

Acute respiratory distress syndrome 40 years later: Time to revisit its definition*

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Objective: Acute respiratory distress syndrome is a common disorder associated with significant mortality and morbidity. The aim of this article is to critically evaluate the definition of acute respiratory distress syndrome and examine the impact the definition has on clinical practice and research.

Data Sources: Articles from a MEDLINE search (1950 to August 2007) using the Medical Subject Heading *respiratory distress syndrome, adult, diagnosis*, limited to the English language and human subjects, their relevant bibliographies, and personal collections, were reviewed.

Data Synthesis: The definition of acute respiratory distress syndrome is important to researchers, clinicians, and administrators alike. It has evolved significantly over the last 40 years, culminating in the American–European Consensus Conference definition, which was published in 1994. Although the American–European Consensus Conference definition is widely used, it has some important limitations that may impact on the conduct of clinical research, on resource allocation, and ultimately on the bedside management of such patients. These limitations stem partially from the fact that as defined, acute respiratory distress

syndrome is a heterogeneous entity and also involve the reliability and validity of the criteria used in the definition. This article critically evaluates the American–European Consensus Conference definition and its limitations. Importantly, it highlights how these limitations may contribute to clinical trials that have failed to detect a potential true treatment effect. Finally, recommendations are made that could be considered in future definition modifications with an emphasis on the significance of accurately identifying the target population in future trials and subsequently in clinical care.

Conclusion: How acute respiratory distress syndrome is defined has a significant impact on the results of randomized, controlled trials and epidemiologic studies. Changes to the current American–European Consensus Conference definition are likely to have an important role in advancing the understanding and management of acute respiratory distress syndrome. (Crit Care Med 2008; 36:2912–2921)

KEY WORDS: acute respiratory distress syndrome; diagnosis; randomized, controlled trials; heterogeneity; reliability; validity

Acute respiratory distress syndrome (ARDS) is a catastrophic form of acute respiratory failure characterized by nonhydrostatic pulmonary edema and severe hypoxemia, which results from alveolar–capillary damage caused by multiple factors (1–3). It is an important public

health problem; more than 100,000 cases of ARDS occur in the United States annually, accounting for millions of days spent in hospitals and intensive care units (4). The mortality rate ranges from 30% to 60% (4–18), and those who survive have protracted reductions in quality of life (19–24). Improving our understanding and treatment of ARDS is therefore a justified priority for researchers, clinicians, administrators, funding organizations, patients, and advocacy groups (25, 26).

Many randomized, controlled trials (RCTs) aimed at reducing the mortality of ARDS have been conducted recently. Unfortunately, trials that have demonstrated improved survival (27–29) are far outnumbered by those that have not (30–63) (Table 1). This may be because the interventions studied are ineffective, but it is just as likely that the broadly inclusive definition of ARDS captures a heterogeneous group of patients who are destined to respond differently to these therapies.

The ARDS definition has evolved since Laennec's 1821 description of "idiopathic anasarca of the lungs" (64). Key steps in this evolution are a) the description of ARDS as a distinct entity by Ashbaugh and colleagues in 1967 (65); b) the use of various nonstandardized definitions until the 1980s (66–69); c) the development of the Lung Injury Score by Murray and colleagues in 1988 (70); and d) the creation of the American–European Consensus Conference (AECC) definition, published in 1994 (71) (Table 2). The current standard for clinical research is the AECC definition (4, 7–12, 28, 29, 32, 34–39, 44–48, 50–54, 58–63, 72–74), namely the acute onset of hypoxemia ($\text{PaO}_2/\text{Fio}_2$ ratio ≤ 200 mm Hg) and diffuse radiologic infiltrates in the absence of left atrial hypertension (71) (Table 2).

Coincident with the AECC definition, the last decade has seen an explosion of research on ARDS. Meanwhile, our enhanced knowledge of ARDS has uncovered important limitations to the AECC definition. In this review, we expand

*For other points of view, see pages 2922 and 2926.

