

Syndromes, diseases and the challenge of definitions in intensive care medicine: the case of acute respiratory distress syndrome

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SUMMARY. The development of Intensive Care Units (ICUs) has been associated with the emergence of new iatrogenic diseases, which reflect a continuous “cross-talk” between various different noxious stimuli, the preserved through the evolution of homeostatic pathophysiological mechanisms and the treatment effects upon organ systems. One such disease or syndrome is the acute respiratory distress syndrome (ARDS). The majority of currently used definitions for ARDS, including that proposed by the American-European Consensus Conference (AECC), apply common diagnostic criteria for different pathological processes, resulting in misclassification of heterogeneous groups of patients within the same syndrome. This brief overview emphasizes the significant questions that were raised by investigators regarding the description of ARDS in the early years. Despite the progress that has been made, many methodological issues remain unresolved. The incorporation of new knowledge into appropriate definitions is a challenge, since the better understanding of the pathophysiology, and the design of clinical trials with positive results both depend on an appropriate description of ARDS. In this article, an attempt is made to emphasize the challenges of adopting a reliable and valid definition for ARDS, as indirectly proposed in the most recent relevant literature. *Pneumon 2009, 22(3):223-229.*

LOOKING FOR AN APPROPRIATE DEFINITION FOR ARDS

‘Physicians think they do a lot for a patient when they give his disease a name’

Immanuel Kant

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The evolution of intensive care medicine has given rise to a unique challenge in medical taxonomy. The problem of description and classification is as old as medicine itself. The development of intensive care units (ICUs)

has increased the complexity of this problem, since the expression of critical illness reflects a limited number of pathological responses to a remarkably heterogeneous group of stimuli. Acute respiratory distress syndrome (ARDS) is induced by a diverse group of insults but its clinical phenotype is common to all insults, and reflects not only the causative stimulus but also the response of the lung to injury. With supportive treatment, the dominant clinical picture becomes no longer that of the primary disease, but the expression of a combination of various different pathological and homeostatic mechanisms and the consequences of treatment, since life-sustaining interventions, such as mechanical ventilation, themselves carry a significant risk of causing harm.¹

The complex nature of critical illness generates a significant descriptive challenge. Intensive care physicians debate the optimal definition of ARDS when its presentation has been characterized as iatrogenic, since it develops only in patients whose death has been forestalled by the use of controlled mechanical ventilation. In addition, as Marshal and Aarts have commented, in contemporary intensive care medicine the physicians are treating *illnesses* rather than *diseases*.¹ In the case of illness, they are dealing mainly with specific signs and symptoms because they lack a fundamental understanding of how these combine as manifestations of a common biological process (i.e., a disease). The transition from illness to disease and syndrome, that is a particular combination of clinical and laboratory findings having a common pathological basis, reflects an advancing understanding of pathogenetic mechanisms, and ultimately, an increased probability of therapeutic success.

In the meantime, what is really happening with ARDS? Why, since 1967 when Ashbaugh first described ARDS², have so many attempts been undertaken to adopt a more accurate and valid definition of the syndrome, questioning the value of the American-European Consensus Conference (AECC) definition?³⁻¹¹ The answer to this dilemma, according to Phua, is associated with a paradox: defining ARDS demands more data on pathophysiology and prognosis, while studying and understanding the disease entity is based on having a reliable and valid definition.⁹ Reliability, both intraobserver and interobserver, characterizes a definition the results of which are reproducible, whereas validity describes a definition that can distinguish those patients with that disease from those without the disease.¹² When attempts are made to further extend definitions in order to provide more pathophysiological information, such syndrome defini-

tions become more difficult to use. Oxygen-refractory hypoxaemia, stiff lungs and diffuse radiographic infiltrates not easily explained by haemodynamic factors have been described as a constellation of signs that reflect high permeability inflammatory oedema, associated with injury to the alveolar-capillary membrane.¹³ This inflammatory response may arise from either the airspace or the vascular side of the membrane.¹³ In addition, basic research has demonstrated a cross-tack between the two sides of that interface, making the understanding of the pathophysiology of the process even more confused.¹⁴ Incorporation of such complex interrelationships into one simple definition seems impossible.

