WORKSHOP

A New Global Definition of Acute Respiratory Distress Syndrome

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Abstract

Background: Since publication of the 2012 Berlin definition of acute respiratory distress syndrome (ARDS), several developments have supported the need for an expansion of the definition, including the use of high-flow nasal oxygen, the expansion of the use of pulse oximetry in place of arterial blood gases, the use of ultrasound for chest imaging, and the need for applicability in resource-limited settings.

Methods: A consensus conference of 32 critical care ARDS experts was convened, had six virtual meetings (June 2021 to March 2022), and subsequently obtained input from members of several critical care societies. The goal was to develop a definition that would *1*) identify patients with the currently accepted conceptual framework for ARDS, *2*) facilitate rapid ARDS diagnosis for clinical care and research, *3*) be applicable in resource-limited settings, *4*) be useful for testing specific therapies, and *5*) be practical for communication to patients and caregivers.

Results: The committee made four main recommendations: *1*) include high-flow nasal oxygen with a minimum flow rate of $\geq$30 L/min; *2*) use $Pa_{O_2}:F_{I_{O_2}} \leq 300$ mm Hg or oxygen saturation as measured by pulse oximetry $Sp_{O_2}:F_{I_{O_2}} \leq 315$ (if oxygen saturation as measured by pulse oximetry is $\leq$97%) to identify hypoxemia; *3*) retain bilateral opacities for imaging criteria but add ultrasound as an imaging modality, especially in resource-limited areas; and *4*) in resource-limited settings, do not require positive end-expiratory pressure, oxygen flow rate, or specific respiratory support devices.

Conclusions: We propose a new global definition of ARDS that builds on the Berlin definition. The recommendations also identify areas for future research, including the need for prospective assessments of the feasibility, reliability, and prognostic validity of the proposed global definition.

Keywords: ARDS; acute lung injury; pulmonary edema

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of acute hypoxemic respiratory failure due to lung inflammation, not caused by cardiogenic pulmonary edema. It was first described in 1967 (1), and in 1988, a more explicit clinical definition quantified the severity of physiologic respiratory impairment (the lung injury score) (2). Since then, the clinical definition of ARDS has been revised, first by an American–European consensus conference convened in 1992 by the American Thoracic Society and the European Society of Intensive Care Medicine (3) and subsequently by the ARDS Definition Task Force convened in Berlin in 2012 by the European Society of Intensive Care Medicine (4, 5). Each revision of the definition was made with the goal of providing a definition that would consistently and accurately identify patients with similar characteristics for clinical care and epidemiological, observational, and interventional research studies. Although the Berlin definition of ARDS was a major step forward, some of its limitations were recognized soon after publication. Specifically, it was recognized that its requirement for noninvasive ventilation (NIV) or invasive ventilation could not be met in settings in which these modalities are not available (6).

In the decade since the Berlin definition was published, several developments in the management and study of ARDS have

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prompted consideration of an expansion of the Berlin definition (7). First, noninvasive pulse oximetric methods for evaluating oxygenation criteria for ARDS have been validated and applied in observational studies and clinical trials (8–12). Second, the use of high-flow nasal oxygen (HFNO) to manage severe hypoxemic respiratory failure increased after the publication of the FLORALI (Clinical Effect of the Association of Noninvasive Ventilation and High Flow Nasal Oxygen Therapy in Resuscitation of Patients With Acute Lung Injury) trial in 2015 (13), and its use became widespread during the coronavirus disease (COVID-19) pandemic (14–16). Patients with acute hypoxemic respiratory failure who are managed with HFNO do not meet the Berlin definition of ARDS, which requires invasive or noninvasive mechanical ventilation with a minimum of 5 cm H_2O of positive end-expiratory pressure (PEEP) (5, 17, 18). Third, the Berlin definition is problematic in resource-limited settings because chest radiography, arterial blood gas (ABG) measurements, and mechanical ventilation are not always available. These limitations led to the proposed Kigali modification of the Berlin definition for resource-limited settings (19); however, the Kigali modification has not been formally incorporated into the current ARDS definition. Finally, ultrasound imaging is increasingly used in critically ill patients with acute hypoxemic respiratory failure, sometimes supplanting traditional chest radiography (20–22).

To address these changes in evidence and practice, a global consensus conference with broad international representation and individuals from diverse backgrounds was convened in June 2021 to make recommendations for updating the ARDS definition. Once consensus on the expanded global definition of ARDS was achieved, input from clinicians, investigators, and allied health professionals from around the world was sought to provide input beyond the members of the consensus conference. This report provides the recommendations from this consensus conference and also includes priorities for prospective research for assessments of feasibility, reliability, and prognostic validity.