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Table 1. Selected randomized controlled trials (1997–2006) in acute respiratory distress syndrome grouped by survival benefits

Therapy	Investigators	Year
With survival benefit		
Lung protective ventilation: volume and/or pressure limited with or without high PEEP	Amato et al (27) ^a	1998
	ARDS network (28) ^{b,c}	2000
	Villar et al (29) ^{c,d}	2006
Prone positioning	Mancebo et al (73) ^e	2006
Systemic steroids	Meduri et al (74) ^{c,d}	1998
No survival benefit		
Volume and/or pressure limited lung protective ventilation	Stewart et al (30)	1998
	Brochard et al (31)	1998
	Brower et al (32)	1999
High PEEP	ARDS network (33)	2004
Pressure versus volume-controlled ventilation	Esteban et al (34) ^f	2000
High frequency oscillatory ventilation	Derdak et al (35)	2002
	Bollen et al (36)	2005
Prone positioning	Gattinoni et al (37) ^g	2001
	Guerin et al (38)	2004
Inhaled nitric oxide	Dellinger et al (39)	1998
	Michael et al (40)	1998
	Troncy et al (41)	1998
	Lundin et al (42)	1999
	Taylor et al (43)	2004
Pulmonary artery catheter	Richard et al (44)	2003
	ARDS network (45)	2006
Conservative fluids	ARDS network (46)	2006
Furosemide and albumin	Martin et al (47)	2002
Albumin	Martin et al (48)	2005
Lipid and antioxidant enriched enteral feeding	Gadek et al (49)	1999
	Singer et al (50)	2006
Albuterol	Perkins et al (51)	2006
Systemic steroids	ARDS network (52)	2006
Exogenous surfactant	Spragg et al (53)	2003
	Spragg et al (54)	2004
Partial liquid ventilation	Hirschl et al (55)	2002
	Kacmarek et al (56)	2006
N-acetylcysteine	Bernard et al (57)	1997
	Domenighetti et al (58)	1997
Ibuprofen	Bernard et al (59)	1997
Liposomal prostaglandin E ₁	Abraham et al (60)	1999
Ketoconazole	ARDS network (61)	2000
Lisofylline	ARDS network (62)	2002
Neutrophil elastase inhibition	Zeiber et al (63)	2004

ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.

^a28-day mortality; ^b180-day mortality; ^chospital mortality; ^dintensive care unit mortality; ^emortality benefit after multivariate analysis; ^fno mortality benefit after multivariate analysis; ^gpossible mortality benefit in quartile with lowest Pao₂/Fio₂ ratio.

on the importance of the definition of ARDS, highlight the heterogeneous nature of ARDS, and critically evaluate the AECC criteria. We discuss the significance of accurately identifying the target population in ARDS trials, particularly as it relates to the definition of ARDS. Finally, we raise issues for consideration in future definition modifications.

To assist with this review, we searched MEDLINE (1950 to August 2007) using the Medical Subject Heading *respiratory distress syndrome, adult, diagnosis*, limited to the English language and human subjects. This strategy yielded 663 potentially relevant articles, for which cita-

tions, abstracts, or both were reviewed. We then reviewed bibliographies of selected articles, and our personal collections, for additional relevant papers.

Why Is the Definition of Adult Respiratory Distress Syndrome Important?

Importance to Researchers. An ARDS definition that captures a broad spectrum of patients, like the AECC definition, facilitates enrollment into multiple RCTs (Table 1) (28, 29, 33–39, 44–48, 50–54, 58–63, 73, 74). However, as discussed, with this definition, we may enroll pa-

tients with varied pathophysiology under one umbrella.

Definitions are also important whenever links are made between basic science and the clinical realm. There has been increasing interest in the basic science of and genetic predispositions to lung injury (75–79). Before we can uncover candidate genes associated with ARDS, we must be certain that the studied population does indeed have ARDS (80, 81).

Importance to Clinicians. After the publication of the ARDS Network trial demonstrating the benefits of tidal volume limitation (or dangers of overdistension), clinicians should feel compelled to identify patients with ARDS (and acute lung injury [ALI]) and intervene appropriately (28). Also, when discussing ARDS prognosis with patients and their families, outcome studies are invaluable (4–16, 82–84). Although a reproducible definition will help clinicians apply these research findings, it is again crucial that the definition truly represents ARDS.