Their lack of simplicity may be the reason that intensive care physicians never fully adopted previous definitions of ARDS (Table 1),²⁻⁶ the Lung Injury Score (LIS) (Table 2)⁸ or the score developed more recently by Ferguson based on the Delphi technique (Table 3).⁷ In contrast, the 1994 criteria of the AECC definition (Table 3)⁸ were easy to understand and were finally applied by the vast majority of physicians in the clinical setting. Adoption of this

TABLE 1. Past definitions of acute respiratory distress syndrome (ARDS)

Authors	Criteria
Ashbaugh et al (1967) ²	<ul style="list-style-type: none"> • Severe dyspnoea, tachypnoea • Cyanosis refractory to oxygen therapy • Loss of lung compliance • Diffuse alveolar infiltration on chest radiograph • Hyperaemia, atelectasis, interstitial and alveolar haemorrhage and oedema, with hyaline membranes at autopsy
Bone et al (1976) ³	<ul style="list-style-type: none"> • PaO₂ ≤70 mmHg with FiO₂ ≥0.5 with PEEP (amount of PEEP not specified)
Pepe et al (1982) ⁴	<ul style="list-style-type: none"> • PaO₂ ≤75 mmHg with FiO₂ ≥0.5 • New diffuse bilateral chest infiltrates with all lung fields involved • PAOP <18 mmHg • Not due to heart failure, pleural effusion, atelectasis or bacterial pneumonia
Fowler et al (1983) ⁵	<ul style="list-style-type: none"> • Sudden onset of bilateral pulmonary infiltrates • PAOP ≤12 mmHg • Compliance ≤50 mL/cm H₂O • PaO₂/PAO₂ ≤0.2

PAO₂ = alveolar oxygen partial pressure, PaO₂ = arterial oxygen partial pressure, PEEP = positive end-expiratory pressure, PAOP = pulmonary artery occlusion pressure.

TABLE 2. Lung injury score (LIS).

Murray et al (1988) ⁶	Hypoxaemia PaO ₂ /FiO ₂	Consolidation on chest radiograph	PEEP (cm H ₂ O)	Compliance (mL/cm H ₂ O)
0	≥ 300	No alveolar	≤ 5	≥ 80
1	225-299	1 quadrant	6-8	60-79
2	175-224	2 quadrants	9-11	40-59
3	100-174	3 quadrants	12-14	20-39
4	<100	4 quadrants	≥ 15	<20

PEEP= positive end-expiratory pressure, Sum scores from each domain and divide by number used. ARDS is diagnosed when LIS >2.5.

TABLE 3. Current American-European Consensus Conference (AECC) definition of acute respiratory distress syndrome (ARDS) and Delphi technique developed by Ferguson.

	Hypoxaemia	Chest radiograph	Onset	Pulmonary artery occlusion pressure (PAOP)
Bernard et al (1994) ⁸ AECC definition <i>Diagnose ARDS when all criteria are present</i>	PaO ₂ /FiO ₂ ≤300 (ALI) PaO ₂ /FiO ₂ ≤200 (ARDS)	Bilateral infiltrates	Acute onset (not specified)	≤18 mmHg or no clinical suspicion of left atrial hypertension
Ferguson et al (2005) ⁷ Delphi definition <i>Diagnose ARDS by the presence of criteria 1-4 and one of 5 or 6</i>	1. PaO ₂ /FiO ₂ ≤ 200 with PEEP ≥ 10 cm H ₂ O	2. Bilateral airspace disease 5. Decreased lung compliance (static respiratory compliance <50 mL/cm H ₂ O with patient sedated, tidal volume (V _T) = 8 mL/Kg and PEEP ≥10 cm H ₂ O)	3. Within 72 hours 6. Predisposition (direct and/or indirect factor associated with lung injury)	4. Noncardiogenic pulmonary edema (no clinical evidence of congestive heart failure-including use of PAOP measurement and/or cardiac echo)

PaO₂ = arterial oxygen partial pressure, PEEP = positive end-expiratory pressure

definition boosted research on therapeutic interventions and many randomized controlled trials (RCTs) aimed at evaluating measures for reducing mortality from ARDS have been conducted recently. Unfortunately, only a few of these studies have demonstrated improved survival,¹⁵⁻¹⁷ which may be due to ineffectiveness of the interventions, or may be because the current AECC definition captures a heterogeneous group of patients whose problems might respond differently to those interventions. As Phua has suggested in a recent review, the confidence intervals of a treatment effect in a RCT are proportional to the square root of the sample size and the signal/noise ratio;^{9,18} signal reflects the absolute risk reduction, and noise is dependent on every source of variation that might affect this reduction. Failure of therapeutic trials can arise from a poor signal as a result of limited understanding of basic pathophysiology, or from excess noise through the inclusion of patients without ARDS. The diagnostic

criteria for inclusion may affect the required sample size, since a narrow definition reduces explanatory accuracy of a therapeutic trial whereas a rather 'liberal' definition weakens the signal/noise ratio, with a risk of failing to detect a true treatment effect.⁹ In conclusion, improved understanding of possible pathophysiological mechanisms has allowed researchers to recognize that there are no simple diagnostic tests for complex syndromes such as ARDS, and that the definition of ARDS *per se* suffers from significant limitations.