Methods

Process for Membership

The goal of the organizers of the consensus conference (M.A.M., T.T., and L.B.W.) was to convene a committee of experts representing diverse clinical, geographic, socioeconomic, racial, ethnic, and gender backgrounds, as well as a patient advocate. The target committee membership was approximately 30 to ensure that it was large enough to obtain diverse perspectives and small enough to allow meaningful contributions from each member. Members were selected through an informal cascading recruitment process. The conference chairs identified subject area experts, who then recommended other members, considering the stated diversity goals. A total of 32 members were selected and agreed to participate. Only one person who was invited declined to participate. Although this process to achieve diversity and expertise has some limitations, the resulting committee was more diverse and represented more areas of the world than prior groups that developed working definitions of ARDS (*see* Figure E1 in the online supplement).

Formation of Working Groups and Development of Criteria for an Updated Definition

Potential topics for an expansion of the Berlin definition were proposed during an initial organizational meeting, after which an anonymous survey was distributed to committee members for their vote on which topics should be addressed. The entire committee agreed to establish working groups to address three major areas for potential revision of the Berlin definition (*see* Appendix E1): *1*) risk factors, timing, and extrapulmonary organ involvement; *2*) chest imaging; and *3*) oxygenation. The committee also agreed that an updated definition of ARDS should meet several criteria: *1*) identify patients with characteristics in keeping with the agreed-on conceptual framework of ARDS, *2*) facilitate rapid recognition and diagnosis of ARDS for clinical care and research, *3*) be applicable in resource-limited settings, *4*) be useful for testing specific therapies, and *5*) be practical for communication to patients and caregivers.

Data Considered

Several sources of published and unpublished data were used by the working groups on the basis of searches of the National Library of Medicine PubMed database, including recent clinical trials and observational studies (*see* Appendix E1) (8, 12–14, 19, 20, 23–33). Although a formal comprehensive literature review was not completed, which is a limitation, the data considered included recent clinical trials that have influenced clinical practice.

Decision-Making Process

Each working group assessed changes in clinical practice and new evidence supporting updates to current diagnostic criteria. From June 2021 through March 2022, working groups convened independently (two or three meetings per group) and then returned recommendations to the entire committee. Proposed revisions to the ARDS definition from each working group were discussed by the entire committee during six video conferences.

Consensus Process

After discussion by the committee, the working group recommendations were incorporated into a draft of the updated ARDS definition. Comments and revisions were invited on multiple drafts before convening a meeting at which the final proposed changes were discussed. The committee members agreed unanimously to use a simple, confidential supermajority vote for approval (defined as 70% or greater agreement). The committee did not use the comprehensive processes described for the development of clinical practice guidelines, because the goal was to update the widely used definition for a clinical syndrome rather than to establish a clinical practice guideline, and expert consensus generates similar results when a high degree of agreement is reached (34). The final revised definition received approval from all committee members.

Input from Global Critical Care Societies

The committee obtained comments from members of a convenience sample of 21 global critical care societies (*see* Appendix E2) that were asked to solicit opinions from their members in any way they deemed appropriate. No requests for formal societal endorsements were made, and the comments do not reflect the official views of individual professional societies. Comments were reviewed and considered by the committee and are included in Appendix E2. Although most society member responses were qualitative, some societies provided quantitative data on member approval of components of the revised definition. The responses do not reflect a comprehensive polling of all members or all leadership of all critical care societies. After these recommendations are published, an interactive website will be established for posting comments that will be available to practitioners and patients around the world (https://globalardsdefinition.org).

Results

The global definition of ARDS is presented in Table 1 and a summary of updates from the Berlin definition in Table 2. Figure 1 provides a visual illustration that captures most of the elements of the expanded global definition of ARDS and a comparison with the Berlin definition. Consensus recommendations for each category together with rationale and comments are as follows.

Conceptual Model

The committee agreed that the conceptual model as put forth in the Berlin definition, with minor revisions, continues to reflect current understanding and evidence of pathophysiology (Table 1). ARDS is an acute, diffuse, inflammatory lung injury precipitated by a risk factor such as pneumonia, nonpulmonary infection, trauma, transfusion, burn, aspiration, or shock. The resulting injury leads to pulmonary edema from an increase in pulmonary vascular and alveolar epithelial permeability. In addition, gravity-dependent atelectasis contributes to a loss of aerated lung tissue. The clinical hallmarks of ARDS are arterial hypoxemia and bilateral radiographic opacities associated with increased shunting, increased alveolar dead space, and decreased lung compliance. The clinical presentation may be influenced by medical management, including the initial degree of PEEP (4), fluid management strategy (35), sedation and neuromuscular blockade (11, 36), and prone positioning (24). Histological findings vary and often include intraalveolar edema, inflammation, hyaline membrane formation, and alveolar hemorrhage, often termed diffuse alveolar damage; however, these histological features are not always present and are not necessary for a clinical diagnosis of ARDS (26). The conceptual model retains essential components of the Berlin definition with minor modifications, as further detailed in Supplement E1 in the online supplement.