Importance to Administrators. Epidemiologic studies on ARDS provide important information to healthcare administrators who determine resource allocation. The results of such studies are influenced by how ARDS is defined. For example, in the late 1980s and early 1990s, studies using various ARDS definitions found relatively low ARDS incidence rates (1.5 to 8.3 cases per 100,000 population per year) (5, 6, 85, 86). However, from 1997 onward, studies using the more liberal AECC criteria found higher incidence rates (4.9 to 75 cases per 100,000 population per year) (4, 7–12, 72).

Adult Respiratory Distress Syndrome: The Problem of Heterogeneity

The AECC definition (along with other definitions) reduces multiple pathophysiological processes and groups very heterogeneous patients into a single syndrome (1–3, 87, 88). Factors that influence heterogeneity (in response to therapies or outcome) include the inciting cause (89–99) and phase of ARDS (52, 74, 100), the timing of ARDS relative to onset of mechanical ventilation (14, 16, 18, 101), and variability in the mechanisms of lung injury (102, 103). This heterogeneity may have contributed to RCTs that failed to find a treat-

Table 2. Definitions of acute respiratory distress syndrome

Authors	Year Published	Criteria	Pros	Cons
Current American-European Consensus Conference definition Bernard et al. (71)	1994	<ul style="list-style-type: none"> ● Acute onset ● $P_{aO_2}/F_{iO_2} \leq 200$ mm Hg = ARDS ● $P_{aO_2}/F_{iO_2} \leq 300$ mm Hg = ALI ● Bilateral infiltrates on chest radiograph ● PAOP ≤ 18 mmHg when measured or no clinical evidence of left atrial hypertension 	<ul style="list-style-type: none"> ● First consensus definition ● Differentiates ARDS and ALI 	<ul style="list-style-type: none"> ● "Acute" not specific ● Cause not emphasized ● P_{aO_2}/F_{iO_2} 200 mm Hg not prognostic ● PEEP not incorporated ● Chest radiograph interpretation subjective ● PAOP often >18 mm Hg
Other definitions Ashbaugh et al. (65)	1967	<ul style="list-style-type: none"> ● Severe dyspnea, tachypnea ● Cyanosis refractory to oxygen therapy ● Loss of lung compliance ● Diffuse alveolar infiltration on chest radiograph ● Hyperemia, atelectasis, interstitial and alveolar hemorrhage and edema, and hyaline membranes at autopsy 	<ul style="list-style-type: none"> ● Original description of ARDS 	<ul style="list-style-type: none"> ● No specific criteria ● Autopsy not usually performed
Bone et al. (66)	1976	<ul style="list-style-type: none"> ● $P_{aO_2} \leq 70$ mm Hg with $F_{iO_2} \geq 0.5$ with PEEP (amount of PEEP not specified) 	<ul style="list-style-type: none"> ● Reasonable threshold for P_{aO_2}/F_{iO_2} 	<ul style="list-style-type: none"> ● No specifics other than oxygenation
Pepe et al. (67)	1982	<ul style="list-style-type: none"> ● $P_{aO_2} < 75$ mm Hg with $F_{iO_2} \geq 0.5$ ● New diffuse bilateral chest infiltrates with all lung fields involved ● PAOP < 18 mm Hg ● Not due to heart failure, pleural effusion, atelectasis or bacterial pneumonia 	<ul style="list-style-type: none"> ● Detailed operational definition similar to current definitions 	<ul style="list-style-type: none"> ● PEEP not incorporated ● PAOP often >18 mm Hg ● Excludes bacterial pneumonia
Fowler et al. (68)	1983	<ul style="list-style-type: none"> ● Sudden onset of bilateral pulmonary infiltrates ● PAOP ≤ 12 mm Hg ● Compliance ≤ 50 mL/cm H_2O ● $P_{aO_2}/P_{aO_2} \leq 0.2$ 	<ul style="list-style-type: none"> ● Detailed operational definition 	<ul style="list-style-type: none"> ● PAOP very often >12 mm Hg ● Compliance not usually measured ● PEEP not incorporated
Murray et al. (70)	1988	<ul style="list-style-type: none"> ● Acute or chronic ● Mild to moderate or severe (ARDS) lung injury based on Lung Injury Score ● Caused by pulmonary disorder or associated with systemic disorder 	<ul style="list-style-type: none"> ● Lung Injury Score describes severity ● PEEP incorporated ● Emphasizes cause 	<ul style="list-style-type: none"> ● Chronic subtype no longer accepted ● Lung Injury Score not prognostic ● Compliance not usually measured ● Does not exclude heart failure

ARDS, acute respiratory distress syndrome; ALI, acute lung injury; PAOP, pulmonary artery occlusion pressure; PEEP, positive end-expiratory pressure; P_{aO_2} , partial pressure of alveolar oxygen.

ment effect that truly exists, because a therapy that benefits one subgroup of patients with ARDS may not benefit another subgroup (104, 105).