EVALUATING THE COMPONENTS OF THE AMERICAN-EUROPEAN CONSENSUS CONFERENCE (AECC) DEFINITION FOR ARDS

One problem in the evaluation of any ARDS definition is the lack of a gold standard. Diffuse alveolar damage (DAD) is the histological equivalent of ARDS.¹³ However,

both Esteban and Ferguson who studied separately the findings from 382 patients who were autopsied after dying in an ICU in Madrid, found that the sensitivity and specificity of the AECC definition, the LIS, and the definition of ARDS based on the Delphi technique were only moderate when compared with the autopsy findings of DAD.^{19,20} Ferguson concluded that the sensitivity of the AECC definition was higher (0.83) than that of the lung injury score (0.74) and the criteria based on Delphi technique (0.69), whereas the specificity was highest with the third method (0.82), suggesting that ARDS had been under-recognized by clinicians in non-survivors.²⁰ In addition, Patel and colleagues, looking at patients who initially presented with the AECC definition criteria for ARDS, found that 60% of all open-lung biopsies performed in these patients did not reveal the presence of DAD.²¹

The first criterion of the AECC definition is *acute onset*.⁸ This definition excludes chronic respiratory failure but does not specify the timelines for 'acute', while the ARDS definition according to the Delphi technique defines specifically *onset within 72 hours*.⁷

The second AECC criterion refers to *hypoxaemia*, and differentiates between acute lung injury (ALI) with a $\text{PaO}_2/\text{FiO}_2$ ratio (P/F) ≤ 300 , and ARDS with $\text{P/F} \leq 200$.⁸ The relationship between FiO_2 and the P/F ratio varies considerably, however, according to the magnitude of the true shunt. Different mathematical models have shown that this relationship exhibits a nonlinear evolution, particularly at high levels of inspired O_2 .²² The magnitude of the true shunt largely influences the shape of the relationship curve, which remains flat or slightly decreased in patients with a high shunting fraction ($\geq 25\text{-}30\%$).^{22,23} Application of high levels of positive end-expiratory pressure (PEEP) can reverse the above effect on oxygenation. Recently, Villar and colleagues have demonstrated that many patients who fulfill the AECC criteria show an improved oxygenation index 24 hours after application of $\text{PEEP} \geq 10\text{cmH}_2\text{O}$ and $\text{FiO}_2 \geq 0.5$, implying that AECC definition can include patients with varying levels of lung injury and mortalities.²⁴ Gattinoni et al noted that patients with recruitable lungs had higher mortality than those with non-recruitable lungs²⁵, but this study included subjects after 5 ± 6 days of mechanical ventilation, meaning that the 'history' of ventilatory support and/or the pathological process may affect disease evolution over time. Conversely to the findings of Villar and co-workers, the patients from Gattinoni's study with pulmonary causes of ARDS had a worse outcome than those with extrapulmonary causes and did not respond to $\text{PEEP} \geq 10\text{cmH}_2\text{O}$ and $\text{FiO}_2 \geq 0.5$.

In conclusion, lack of mention of application of PEEP, respiratory mechanical properties or other ventilatory conditions at the time of oxygenation assessment limit both the reliability and the validity of the current AECC ARDS definition.

The other 2 criteria required for a definite diagnosis of ARDS are *bilateral infiltrates on chest radiograph* which 'should be consistent with pulmonary oedema' and absence of *clinical evidence of left atrial hypertension or pulmonary artery occlusion pressure (PAOP) ≥ 18 mmHg*.⁸ Radiological findings are confusing, since interobserver agreement between intensive care physicians concerning whether radiographic opacities qualify for the ARDS definition, was moderate and highly variable in a survey aimed at reviewing 28 randomly selected chest radiographs from critically ill patients with hypoxemia.²⁶ Moreover, Rouby et al found that chest computed tomography (CT) of 10 patients showed parenchymal abnormalities when the plain chest X-ray films were unhelpful.²⁷