Timing, Risk Factors, and Extrapulmonary Factors

The committee agreed that the current time frame for the diagnosis of ARDS should be retained: acute onset or worsening of hypoxemic respiratory failure is defined as occurring within 1 week of the onset of the predisposing risk factor or within 1 week of new or worsening respiratory symptoms. Prolonging the time to onset of hypoxemic respiratory failure was considered, as protracted symptoms may precede progression to frank respiratory failure, as in the case of COVID-19; however, expanding the definition to include HFNO (detailed below) should allow earlier diagnosis, so the time frame of 1 week for acute onset of respiratory failure was maintained. The acute onset or worsening of hypoxemic respiratory failure and pulmonary edema should not be exclusively or primarily attributable to cardiogenic pulmonary edema or fluid overload, atelectasis or lung collapse, pleural effusion, or pulmonary embolism. ARDS can be diagnosed in the presence of these conditions if a predisposing risk factor for ARDS is also present, and the clinician believes that these other conditions (e.g., fluid overload, atelectasis) are unlikely to be the primary causes of the hypoxemia. ARDS also can be diagnosed in the presence of chronic lung disease, such as chronic obstructive pulmonary disease, interstitial lung disease, or pulmonary hypertension, providing that acute hypoxemic respiratory failure is not primarily attributable to these underlying conditions. Further rationale for these recommendations is provided in Supplement E2 and Tables E1 and E2.

Chest Imaging

The committee agreed that chest imaging criteria should include bilateral radiologic (chest radiography or computed tomography) or ultrasound findings suggestive of loss of lung aeration that are not fully explained by effusions, atelectasis, or nodules/masses. Although the identification of bilateral opacities by chest radiography has poor interrater reliability (28), chest radiography is the most common imaging modality in critically ill patients, which contributed to the recommendation to

Table 1. Diagnostic Criteria for the New Global Definition of ARDS

Conceptual model: ARDS is an acute, diffuse, inflammatory lung injury precipitated by a predisposing risk factor, such as pneumonia, nonpulmonary infection, trauma, transfusion, burn, aspiration, or shock. The resulting injury leads to increased pulmonary vascular and epithelial permeability, lung edema, and gravity-dependent atelectasis, all of which contribute to loss of aerated lung tissue. The clinical hallmarks are arterial hypoxemia and diffuse radiographic opacities associated with increased shunting, increased alveolar dead space, and decreased lung compliance. The clinical presentation is influenced by medical management (position, sedation, paralysis, positive end-expiratory airway pressure, and fluid balance). Histological findings vary and may include intraalveolar edema, inflammation, hyaline membrane formation, and alveolar hemorrhage.

	Criteria That Apply to All ARDS Categories
Risk factors and origin of edema	Precipitated by an acute predisposing risk factor, such as pneumonia, nonpulmonary infection, trauma, transfusion, aspiration, or shock. Pulmonary edema is not *exclusively or primarily* attributable to cardiogenic pulmonary edema/fluid overload, and hypoxemia/gas exchange abnormalities are not primarily attributable to atelectasis. However, ARDS can be diagnosed in the presence of these conditions if a predisposing risk factor for ARDS is also present.
Timing	Acute onset or worsening of hypoxemic respiratory failure within 1 week of the estimated onset of the predisposing risk factor or new or worsening respiratory symptoms.
Chest imaging	Bilateral opacities on chest radiography and computed tomography or bilateral B lines and/or consolidations on ultrasound* not fully explained by effusions, atelectasis, or nodules/masses.

	Criteria That Apply to Specific ARDS Categories		
	Nonintubated ARDS†	**Intubated ARDS**	**Modified Definition for Resource-Limited Settings‡**
Oxygenation§‖	Pa_{O_2}:$F_{I_{O_2}} \leq 300$ mm Hg or Sp_{O_2}:$F_{I_{O_2}} \leq 315$ (if $Sp_{O_2} \leq 97\%$) on HFNO with flow of ⩾30 L/min or NIV/CPAP with at least 5 cm H_2O end-expiratory pressure	Mild¶: $200 < Pa_{O_2}$:$F_{I_{O_2}} \leq 300$ mm Hg or $235 < Sp_{O_2}$:$F_{I_{O_2}} \leq 315$ (if $Sp_{O_2} \leq 97\%$) Moderate: $100 < Pa_{O_2}$:$F_{I_{O_2}} \leq 200$ mm Hg or $148 < Sp_{O_2}$:$F_{I_{O_2}} \leq 235$ (if $Sp_{O_2} \leq 97\%$) Severe: Pa_{O_2}:$F_{I_{O_2}} \leq 100$ mm Hg or Sp_{O_2}:$F_{I_{O_2}} \leq 148$ (if $Sp_{O_2} \leq 97\%$)	Sp_{O_2}:$F_{I_{O_2}} \leq 315$ (if $Sp_{O_2} \leq 97\%$)†. Neither positive end-expiratory pressure nor a minimum flow rate of oxygen is required for diagnosis in resource-limited settings.