Evaluating the Definition for Adult Respiratory Distress Syndrome

To evaluate the quality of any definition, two questions are asked (Table 3): 1) Is the definition reliable; that is, are the results of the definition reproducible? 2) Is the definition valid; that is, does it distinguish those with a disease from those without (106, 107)?

One hurdle in evaluating any ARDS definition is the lack of a gold standard; this makes the usual type of validity we talk about for diagnostic tests (concurrent criterion validity; Table 3) unavailable. Diffuse alveolar damage is the histologic equivalent of ARDS (1–3, 108). However, using histology as the reference standard for defining ARDS is problematic because of the risks of (and feasibility barriers to) lung biopsies, the patchy nature of ARDS (109), and the nonspecific nature of diffuse alveolar damage (110).

Despite our increasing knowledge of the pathophysiology of ARDS, the syndrome's definition is dissociated from its

underlying mechanisms. We should therefore ask if the AECC definition reflects the current understanding of the pathophysiology and manifestations of ARDS.

How Reliable and Valid Are the Components of the American-European Consensus Conference Definition?

Hypoxemia. The AECC defines ARDS and ALI (a milder manifestation of ARDS) when the P_{aO_2}/F_{iO_2} ratios are ≤ 200 mm Hg and ≤ 300 mm Hg, respectively (71). However, the P_{aO_2}/F_{iO_2} ratio varies considerably

Table 3. Types of reliability and validity as applied to diagnostic criteria for acute respiratory distress syndrome

Measure	Question
Reliability	
Interobserver reliability	Will different clinicians make the same diagnosis of ARDS in one patient using the diagnostic criteria?
Intraobserver reliability	Will one clinician make the same diagnosis of ARDS in one unchanged patient at different time points using the diagnostic criteria?
Validity	
Face validity	Subjectively, and at face value, do the diagnostic criteria appear to describe the disease entity known as ARDS?
Content validity	Do the diagnostic criteria describe all the important components of ARDS (and are none irrelevant)?
Criterion validity ^a	Do the diagnostic criteria correlate well with a gold standard for the diagnosis of ARDS (concurrent validity) or outcomes of ARDS (predictive validity)?
Concurrent validity	Do the diagnostic criteria correlate well with a gold standard measure for the diagnosis of ARDS if both measures are used at the same time?
Predictive validity	If a patient fulfils the diagnostic criteria for ARDS, does this predict a certain outcome or response to a therapy?
Construct validity ^b	In the absence of an available gold standard for the diagnosis of ARDS, do the diagnostic criteria satisfy a series of hypotheses related to the pathophysiology and manifestations of ARDS (convergent validity) and not other diseases (discriminant validity)?
Convergent validity	Do the diagnostic criteria describe the pathophysiology of ARDS, including inflammation, permeability edema and surfactant abnormalities, and the clinical manifestations, i.e., acute hypoxemic respiratory failure and lung infiltrates?
Discriminant validity	Do the diagnostic criteria discriminate ARDS from mimickers like cardiogenic pulmonary edema?

ARDS, acute respiratory distress syndrome.

^aConcurrent validity and predictive validity are subcategories of criterion validity; ^bconvergent validity and discriminative validity are subcategories of construct validity.



