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EDITORIAL

The Berlin definition met our needs: no

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"It's far more important to know what person the disease has than what disease the person has."—Hippocrates.

Introduction

According to the European Telecommunications Standards Institute [1], standardization provides a solid foundation upon which to develop new technologies and to enhance existing practices. Adherence to standards helps improve safety, reduce costs, ensure reliability, encourage innovation, increase awareness of technical developments, and provide the foundation for new options. Developing standards for defining disease processes improves quality in health care [2]. However, although definitions are an essential component of medical progress, they need to be continuously refined as new knowledge is accrued.

The acute respiratory distress syndrome (ARDS) cannot be diagnosed or described by any single laboratory test and is not associated with or caused by any single etiology. Although there is a general agreement on the criteria on which to base a definition for ARDS (severe hypoxemia, bilateral pulmonary infiltrates, decreased pulmonary compliance, and a risk factor in the setting in which cardiogenic pulmonary edema is excluded), the specific ranges and conditions under which to evaluate the hypoxemia vary among clinicians and researchers. Since no biomarker has yet been described that is specific for ARDS, it is plausible that ARDS prevalence is overestimated, since many patients with acute hypoxemic respiratory failure from other diseases with bilateral pulmonary infiltrates could be incorrectly diagnosed as having ARDS [3, 4]. Misdiagnosis can also occur if clinicians consider qualifying PaO_2 values resulting from acute events unrelated to the disease process (such as patient–ventilator asynchrony, endotracheal tube obstruction, pneumothorax, or hemodynamic instability), instead of considering only PaO_2 values while patients are clinically stable. Today, the term ARDS is used with greater care than previously, since several patients from the first clinical report [5] would not be diagnosed as having ARDS.

Searching for a satisfactory ARDS definition

The original description of ARDS proved to be incapable of identifying a uniform group of patients in terms of severity and prognosis. From a therapeutic point of view, we need a rigorous stratification of lung injury severity since the intensity and modality of ventilatory support and adjunctive therapies should differ depending on the degree of hypoxemia. From the research perspective, a precise definition helps to standardize studies on etiology, pathophysiology and treatment [6], improves our ability to compare data among studies and centers, and helps in evaluating the natural history, incidence, and prognosis of ARDS [7].

In 1994, an American-European Consensus Conference (AECC) [8] formalized the criteria for the diagnosis of ARDS by quantifying lung damage based on PaO_2/FiO_2 ratio, regardless of applied FiO_2 and positive end-expiratory pressure (PEEP):ARDS ($PaO_2/FiO_2 \leq 200$ mmHg) and "acute lung injury" ($300 \geq PaO_2/FiO_2 > 200$). This definition was challenged by Villar et al. [7, 9, 10], when they demonstrated that the PaO_2 response to standardized ventilatory settings (which included a specific level of PEEP and FiO_2) allowed the separation of ARDS patients into several groups with different severity and outcome. They observed that: (1) about half of the patients were improperly classified, and (2) ARDS patients could be uniformly stratified according to their response to a PEEP-FiO_2 trial. Their findings illustrated the problems of trying to compare the results of clinical trials, since most trials have used different ARDS definitions and enrolled patients with different levels of lung dysfunction [11].

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The Berlin definition does not resolve the problems with the AECC definition