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CPAP = continuous positive airway pressure; HFNO = high-flow nasal oxygen; NIV = noninvasive ventilation; PEEP = positive end-expiratory pressure; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.
*The ultrasound operator should be well trained in the use of ultrasound for identifying bilateral loss of lung aeration (e.g., multiple B lines and/or consolidations) and other ultrasound findings suggestive of noncardiogenic pulmonary edema (e.g., pleural line abnormalities).
†Estimated $F_{I_{O_2}}$ = ambient $F_{I_{O_2}}$ (e.g., 0.21) + 0.03 × O_2 flow rate (L/min).
‡Modified oxygenation criteria can be applied in settings in which arterial blood gas and/or HFNO, NIV, and mechanical ventilation are not routinely available.
§Blood gas and oximetry measurements should be made when the patient is comfortably at rest and at least 30 minutes after changes in position, $F_{I_{O_2}}$, or flow rate. For pulse oximetry, ensure an adequate waveform and oximeter placement. Sp_{O_2}:$F_{I_{O_2}}$ is not valid above saturation values of 97%. Pulse oximetry is not recommended for diagnosis if a hemoglobin abnormality is suspected (e.g., methemoglobinemia or carboxyhemoglobinemia).
‖If altitude is >1,000 m, apply the following correction factor: (Pa_{O_2} or Sp_{O_2})/$F_{I_{O_2}}$ × (barometric pressure/760).
¶For all severity categories of intubated ARDS, a minimum PEEP of 5 cm H_2O is required. Patients may move from one category to another throughout their disease course.

retain it in the definition despite its limitations. In addition, the committee recommended that ultrasound be accepted as a modality for identifying signs of loss of lung aeration consistent with (noncardiogenic) pulmonary edema or lung consolidation, especially when chest radiography or computed tomography is not available (37–39). There is evidence that ultrasound can be reliable if the operator is trained to detect bilateral consolidations and noncardiogenic pulmonary edema, an approach that should have value, especially in resource-limited areas (19–21). Further discussion of the rationale for these recommendations is provided in Supplement E3.

Oxygenation

The committee recommended creating three categories of ARDS to expand the current ARDS definition: nonintubated ARDS, intubated ARDS, and a modified category of ARDS for resource-limited settings (Table 1 and Figure 1). The committee recommended including patients who require a minimum degree of support with either NIV (as in the Berlin definition) or HFNO in the definition under the category of nonintubated ARDS. This approach, however, limits the definition to care settings in which there is access to these respiratory support devices. The committee agreed that the potential to meet diagnostic criteria for a syndrome should not be affected by resource limitations. Therefore, a formal adoption of the Kigali modification of the clinical definition of ARDS (19, 31) is recommended for settings in which advanced respiratory support devices are not available (full definition of the Kigali recommendation is included in Supplement E5).

Table 2. Summary of Key Differences between the New Global Definition of ARDS and the Berlin Definition Together with the Rationale for Updating Specific Diagnostic Criteria

Berlin Definition	Rationale for Updating Criteria	How This is Addressed in the Global Definition
Acute onset within 1 week of known insult or new or worsening respiratory symptoms	Onset may be more indolent for some insults, such as COVID-19	The inclusion of patients with HFNO will capture patients with more indolent courses, and therefore the timing criterion has not been changed
Bilateral opacities on chest radiography or computed tomography not fully explained by effusions, lobar/lung collapse, or nodules	Chest radiography and computed tomography not available in some clinical settings	Ultrasound can be used to identify bilateral loss of lung aeration (multiple B lines and/or consolidations) as long as operator is well trained in the use of ultrasound
Three severity categories defined by Pa_{O_2}:Fi_{O_2}	Pulse oximetric measurement of Sp_{O_2}:Fi_{O_2} is widely used and validated as a surrogate for Pa_{O_2}:Fi_{O_2}	Sp_{O_2}:Fi_{O_2} can be used for diagnosis and assessment of severity if Sp_{O_2} is ⩽97%
Requirement for invasive or noninvasive mechanical ventilation such that PEEP ⩾ 5 cm H_2O is required for all categories of oxygenation severity except mild, which can also be met with CPAP ⩾ 5 cm H_2O	HFNO increasingly being used in patients with severe hypoxemia who otherwise meet ARDS criteria Invasive and noninvasive mechanical ventilation not available in resource-limited settings	New category of nonintubated ARDS created for patients on HFNO at ⩾30 L/min who otherwise meet ARDS criteria Modified definition of ARDS for resource-limited settings does not require Pa_{O_2}:Fi_{O_2}, PEEP, or HFNO

Definition of abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; CPAP = continuous positive airway pressure; HFNO = high-flow nasal oxygen; PEEP = positive end-expiratory pressure; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