Figure 1. Influence of airway pressures on oxygenation and chest radiograph. Chest radiograph 1 is from a patient with acute respiratory distress syndrome on conventional mechanical ventilation with a $\text{PaO}_2/\text{FIO}_2 = 80$ mm Hg, with an $\text{FIO}_2 = 1.0$, and a mean airway pressure of 22 cm H_2O . Chest radiograph 2 is from the same patient taken 30 mins after chest radiograph 1. Here the patient has been placed on high-frequency oscillatory ventilation, with a $\text{PaO}_2/\text{FIO}_2 = 281$ mm Hg, an $\text{FIO}_2 = 1.0$, and a mean airway pressure of 30 cm H_2O .

across levels of FIO_2 , particularly when the FIO_2 is $<.5$, the PaO_2 is >100 mm Hg, or when the shunt fraction is low (111). Moreover, many patients who initially fulfill the AECC criteria may improve their $\text{PaO}_2/\text{FIO}_2$ ratio above 200 mm Hg after a short duration of applied positive end-expiratory pressure (PEEP) or higher FIO_2 (this improvement may be associated with lower mortality) (112–116) (Fig. 1). Hypoxemia in ARDS may also be related to atelectasis (117), a low cardiac output (118), and shunt through a patent foramen ovale (119).

To address the inconsistency of the $\text{PaO}_2/\text{FIO}_2$ ratio, future ARDS definitions may use standardized ventilator settings, for example, requiring a $\text{PaO}_2/\text{FIO}_2$ ratio ≤ 200 mm Hg with a set PEEP (for example, 10 cm H_2O) and FIO_2 (for example, .5) or using the oxygenation index ($100 \times \text{mean airway pressure} \times \text{FIO}_2/\text{PaO}_2$) (112, 113, 116). How long should one wait before assessing oxygenation on these settings? Persistence of hypoxemia at 24 hrs selects patients with a higher risk of mortality (115, 116); however, a delay in institution may result in a reduction of effectiveness for some treatments. Investigators must balance these competing interests when selecting their duration for a particular trial.

Bilateral Radiologic Infiltrates. The AECC definition requires bilateral infiltrates on chest radiograph, which “should be consistent with pulmonary edema” (71). When intensivists and radiologists were asked to evaluate whether chest radiographs would qualify for the AECC definition, agreement was no better than chance in half the radiographs (120, 121). Radiographic opacities may also be altered with higher mean airway pressures (Fig. 1). Although computed tomography scans may be more reliable, and may help determine recruitability, these are not currently feasible (91–94, 117, 122).

To improve interobserver reliability, we believe guidelines should be created to define “bilateral infiltrates” on a chest radiograph. A standardized training set of radiographs could be generated (121). To improve validity, we could move back to a definition that specifies more severe airspace disease based on data from clinical-pathologic correlations (67, 70, 123, 124).

Left Atrial Hypertension. To distinguish ARDS from cardiogenic pulmonary edema, the AECC definition requires that the pulmonary artery occlusion pressure (PAOP) be ≤ 18 mm Hg, or there should be “no clinical evidence of left atrial hy-

pertension” (71). The measurement of PAOP is fraught with problems of inter-observer reliability (125, 126). Moreover, one third to one half of patients with ARDS/ALI have PAOP >18 mm Hg; often these are related to transmitted airway pressures or fluid resuscitation (45, 127, 128).

We therefore believe that PAOP thresholds should not be included in future ARDS definitions. Indeed, no perfect test exists that distinguishes noncardiogenic from cardiogenic pulmonary edema. B-type natriuretic peptide measurements (129, 130) and indices of pulmonary permeability (131) are examples of measures that may be helpful in the future. Moreover, it is important to note that patients with ARDS can also have acute heart failure and vice versa. We favor an approach whereby clinicians use clinical judgment to determine the predominant pathophysiological process. Further investigations, including right heart catheterization and/or echocardiography, may assist in determining this in appropriate situations such as cases without a clear ARDS risk factor or in RCTs with stringent inclusion criteria.

Acute Onset. The AECC definition excluded chronic respiratory failure (71), but did not specify the timelines for “acute.” This introduces undesirable subjectivity.

We propose that the timeline of development of respiratory failure should be better explicated, for example, within 1 wk from the diagnosis of a known clinical insult leading to ARDS, or from the onset of dyspnea to the meeting of the diagnostic criteria when no clinical insult is recognized.

How Does the American-European Consensus Conference Definition Perform as a Whole?