Distinction of ARDS from cardiogenic pulmonary oedema is based mainly on findings from the pulmonary artery catheter (PAC) and use of PAOP cutoff values of 18 mmHg, based on the Forester classification of heart failure after acute myocardial infarction.²⁸ However, PAOP may be increased due to aggressive iv fluid administration, low pulmonary compliance and high levels of PEEP and mean airway pressure.²⁹⁻³¹ Increase in both PAOP and cardiac output in patients with septicaemia may deter the development of pulmonary oedema from hydrostatic origin. As Marini has suggested, unlike the vascularisation of healthy lungs, injured vessels leak at all pressures and since there is no sharp pressure cutoff for oedema formation, patients may slip from acute lung injury (ALI) to ARDS or vice versa according to fluid management.¹⁰ In addition, extensive use of echocardiography has shown that both systolic and diastolic left and/or right ventricular dysfunction may arise temporarily during severe sepsis and septic shock even in the absence of pre-existing heart disease.³² Ferguson has determined the incidence and severity of PAOP elevations in 71 patients with ALI/ARDS in 8 ICUs and found that those who met the AECC criteria were more likely to develop high PAOP, and also had increased mortality, even in the absence of risk factors for congestive heart failure.³¹ He concluded that the exclusion of patients with $\text{PAOP} \geq 18\text{mmHg}$ probably increases the specificity of the AECC definition, but at the cost of significant reduction in sensitivity. Using indirect cardiac echo derived measures for evaluation of PAOP can overcome known pitfalls that arise from its measurement

from the PAC, such as placement outside the West zone III or unknown left ventricular compliance.^{33,34}

DO WE REALLY NEED A NEW DEFINITION FOR ARDS?

Based on earlier discussions, many researchers have suggested that in order to improve reliability and validity a new definition of ARDS incorporating various aspects of the mechanical properties of the respiratory system needs to be applied.^{9,10,35} The inclusion of heterogeneous groups of patients with different pathologies, the lack of suitable biomarkers for early detection of a high permeability inflammatory pulmonary edema, and confusion with left heart failure, all decrease the signal/noise ratio and lead to negative results in many clinical trials. The debate between 'lumpers' who adopt a more liberal definition for ARDS and 'splitters' who support a restrictive definition originates from 1975, when Tom Petty as a 'lumper' and John Murray as a 'splitter' were discussing differences in survival for the various predisposing causes of ARDS.^{36,37} Ultimately, the 'lumpers' won out, although as Marini has commented, at the present time the concept of ARDS is more or less like that of congestive heart failure, but 'no modern day cardiologist would apply treatment without knowing which specific category of congestive heart failure he is dealing with',¹⁰ and for that reason, 'our ARDS image resembles one painted by Picasso, but what is really needed is the detail of Van Eyck'.¹⁰ Interstitial lung disease (ILD) constitutes a similar situation, in that it consists of different diseases presenting clinically and on chest radiographs in a similar way. In the case of ILD, however, the different entities respond differently to various treatments, which facilitates effective management when the subgroup category is identified.³⁸

Another issue that has emerged recently concerns the possibility of diagnosing and treating patients with ARDS outside the ICU. In a retrospective study by Quartin and co-workers, it was found that a subgroup of patients diagnosed as ARDS using the AECC criteria was adequately and safely treated in a non-ICU setting.³⁹ This group had a mortality rate significantly lower than that of patients with ALI/ARDS who were initially admitted to the ICU. The importance of these findings is related to the possibility that non-ICU ALI/ARDS patients with single-organ failure represent a less severe manifestation of the syndrome, and that the inclusion of a severity score for the design of new RCTs might help in deciding which patients need admission to the ICU and which can safely stay in a non-

ICU environment, reducing the cost of treatment without increasing their risk.³⁵

The second AECC for ARDS definition, held in 1998, reviewed different aspects of the clinical definition and its impact on clinical trials, but decided not to change it.⁴⁰ However, it proposed an alternative system for classification of patients, similar to the Tumor-Node-Metastases (TNM) staging for malignancies, the so called GOCA system (i.e., Gas exchange, Organ failure, Cause, Associated disease).⁴⁰ This system is not aimed at evaluating prognosis but rather describing with simplicity and clarity all the available clinical data related to the syndrome. It appears that the solution to the 'definition paradox' of ARDS lies in the deeper understanding of its pathophysiology and pathogenesis. The more we learn the more we approach an ideal definition by elucidating the underlying mechanisms of the disease. In the meantime, perhaps the most realistic method for dealing with the limitations of the definition is to use the current AECC criteria and then modify them for each individual RCT, using a standard framework. For example, alveolar recruitment should be applied to those with a true treatment effect.⁹ Patients with different causes of ARDS, mechanical respiratory properties or pulmonary artery pressures have demonstrated different therapeutic responses to various forms of treatment, such as selection of PEEP and FiO₂,¹⁷ or prone positioning.⁴¹ Advances in basic research could unmask potential pathogenetic mechanisms that might become therapeutic targets in the near future.

In conclusion, as Roger Bone liked to remind us, since we are dealing with such complex diseases we must become better clinicians and enhance our judgment continuously at the patient's bedside, in order to improve quality of care and generate clinically relevant questions that could be answered with well designed RCTs.⁴² In the meantime, to quote Faruqi and co-workers 'when all patients with ARDS are receiving what we already know to be the best available care, then we may seek more stringent definitions'.¹¹

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