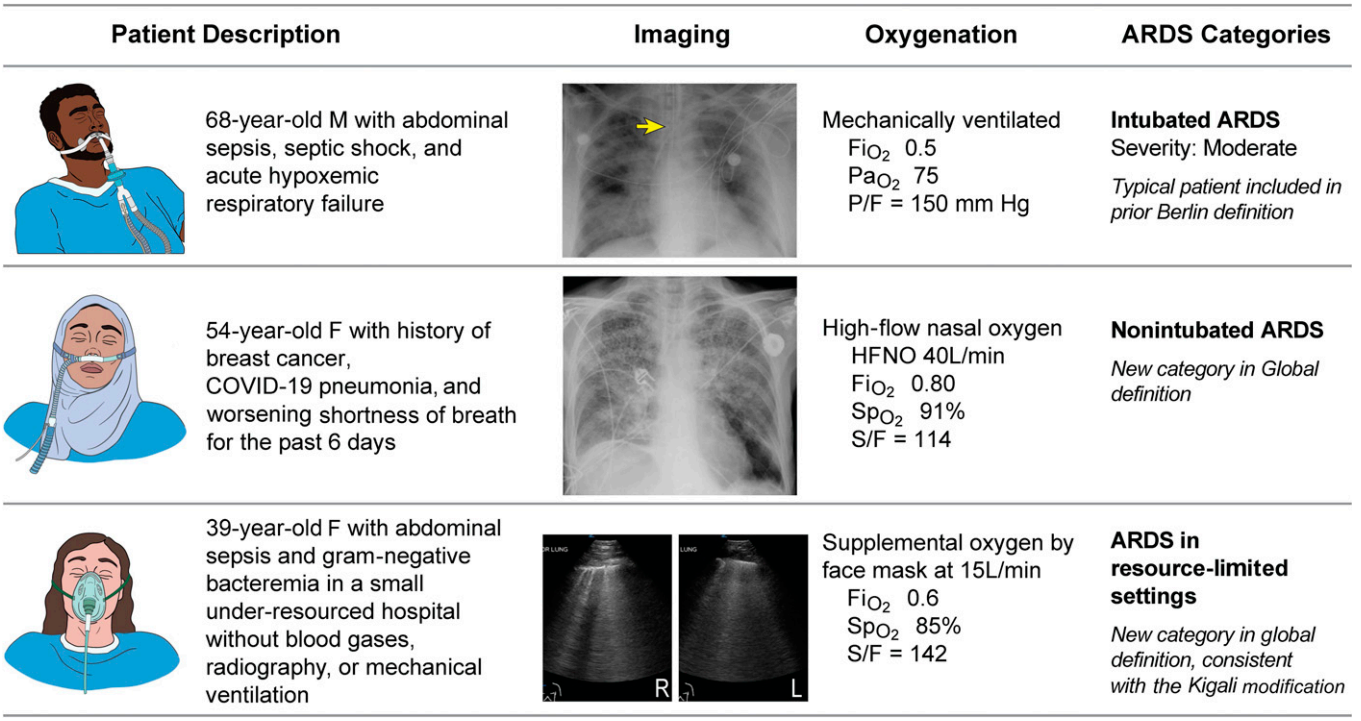

Figure 1. Illustrative cases with patient descriptions, representative lung imaging, and oxygenation data for the three categories of acute respiratory distress syndrome (ARDS) in the global definition: intubated ARDS (top), nonintubated ARDS (middle), and ARDS in a resource-limited setting (bottom). Note the patient in the resource-limited setting can be identified using either ultrasound (bottom, demonstrating bilateral diffuse B-lines in nondependent areas of the lung) or chest radiography or computed tomography. Also, only the patient with intubated ARDS (top) meets criteria for the Berlin definition of ARDS. Arrow, endotracheal tube. COVID-19 = coronavirus disease; F = female; HFNO = high-flow nasal oxygen; M = male; P/F = Pa_{O_2}:Fi_{O_2}; S/F = Sp_{O_2}:Fi_{O_2}; Sp_{O_2} = oxygen saturation as measured by pulse oximetry. The OpenCriticalCare.org Project, Creative Commons SA-BY-NC for the patient drawings.

Table 3. Areas for Future Prospective Research

1. Conduct large multicenter studies (similar to LUNG SAFE) (27) to determine how often patients treated with HFNO or NIV advance to requiring intubation and mechanical ventilation, including outcomes such as mortality for patients in each of these categories
2. Assess the prognostic value and clinical implications of unilateral vs. bilateral opacities on chest radiography
3. Identify the limitations to operationalization of the new ARDS definition (e.g., how often pulse oximetry was not accurate for quantifying hypoxemia because of shock or skin pigmentation)
4. Carry out research (e.g., in resource-limited areas) to determine the incidence of ARDS diagnosis in the absence of any oxygen therapy (room air) compared with subjects treated with supplemental oxygen and the associated outcomes, specifically mortality
5. Evaluate prognostic and clinical utility (e.g., whether the oxygenation severity categories have prognostic value in nonintubated patients)
6. Evaluate the specificity of lung ultrasound diagnosis of ARDS among different operators in diverse clinical settings using different acquisition/interpretation protocols
7. Determine the relationship of biological categories of ARDS, such as hyper- and hypo-inflammatory subphenotypes, in the new global definition of ARDS and assess these biological categories in the context of sepsis and pneumonia
8. Prospectively evaluate this new global definition of ARDS on the basis of large clinical trials and observational studies around the world, including evaluation of how the new definition affects estimates of ARDS incidence
9. Evaluate the long-term outcomes of patients with diagnoses of ARDS using the new global definition of ARDS in prospective epidemiological studies

Definition of abbreviations: ARDS = acute respiratory distress syndrome; HFNO = high-flow nasal oxygen; LUNG SAFE = Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure; NIV = noninvasive ventilation.