Comparison with Autopsy Findings. Esteban and colleagues compared clinical definitions with autopsy findings of diffuse alveolar damage. The sensitivity and specificity of the AECC definition for detecting diffuse alveolar damage were 75% and 84%, respectively, when clinical information from the entire ICU stay was used to judge the presence of ARDS and diffuse airspace disease was required on chest radiograph (132). When judged on a daily basis and with a radiographic definition of “bilateral infiltrates,” the sensitivity of the definition remained good, but specificity was less than 50% (124).

Comparison with the Lung Injury Score. Three studies showed varying degrees of agreement between the AECC definition and the Lung Injury Score (124, 133, 134). When disagreements exist, it is not clear which definition is correct.

Predictive Validity of the American-European Consensus Conference Definition. If a patient fulfills the criteria, does this predict a certain outcome (Table 3)? The presence of ARDS based on the AECC definition predicts a higher mortality as compared with patients without ARDS (18, 135, 136). Data regarding the prognosis of ARDS versus ALI are more controversial. Although several studies have shown that baseline P_{aO_2}/F_{iO_2} ratios do not predict mortality (10, 82, 137), and that no difference in mortality exists between ARDS versus ALI (7, 8), others have shown worse outcomes for ARDS than ALI (17, 136) or with a progression of severity from ALI to ARDS (4).

Predictive validity may also be viewed in terms of therapeutic response. Does the fact that the AECC definition was used to define a population who benefited from tidal volume limitation make the definition valid (28, 29)? Until similar findings are seen with other interventions, it is too early to label the definition as generally valid. (Otherwise, should we label it as invalid because of multiple studies that did not show mortality benefits?) Nevertheless, we should currently continue to use the AECC definition to identify patients who may benefit from tidal volume limitation (recognizing that many may not really have ARDS and that other mechanically ventilated patients may also benefit [138, 139]).

How Does the Definition for Adult Respiratory Distress Syndrome Impact on Study Results?

The following formula explicates how definitions can affect outcomes in clinical research:

Confidence = (signal/noise) × (square root of sample size) (105, 140).

Confidence describes how narrow the confidence interval is around the effect of treatment in a RCT, signal reflects the absolute risk reduction, and noise describes the sources of variation that may affect this reduction. Correspondingly, the choice of the study population based on a certain definition of ARDS may result in a trial that fails to detect a true

treatment effect in several ways. First, the signal may be poor as a result of a low mortality rate attributable to ARDS either because patients are not sick enough or are too sick and die of irreversible causes. Second, the signal may be poor because the therapy does not address the underlying pathophysiology. Third, definitions may lead to excess noise through the inclusion of patients without ARDS.

The choice of an ARDS definition also affects the required sample size. A narrow definition promotes a smaller explanatory trial that studies the efficacy of a therapy in select patients (140, 141). A wide-encompassing definition facilitates a large pragmatic and widely generalizable trial that assesses the effectiveness of a therapy in a general population. However, in a pragmatic trial, the risk of failing to detect a true treatment effect is high as a result of a weaker signal-to-noise ratio associated with a liberal ARDS definition; hence, a “negative” trial does not rule out an efficacious therapy. Given the preponderance of “negative” trials in ARDS (Table 1), we favor a stepwise approach of initial explanatory trials (with narrower generalizability) and subsequent pragmatic trials after establishing efficacy.

Future Considerations

There is room for improvement in the AECC definition’s reliability and validity. Meanwhile, the signal-to-noise ratio in RCTs may also be undermined by how the AECC definition groups vary heterogeneous types of patients together (1–3). The debate about whether it is appropriate to lump these patient types has been ongoing for decades (142).

A TNM-like Classification System: Are We Ready? ARDS is a heterogeneous entity; perhaps it is insufficient to merely label a patient as having ARDS. None of us would test a therapy for “cancer,” nor even “lung cancer”; rather, the specific pathology and stage are essential prerequisites. A further classification system to describe patients with ARDS may be considered, such as the GOCA system (Gas exchange, Organ failure, Cause, Associated diseases) proposed at a second AECC meeting (143). Such a classification system is akin to the TNM classification (Tumor, Nodes, Metastases) for malignancies (144) and the PIRO classification (Predisposition, Infection, Response, Organ dysfunction) for sepsis (145). Additional factors to consider incorporating include

candidate genes associated with ARDS (75–79), markers of endothelial activation like von Willebrand factor (102), markers of epithelial injury like the alveolar type 1 cell-specific biomarker HTI₅₆ (146), and serum Clara cell protein concentrations (147), various indices of pulmonary permeability (131), and markers of collagen synthesis like procollagen peptide (103).