Patients can easily meet the AECC PaO_2/FiO_2 criteria because of a lack of PEEP and FiO_2 requirements. In 2012, the Berlin definition [12, 13] attempted—but failed—to address this limitation by classifying patients into three categories based on thresholds for baseline PaO_2/FiO_2 on PEEP $\geq$ 5 cmH_2O regardless of FiO_2: mild (300 $\geq$ PaO_2/FiO_2 > 200), moderate (200 < PaO_2/FiO_2 > 100), and severe (PaO_2/FiO_2 $\leq$100). There are no data that link a particular baseline PaO_2/FiO_2 to predictable structural changes in the alveolar–capillary membrane. Two recent studies [14, 15] showed that the use of non-standardized baseline PaO_2/FiO_2 were incapable of separating patients into distinct categories of severity with significantly different mortalities. An autopsy study revealed that the Berlin criteria did not correlate with the presence of diffuse alveolar damage in more than 50 % of patients categorized as moderate and severe ARDS [16]. However, this correlation improved significantly only when patients met PaO_2/FiO_2 criteria beyond 24 h of persistent ARDS. The requirement of a minimum PEEP of 5 cmH_2O has essentially no impact on the definition, since it is hard to conceive a patient with hypoxemic respiratory failure on PEEP <5 cmH_2O. Also, it is well established that changes in PEEP and FiO_2 alter the PaO_2/FiO_2 in lung-injured patients. If assessment of ARDS severity is of crucial importance, it should be mandatory to set standard rules for quantifying the degree of lung injury. If PaO_2 measurements are not standardized, the calculated PaO_2/FiO_2 may mask the severity of the underlying lung pathology in a substantial proportion of patients. By only adding a PEEP $\geq$5 cmH_2O to the assessment of PaO_2/FiO_2, the AECC and the Berlin definitions are essentially identical.

The success of personalized medicine [17] depends on the development of diagnostic tests that can accurately identify and stratify appropriate patients for a given therapy. The use of non-standardized criteria to enroll patients into clinical trials may negatively impact the outcome of the trial and potentially harm patients. If PaO_2/FiO_2 ratio is used to select patients for a trial, a standard validated method should be applied at the time of trial initiation to insure that patients within an identical baseline PaO_2/FiO_2 range have similar degrees of lung injury and prognosis. Otherwise, it becomes difficult—if not impossible—to interpret trial results [11]. Villar et al. [18] studied 478 patients with moderate and severe ARDS and examined the PaO_2/FiO_2 at ARDS onset, after 24 h of usual care, and at 24 h under standardized ventilator settings. Their standardized model outperformed the Berlin criteria and non-standardized PaO_2/FiO_2 at 24 h. More than 60 % of patients with severe ARDS according to Berlin criteria were reclassified as moderate, mild or non-ARDS after 24 h of usual care, while hospital mortality changed significantly with every PaO_2/FiO_2 category under the standardized method. If patients are identified as severe ARDS by the Berlin criteria, they could be forced to receive highly invasive and aggressive therapies that provide no benefit (useless) or could be harmful (worse than usual care), since after 24 h of routine care a high percentage evolve to milder forms of ARDS.

In conclusion, the stratification of ARDS patients as proposed by the Berlin criteria is useless for assessing severity of lung injury and could be harmful for enrolling patients into clinical trials. Current data support the need for a new standardized method for evaluating oxygenation criteria (Table 1).

Table 1 Proposal of a two-step process for appropriate assessment of hypoxemia for the diagnosis of acute respiratory distress syndrome (ARDS)

Parameters	Values
A known predisposing factor	–
Radiographic bilateral pulmonary infiltrates consistent with bilateral alveolar edema	–
Heart failure or fluid overload must be excluded as a cause of pulmonary edema	No clinical (or ecocardiographic or hemodynamic) signs of heart failure
Hypoxemia (assessed by PaO_2/FiO_2), mmHg	1st step (ARDS onset): PaO_2/FiO_2 $\leq$300 on PEEP $\geq$5 cmH_2O 2nd step (reassessment at 24 h on PEEP $\geq$10 and FiO_2 $\geq$0.5)[a]: Severe ARDS: PaO_2/FiO_2 $\leq$100 Moderate ARDS: 100 < PaO_2/FiO_2 $\leq$ 200 Mild ARDS: 200 < PaO_2/FiO_2 $\leq$ 300 Non-ARDS: PaO_2/FiO_2 >300
Specific biomarker(s) of lung injury	Specific threshold values (easy to measure in blood, exhaled air, or any other biological sample)

[a] See Ref. [18] for rules for setting PEEP and FiO_2 during assessment on standardized settings at 24 h of ARDS diagnosis

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Compliance with ethical standards

Conflicts of interest
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