Since the publication of the FLORALI trial (13), the use of HFNO has increased substantially. The COVID-19 pandemic demonstrated that patients treated with HFNO may indeed have ARDS (30). In one study, 93% of patients with COVID-19 treated with HFNO continued to meet ARDS oxygenation criteria, including criteria for severe ARDS, after intubation and treatment with mechanical ventilation and PEEP (14). Although the mortality of patients treated with HFNO alone (i.e., who never progressed to invasive mechanical ventilation) was lower, it was similar to those treated with NIV alone (14), who currently meet the Berlin criteria for ARDS. An important advantage of including patients on HFNO in the revised definition is that ARDS may be recognized earlier, making trials of early interventions more feasible.

These updates to the current definition will allow researchers to compare treatments and outcomes for patients in each category of ARDS (nonintubated, intubated, and resource-limited). The resource-limited option will allow researchers in low-income countries to identify ARDS populations in their hospitals and to conduct clinical studies.

The committee agreed on allowing the use of oxygen saturation as measured by pulse oximetry Sp_{O_2}:FI_{O_2} as an alternative to Pa_{O_2}:FI_{O_2} for the diagnosis of ARDS. Although ABG measurements have been the gold standard for assessing hypoxemia in ARDS, the alternative use of Sp_{O_2}:FI_{O_2} was added for two reasons: *1*) inconsistent availability of ABGs in resource-limited settings and *2*) declining frequency of ABG monitoring in high-income countries. Both linear and nonlinear imputations of Pa_{O_2}:FI_{O_2} from Sp_{O_2}:FI_{O_2} demonstrate good performance as long as Sp_{O_2} is $\leqslant$97% (and a Hb abnormality is not present, addressed in a footnote to Table 1) (8, 9, 40, 41). Recent clinical trials in ARDS have used Sp_{O_2}:FI_{O_2} for patient selection (11), and patients with diagnoses of ARDS using Sp_{O_2}:FI_{O_2} have similar clinical outcomes to those diagnosed by ABG measurement (42). The committee agreed on using the Rice linear equation to define cutoff values of Sp_{O_2}:FI_{O_2} (8) because its sensitivity and specificity for hypoxemia are comparable with nonlinear imputations, and it is simpler to calculate (40, 43). Further discussion of the rationale for this recommendation is included in Supplement E4, including a recommendation to measure ABGs if there is uncertainty that would affect patient diagnosis or management.

Although the availability of a validated, noninvasive, and inexpensive method for evaluating oxygenation has obvious advantages, pulse oximeters may lack adequate sensitivity for hypoxemia in patients with darker skin and patients in shock (44–49). These limitations are concerning given the mandate to ensure that an updated definition advances equity in healthcare and is applicable across most patient populations, and because many patients with ARDS have poor systemic perfusion. Nevertheless, the committee believed that the ready availability of pulse oximetry in all healthcare settings outweighed the disadvantage of missing hypoxemia in some patients using pulse oximetry, because the overall effect will be to increase health equity in settings in which ARDS is currently underdiagnosed.

Several trials have enriched their populations for higher predicted mortality by including only patients with an enrollment Pa_{O_2}:FI_{O_2} $<$ 150 mm Hg, which is not a cutoff specified in the Berlin definition. Clinical studies have shown that the Berlin severity categories identify increasing mortality with increasing severity, whether using the original Pa_{O_2}:FI_{O_2} ratios (4) or the Sp_{O_2}:FI_{O_2} imputations (50). There was no compelling evidence-based reason to change the severity categories, with the exception of allowing corresponding Sp_{O_2}:FI_{O_2} values to meet the hypoxemia criterion for each category.

Input from Global Critical Care Societies

Comments from members of 21 global critical care societies are listed in Appendix E2. These comments are the opinions of individuals and do not reflect societal endorsements. Most comments were supportive, but there were concerns about interrater variability for ultrasound and the use of pulse oximetry in subjects with darker skin, both of which merit further investigation (Table 3).

