PERSPECTIVE

# What Does Acute Respiratory Distress Syndrome Mean during the COVID-19 Pandemic?

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Acute Respiratory Distress Syndrome (ARDS) was first described in 1967 as a syndrome of severe hypoxemia and diffuse bilateral opacities (1). From the beginning, diagnosis of this syndrome has been context dependent. Before unification of the ARDS nomenclature, patients had "shock lung," "Da Nang lung," "wet lung," and other diagnoses contingent on their precipitating insult and management in a military, civilian trauma, or medical setting. In fact, the syndrome's very existence is contingent on advancements in traumatic and medical resuscitation and the broad use of invasive mechanical ventilation for hypoxemic respiratory failure, which together allowed patients to live long enough to be diagnosed with ARDS.

Years ago, as it became apparent that ARDS was the common clinical manifestation of serious acute lung injury of multiple causes, serial consensus efforts sought to harmonize various definitions of this sprawling syndrome (2, 3). The most recent classification system is the Berlin consensus definition, which requires bilateral opacities after an identifiable trigger leading to hypoxemia (arterial oxygen pressure [$Pa_{O_2}$]:fraction of inspired oxygen [$F_{I_{O_2}}$] $<$ 300 on positive pressure ventilation providing at least 5 cm $H_2O$ of positive end-expiratory pressure [PEEP] or with continuous positive airway pressure by face mask allowed in mild cases). This constellation of findings should not be primarily hydrostatic in origin (4).

Since its publication less than a decade ago, however, two important modifications have been required to adapt this definition to real-world contexts. First, the Kigali definition adapted the Berlin definition to resource-constrained environments, broadening chest imaging to include ultrasound, removing PEEP requirements, and advocating the oxygen saturation as measured by pulse oximetry ($Sp_{O_2}$):$F_{I_{O_2}}$ ratio in place of the $Pa_{O_2}$:$F_{I_{O_2}}$ ratio (using an $Sp_{O_2}$:$F_{I_{O_2}}$ threshold of $<$315 rather than $Pa_{O_2}$:$F_{I_{O_2}}$ ratio of $<$300) given the limited availability of arterial blood gas analyses in many settings (5). Second, the increasing use of high-flow nasal oxygen (HFNO) prompted Matthay and colleagues to advocate that HFNO be considered equivalent to mechanical ventilation for the purpose of diagnosis (6).

The coronavirus disease (COVID-19) pandemic has been a pivotal time for clinicians and trialists concerned with prevention, treatment, and rehabilitation of ARDS. Although COVID-19 can cause death and disability through other pathologies (e.g., thromboembolic complications), the overwhelming majority of deaths from COVID-19 occur in patients with viral pneumonia and associated hypoxemia (7). Patients with such hypoxemic respiratory failure are commonly managed with HFNO, noninvasive ventilation (NIV), or invasive mechanical ventilation (IMV). In other words, COVID-19 causing respiratory failure is almost always ARDS, even if managed with HFNO alone. An unprecedented number of patients is therefore suffering from ARDS and its sequelae, resulting in healthcare resources stretched perilously thin and trialists—including investigators new to the ARDS arena—called to be both nimble and rigorous.

A consistent, simple, and meaningful definition for COVID-19–associated ARDS is therefore crucial for clinical care

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and trials targeting this condition. At present, however, a patient's COVID-19–associated respiratory failure is typically classified with a scale that was developed early in the pandemic and aligns poorly with established ARDS definitions. COVID-19 severity has been defined variously on the basis of the World Health Organization/National Institutes of Health ordinal scales (which largely divide patients on the basis of the amount of respiratory support provided), the location of therapy, or the type of life support therapies administered. Under these early definitions, patients with COVID-19 ARDS may be classified variously as "severe" or "critical" COVID-19, and patients with similar severity respiratory failure may nevertheless be scored a 5, 6, or 7 on common 8-point ordinal scales (8) (in which 8 is deceased) contingent on the specific mode of advanced respiratory support applied, which, in turn, depends on resource availability, clinician- and hospital-level practice patterns, and patient preferences. Both ARDS and COVID-19 clinical trials focus on early intervention; waiting for patients on HFNO to progress to intubation to intervene defies current treatment paradigms. Rather than waiting for endotracheal intubation, an expanded definition that identifies patients at an earlier time point in their ARDS could focus the attention of clinicians and trialists on patients at a pivotal time for potential interventions, including trial enrollment.

The nature of COVID-19 nevertheless simplifies the application of the Berlin definition within the pandemic. Specifically, the time course of COVID-19–associated ARDS is well known and predictable (5–14 d); severe hypoxemia is common, and opacities are generally bilateral (consistent with the definition of compatible opacities in the Berlin definition). It may thus be possible to employ pragmatic approaches to the ARDS definition within COVID-19 without meaningfully altering the specificity of the resulting diagnosis or the relevance of ARDS-specific treatments. We therefore propose a pragmatic definition of ARDS owing to COVID-19: a patient receiving HFNO, NIV, or IMV for acute hypoxemic respiratory failure owing to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. In the setting of COVID-19, this definition is fully consistent with the pathophysiological rationale underpinning the Berlin definition (Table 1).

