radiologic criteria more specific	Does not include MAP Does not exclude heart failure Does not identify individual risk factors Prognostic ability not validated
Delphi¹⁶	Defines criteria for onset(<72 h) Risk factor emphasized Takes PEEP into consideration Objectively rules out heart failure	Excludes P/F >200 and < 300 Does not include compliance or MAP
Oxygenation Index¹⁸	Takes MAP into consideration Prognostic ability validated	Does not take PEEP and compliance in consideration Does not exclude heart failure Does not evaluate radiologic signs

PEEP = Positive end-expiratory pressure

MAP = mean airway pressure

P/F = Partial pressure of arterial oxygen /Fraction of inspired oxygen

Table 4

Severity of hypoxemia and outcome in ALI/ARDS

Study	n	PaO ₂ /FiO ₂ ratio (mm Hg)	Mortality	
Meade 2008 ³²	983		<u>Hospital Mortality</u>	
			<u>Lung Open Ventilation</u>	<u>Control</u>
		41–106	57 (50%)	77 (58%)
		> 106–142	46 (39%)	55 (43%)
		>142–180	43 (33%)	40 (33%)
		> 180–250	27 (25%)	33 (26%)
Villar 2011 ³³	220		<u>Hospital Mortality</u>	
		< 112	47%	
		112–142	30%	
		>142	23%	
Cooke 2008 ³⁴	1113		<u>Hospital Mortality</u>	
		≤100	50%	
		≤100 + shock	58%	
		≤100 + oliguric renal failure	71%	
Villar 2007 ³⁵	170		<u>ICU Mortality</u>	<u>Hospital Mortality</u>
		< 112	45 (45.5%)	45 (45.5%)
		112–142	11 (20%)	11 (20%)
		>142	1 (6.3%)	2 (12.6%)
Rubenfeld 2005 ⁶	1113		<u>Hospital Mortality</u>	
		< 200 (ARDS)	41.1%	
		200–300 (ALI)	38.5%	
		ALI progressed to ARDS on day 3 or day 7	41.0%	
		ALI – no progression to ARDS on day 3 or day 7	28.6%	
Brun-Buisson ALIVE study 2004 ³⁶	463		<u>ICU Mortality</u>	<u>Hospital Mortality</u>
		< 200 (ARDS)	49.4%	57.9%
		200–300 (ALI)	22.6%	32.7%
Esteban 2002 ¹²	120		<u>ICU Mortality</u>	
		< 100	83%	
		100–149	47%	
		150–199	31%	
		200–300	25%	
		> 300	24%	
Taccone Prone-Supine II 2009 ³⁷	342		<u>ICU Mortality</u>	<u>Hospital Mortality</u>
		< 100 (Severe ARDS)	42.0%	50.7%
		100–200 (ARDS)	24.0%	31.8%