Discussion

The recommendation for a global definition of ARDS builds on the accepted Berlin definition of ARDS by incorporating changes in clinical practice and scientific evidence

and facilitating application in settings with limited access to diagnostic and therapeutic resources, including respiratory support devices, chest radiography, and ABG analysis. In addition, it addresses several limitations of the Berlin definition and expands the ability to study the natural history of ARDS (6). The major conceptual model for the pathophysiology of ARDS has not changed from the Berlin definition, but minor revisions were made to the conceptual model to emphasize the lack of consistent histological findings or biomarkers for ARDS and the importance of initial clinical management on the basis of the clinical presentation of ARDS (51–53). It should also be noted that our ability to distinguish between the specific pathology of ARDS and the more general syndrome of noncardiogenic acute hypoxemic respiratory failure remains limited. The NHLBI has recently funded a consortium of six university centers, including several participating hospitals, to prospectively study the clinical and biological determinants of ARDS, pneumonia, and sepsis, including longer-term outcomes, a key issue for the broad category of critically ill patients and their caregivers, as recently reviewed (54).

The proposed global definition of ARDS accounts for the expanding use of noninvasive support for acute hypoxemic respiratory failure (13, 55). The category of nonintubated ARDS comprises patients on HFNO or NIV at the time of diagnosis. The committee agreed on a threshold of oxygen delivery of 30 L/min with HFNO because 30 L/min can provide low levels of PEEP (56).

The Kigali modification is included in the expanded global definition of ARDS for resource-limited settings, which addresses a major limitation of the Berlin definition. The committee also considered whether this modified definition should be universally applicable (i.e., also in settings in which advanced technologies are available). Allowing any respiratory device (rather than requiring HFNO, NIV, or ventilation) is important for resource-limited settings in which advanced respiratory support is not always available. However, the consensus was that allowing any respiratory device in all settings would not support the face validity of ARDS as a syndrome of critical illness, as very mildly hypoxemic patients could be included. To balance the need for a definition that can be applied in various settings while still being broadly acceptable to clinicians and researchers, a separate category for resource-limited settings was created. How the pathophysiology, natural history, and outcomes of ARDS using this global definition compare with those using the Berlin definition will be an important area of prospective research.

The global definition of ARDS allows the use of pulse oximetry–based rather than ABG-based measurements to diagnose ARDS when Sp_{O_2} is ⩽97%. This latter criterion ($Sp_{O_2} \leqslant 97\%$) is critical, as Sp_{O_2}:FI_{O_2} is not a good index of severity of gas exchange when Sp_{O_2} is higher than 97% because of the shape of the oxyhemoglobin dissociation curve. Although Sp_{O_2}:FI_{O_2} may inappropriately categorize some patients as having ARDS when they would not meet hypoxemia criteria by Pa_{O_2}:FI_{O_2}, available data support that these two populations are clinically similar (11, 42), and this change facilitates early identification and supportive care. The use of pulse oximetry also limits exposure of patients to the risks associated with repeated arterial blood draws (57–59). Data on racial bias in pulse oximetry measurements (45, 46, 49), driven in part by inaccuracies in pulse oximetry readings among patients with dark skin tones, deserve special consideration (60). Recent data suggest that occult hypoxemia, meaning a true Sa_{O_2} of <88% with a pulse oximetric saturation of 92–96%, occurs up to four times more frequently among patients who identify as Black than in those who identify as White, and that racial discrepancies in the accuracy of pulse oximetry contribute to care disparities (44, 49). This issue highlights an important limitation of Sp_{O_2}:FI_{O_2}; however, the committee agreed that on balance, including Sp_{O_2}:FI_{O_2} is likely to identify cases of ARDS that might otherwise be unrecognized. Limited studies of the effect of skin pigmentation (not self-identified race) on the imputation of Pa_{O_2}:FI_{O_2} have not identified an effect (40). Most studies have shown that the mean absolute difference between pulse oximetric and ABG saturations is greater among non-White than White patients, but the intermeasurement difference between pulse oximetric saturation and saturation by ABG is most often <5% regardless of race (45, 47). In most cases, these absolute differences will not be sufficient to affect the diagnosis or classification of patients with ARDS; however, there will be instances of clinically important differences between pulse oximetry and ABG measurements, and these will likely occur more frequently in patients with dark skin. Therefore, the committee agreed that if the clinical suspicion for ARDS is high but the hypoxemia threshold is not met by pulse oximetry, ABG should be obtained if available. Similarly, clinicians should consider obtaining ABG measurements when a classification error would affect management decisions or eligibility for clinical trials. The effect of skin tone and patient-identified race on the accuracy of pulse oximetric diagnosis and classification of ARDS is an important area for prospective study. Additional information about pulse oximetry is provided in Supplement E4.

In keeping with the conceptual model of ARDS as a diffuse process, the committee retained the requirement for bilateral opacities on chest imaging, though they recognized that both chest radiography and lung ultrasound, though widely available, are highly interpreter-dependent. Furthermore, though promising, radiographic scoring systems such as the Radiographic Assessment of Lung Edema Score, were ultimately not included, because they require further prospective validation (61–63). Future research should consider whether formal radiographic scoring systems should be integrated into the definition of ARDS. The committee did not select a preferred imaging modality for the diagnosis of ARDS, as there is insufficient evidence to support a single modality as the gold standard.