We anticipate that our proposal's omission of formal requirements for PEEP and a $Pa_{O_2}$:$F_{I_{O_2}}$ ratio may be controversial (notably, diffuse opacities and noncardiogenic source are still included in the definition given the requirement for SARS-CoV-2 pneumonia). As noted above, however, the Kigali modification of the Berlin criteria already eliminated requirements for PEEP and positive pressure ventilation in the interests of generalizability and pragmatism. HFNO, moreover, appears to deliver PEEP approaching 5 cm $H_2O$ at the flow rates commonly used in clinical practice (9), and patients with ARDS managed with HFNO are known to have high morbidity and mortality (10). With regard to chest imaging findings, most patients meeting our COVID-19 ARDS definition will have some form of chest imaging to assure the diagnosis of COVID-19 pneumonia. We are mindful of the poor reproducibility of plain chest radiographs (11) as well as the evidence that SARS-CoV-2 pneumonia is a bilateral process at least 88% of the time (12) and that adjusted mortality is similar for unilateral versus bilateral opacities (13). Unpublished data from the PETAL RED CORAL cohort suggest that 82% of patients receiving HFNO, NIV, or IMV will have bilateral opacities on their first postadmission imaging. Finally, in terms of $Pa_{O_2}$:$F_{I_{O_2}}$ or $Sp_{O_2}$:$F_{I_{O_2}}$ ratios, the vast majority of patients will meet Kigali $Sp_{O_2}$:$F_{I_{O_2}}$ ratio thresholds, as an $Sp_{O_2} < 94\%$ on an $F_{I_{O_2}}$ of 0.3 (and any $Sp_{O_2}$ on an $F_{I_{O_2}}$ of 0.35) would qualify as meeting the threshold of $Sp_{O_2}$:$F_{I_{O_2}}$ ratio $< 315$. We acknowledge the use of variable definitions of HFNO by regulators and trialists and emphasize the need for higher flow rates (>20 L/min), titratable $F_{I_{O_2}}$, and delivery of modest levels of PEEP.

We believe this approach to defining COVID-19 ARDS strikes the correct balance

**Table 1.** Features of a pragmatic definition of COVID-19 ARDS: "a patient receiving HFNO, NIV, or IMV for acute hypoxemic respiratory failure owing to SARS-CoV-2 pneumonia"

| Feature of Definition | Berlin Criterion | COVID-19 Application |
|---|---|---|
| Associated with COVID-19 | No restriction by pathogen | Limited to patients with SARS-CoV-2 pneumonia |
| Acute | <7 d since onset | 5–14 d is common; most important factor is that the respiratory failure be from COVID-19 |
| Bilateral opacities | Bilateral opacities consistent with pulmonary edema "may be very mild, patchy, and asymmetric" | COVID-19 pneumonia is generally a bilateral process |
| Hypoxemic | Positive pressure ventilation with PEEP ⩾5 cm $H_2O$ and $Pa_{O_2}$:$F_{I_{O_2}} < 300$ (Kigali modification $Sp_{O_2}$:$F_{I_{O_2}} < 315$ and eliminates PEEP and positive pressure ventilation requirements) | Hypoxemic respiratory failure treated with HFNO, NIV, IMV ($F_{IO2}$ ⩾0.35 guarantees $SpO_2$:$F_{I_{O_2}} < 315$ regardless of $Sp_{O_2}$) |
| Not primarily cardiogenic/hydrostatic | Clinical assessment and judgment | Respiratory failure primarily owing to COVID-19 pneumonia |

*Definition of abbreviations*: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; $F_{I_{O_2}}$ = fraction of inspired oxygen; HFNO = high-flow nasal oxygen; IMV = invasive mechanical ventilation; NIV = noninvasive ventilation; $Pa_{O_2}$ = arterial oxygen pressure; PEEP = positive end-expiratory pressure; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $Sp_{O_2}$ = oxygen saturation as measured by pulse oximetry.

between pragmatism and rigor: in the context of COVID-19, this definition will identify a target population physiologically consistent with the intent of the Berlin consensus, especially as extended in the Kigali definition and the recent proposal of Matthay and colleagues. Further analyses of ultrasound, chest radiographs, and $Sp_{O_2}$:$F_{I_{O_2}}$ ratios from clinical trial and observational COVID-19 cohorts are needed to guide further iterative refinement of pragmatic definitions of ARDS. ■

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## References


1 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;2:319–323.
2 Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;138: 720–723.
3 Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824.
4 Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, *et al.*; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–2533.
5 Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, *et al.* Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. *Am J Respir Crit Care Med* 2016;193:52–59.
6 Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included? *Lancet Respir Med* 2021;9:933–936.
7 Elezkurtaj S, Greuel S, Ihlow J, Michaelis EG, Bischoff P, Kunze CA, *et al.* Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci Rep* 2021;11:4263.
8 World Health Organization. WHO R&D Blueprint: novel coronavirus: therapeutic trial synopsis. Geneva: World Health Organization; 2020 [accessed 2021 Oct 13]. Available from: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf.
9 Chertoff J. High-flow oxygen, positive end-expiratory pressure, and the Berlin definition of acute respiratory distress syndrome: are they mutually exclusive? *Am J Respir Crit Care Med* 2017;196: 396–397.
10 Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, *et al.* Timing of intubation and clinical outcomes in adults with acute respiratory distress syndrome. *Crit Care Med* 2016;44:120–129.
11 Rubenfeld GD, Caldwell E, Granton J, Hudson LD, Matthay MA. Interobserver variability in applying a radiographic definition for ARDS. *Chest* 1999;116:1347–1353.
12 Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, *et al.* Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology* 2020;295: 200463.
13 Pham T, Pesenti A, Bellani G, Rubenfeld G, Fan E, Bugedo G, *et al.* Outcome of acute hypoxaemic respiratory failure: insights from the LUNG SAFE Study. *Eur Respir J* 2021;57: 2003317.