Such a system may help select the appropriate patients for RCTs. Unfortunately, to prematurely create a TNM-like system is like creating a staging system for a generic “cancer” rather than non-small cell lung cancer. More data on pathophysiology and prognosis are required, which brings about a paradox: we cannot gain better insights into the ideal definition without a better understanding of the disease; yet, we cannot study and understand the disease better without an improved definition. The only solution is small incremental steps on both sides of this equation with iterative improvements incorporated into the definition over time. Meanwhile, a demand that all future studies on ARDS collect sufficient GOCA-like information will help enhance our understanding of the syndrome.

Framework for Defining an Adult Respiratory Distress Syndrome Study Population. A pragmatic approach is to use a generic ARDS definition derived from the current AECC criteria and then modify it for each individual RCT using a standard framework. When designing an RCT’s inclusion criteria, the focus should be on optimizing therapeutic response.

Potential therapies for ARDS may be differentiated into pulmonary-specific versus systemic ones. Pulmonary-specific therapies include ventilatory techniques and their adjuncts such as prone positioning and inhaled therapies. Here, the definition of pulmonary dysfunction and ARDS is paramount alongside a good grasp of pulmonary pathophysiology. To illustrate, a trial using inhaled beta-agonists to decrease lung water could enroll only patients with high levels of lung water (51). Trials on recruitment maneuvers and PEEP should focus on largely recruitable lungs (117, 148, 149). Systemic therapies include anticoagulant and anti-inflammatory agents. Here, because the lung is often just one of many organ dysfunctions, the definition of pulmonary dysfunction is perhaps less critical. Nevertheless, therapeutic response remains the focus; for example, a trial on a treatment targeting endothelial activa-

Table 4. Proposed modified definition and future considerations for acute respiratory distress syndrome and acute lung injury

Characteristic	Remarks
Proposed modified diagnostic criteria	
Acute onset	Within 1 week from the diagnosis of a known clinical insult leading to ARDS/ALI, or from the onset of dyspnea to meeting of the diagnostic criteria when no clinical insult is recognized
Hypoxemia	Pao ₂ /Fio ₂ ≤200 mmHg for ARDS and ≤300 mm Hg for ALI on standardized ventilator settings, e.g., set PEEP ≥10 cm H ₂ O and Fio ₂ ≥0.5
Diffuse radiologic infiltrates	Bilateral airspace disease involving ≥2 full quadrants on frontal chest radiograph; use a training set of chest radiographs to improve standardization when applicable
Predominantly non-cardiogenic	No clinical evidence of heart failure as the predominant pathophysiologic process (including use of supporting evidence as clinically indicated)
Tailor definition to optimize therapeutic response for specific randomized controlled trials	
Type of trial	Step-wise approach of narrow definition for initial explanatory trials, followed by wide-encompassing definition for pragmatic trials
Type of therapy	Modify inclusion criteria to select only patients who will likely respond based on existing knowledge of pathophysiology

ARDS, acute respiratory distress syndrome; ALI, acute lung injury; PEEP, positive end-expiratory pressure.

tion could enroll only patients with high von Willebrand factor levels (102).

There is perhaps no right answer on whether to lump or split different ARDS subpopulations. More importantly, one should choose a study population using inclusion criteria with potentially good predictive validity for the therapy in question and thereby increase the RCT’s signal-to-noise ratio. This would allow the demonstration of a true treatment effect with a smaller sample size.

Given the issues that we have discussed in this article, we present in Table 4 a summary of our recommendations for consideration regarding the current definition of ARDS and ALI. We stress that these are proposals that should act only as a starting point for further discussion and revision by the international community.

CONCLUSION

The importance of ARDS is clear. How it is defined has a significant impact on the results of RCTs and epidemiologic studies, whose findings impact researchers, clinicians, and administrators alike. The current AECC definition of ARDS has helped contribute to major advances in research; however, changes are necessary

to advance the understanding and management of ARDS.

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