The committee also endorsed the use of ultrasound for detection of bilateral (noncardiogenic) pulmonary edema or consolidation, especially when chest radiography or computed tomography is not available, with the caveat that the operator must be trained in thoracic ultrasound for this purpose (32, 64). Ultrasound is particularly useful in resource-limited settings in which radiography is not routinely available (19). When performed by adequately trained operators, ultrasound can reliably detect signs that are associated with noncardiogenic pulmonary edema (19, 65, 66). Although the presence of multiple B lines and/or consolidations (i.e., ultrasound findings associated with loss of aeration) bilaterally can be useful in diagnosing ARDS (38, 39, 67), it has been suggested that relying exclusively on them might lead to oversensitivity and only moderate specificity (10). Recent studies suggest that integrating these findings with other sonographic signs, such as pleural line abnormalities, may improve diagnostic

accuracy, especially specificity (22, 68, 69). Further studies should involve multiple operators across a range of clinical settings (Table 3). One recent study and an accompanying commentary considered several of these issues (22, 70). The committee recommended that appropriate training in the use of lung ultrasound should be emphasized.

For clinical trials, investigators may elect more stringent criteria for enrollment for prognostic enrichment. For example, if there is concern that including patients on HFNO will select for less severely ill patients, investigators may choose to limit their study populations to moderate to severe intubated ARDS. Conversely, investigators who choose to focus on preventing progression to mechanical ventilation may elect to enroll only patients in the nonintubated ARDS category. This proposed definition lends flexibility to the investigation of ARDS and opens important avenues for prospective study (Table 3).

Several additional topics that were considered by the committee but not included in the final global definition merit discussion. First, underrecognition of ARDS is a common problem with the Berlin definition. In LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure), 20% of patients with severe ARDS and up to 50% of those with mild ARDS were not recognized as having ARDS (29). Clearly the revised definition needs a similar evaluation for reliability.

Second, because ARDS is a dynamic syndrome where some patients improve rapidly whereas others may have protracted courses (71), investigators may choose to focus on subjects with a diagnosis of ARDS that persists beyond 24 hours if they wish to exclude rapidly improving patients from their study population.

Third, the global definition also does not capture differences in the long-term functional outcomes of patients with ARDS. Although the committee acknowledges the importance of long-term outcomes in ARDS, they are not a fundamental component of the initial diagnosis. The long-term outcomes of patients with diagnoses of ARDS using the new global definition of ARDS should be prioritized in prospective epidemiological studies.

Last, developments in ARDS subphenotyping, specifically latent class analysis–based hyper- and hypo-inflammatory phenotypes based on plasma biomarkers and clinical data, were not integrated into the current definition (33, 72–78). Although these phenotypes have been demonstrated across multiple clinical trial populations and observational cohorts (79), prospective validation with point-of-care biomarker platforms is needed to determine if these phenotypes are unique to ARDS or have broader applicability to sepsis, and how they may affect management.

Limitations

Some limitations to the consensus process merit consideration. First, the committee did not use a stringent methodology for reviewing literature published since the Berlin definition, although efforts were made by each working group to be comprehensive in the approach to literature review and new published evidence included in the National Library of Medicine PubMed database (*see* Appendix E1).

Second, the recommendations are based on consensus opinion, although input from members of several critical care societies around the world provided a mechanism for an initial review of these recommendations for an expanded definition. Once these recommendations are published, a website will be created (https://globalardsdefinition.org) that will invite comments and suggestions from clinicians, patients, and societies around the world and will be a dynamic and living document that will facilitate dialogue in a global setting.

Third, no formal prospective testing of the predictive validity of the various Sp_{O_2}:$F_{I_{O_2}}$ thresholds or the noninvasive ARDS subset was done, and the committee endorses further study of these and other research questions, as outlined in Table 3. Fourth, there is risk of some misclassification with the removal of PEEP and the use of ultrasound in resource-limited areas that could lead to a false-positive diagnosis of ARDS.

Fifth, although the consensus committee had global representation, including two members from resource-limited areas and three members with extensive clinical experience in resource-limited areas, more input will be needed in the future from these areas of the world, which should be facilitated by the new website. These and future refinements of the ARDS definition may benefit from approaches used in other disciplines that include a framework for empirically testing expanded definitions, including the goal of establishing frameworks for testing reliability, feasibility, and validity (80).

Conclusions

The new global definition of ARDS provides recommendations for updating the Berlin definition of ARDS in several key areas on the basis of current evidence and clinical practice. Patients being treated with HFNO at $\geqslant$30 L/min can be included, and oxygen saturation measured by pulse oximetry can be used instead of ABGs in the diagnosis of ARDS. Patients in resource-limited settings will no longer be excluded from a definition of ARDS and can be included in epidemiological and clinical research, including clinical trials. Ultrasound can be used for imaging when chest radiography and/or computed tomography are not readily available, providing that the operator is well trained. Last, the updated recommendations for a new global definition of ARDS will foster several important areas for future research. ■

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