Diagnosing acute respiratory distress syndrome in resource limited settings: the Kigali modification of the Berlin definition

Elisabeth D. Riviello\textsuperscript{a,b}, Egide Buregeya\textsuperscript{c}, and Theogene Twagirumugabe\textsuperscript{c}

Purpose of review
The acute respiratory distress syndrome (ARDS) was re-defined by a panel of experts in Berlin in 2012. Although the Berlin criteria improved upon the validity and reliability of the definition, it did not make diagnosis of ARDS in resource limited settings possible. Mechanical ventilation, arterial blood gas measurements, and chest radiographs are not feasible in many regions of the world. In 2014, we proposed and applied the Kigali modification of the Berlin definition in a hospital in Rwanda. This review synthesizes literature from the last 18 months relevant to the Kigali modification.

Recent findings
In the last 18 months, the need for a universally applicable ARDS definition was reinforced by advances in supportive care that can be implemented in resource poor settings. Research demonstrating the variable impact of positive end expiratory pressure on hypoxemia, the validity of using pulse oximetry rather than arterial blood gas to categorize hypoxemia, and the accuracy of lung ultrasound support the use of the Kigali modification of the Berlin definition.

Summary
Studies directly comparing the Berlin definition to the Kigali modification are needed. Ongoing clinical research on ARDS needs to include low-income countries.

Keywords
acute respiratory distress syndrome, epidemiology, resource poor settings

INTRODUCTION
Since the first description of 12 patients with a syndrome of refractory hypoxemia and poor lung compliance [1], defining the acute respiratory distress syndrome (ARDS) has been a ‘vexing yet essential challenge’ [2]. The 1994 American European Consensus Conference (AECC) definition of acute hypoxemia (PaO\textsubscript{2}/FiO\textsubscript{2} < 200 mmHg) with bilateral infiltrates on chest radiograph not caused by heart failure [3] enabled the first generation of research to occur. The 2012 Berlin definition improved upon AECC by specifying acute onset to be 1 week from a clinical insult, categorizing severity based on PaO\textsubscript{2}/FiO\textsubscript{2} ratio, requiring positive end expiratory pressure (PEEP) of at least 5 cm H\textsubscript{2}O, clarifying chest radiograph requirements, and elucidating the exclusion of heart failure as the primary cause of hypoxemia [4]. In the last year, new studies examining autopsies, open lung biopsies, and inflammatory biomarkers have moved toward better stratification of ARDS related to pathophysiology [5–9], leading to the possibility that therapies targeting specific mechanisms of disease could be developed [10].

Nonetheless, the definition of ARDS, carefully elaborated and applied in resource rich settings, cannot be applied in resource constrained settings. Because the Berlin definition requires positive pressure ventilation, arterial blood gas measurements, and chest radiography, patients with ARDS cannot

\textsuperscript{a}Department of Medicine, University Teaching Hospital of Kigali, Kigali, Rwanda; \textsuperscript{b}Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA; and \textsuperscript{c}Department of Anesthesia, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda

Correspondence to Elisabeth D. Riviello, MD, MPH, Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02215, USA. Tel: +1 617 667 4895; e-mail: beth_riviello@post.harvard.edu

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be diagnosed in many areas of the world. This matters, because a failure of recognition leads to a failure of treatment [11**], and much of the supportive care that has been found to be effective for ARDS can be applied in low resource settings.

We developed the ‘Kigali modification’ of the Berlin definition and applied it to a single large referral hospital in a resource constrained setting [12**]. Although the modification and its validation are imperfect, several studies in the past year have strengthened the propositions that a less resource-dependent definition of ARDS is in fact important, and that the modification may be a reasonable approximation. We review these studies here, and propose future areas of study.

Moving toward a universally applicable definition of acute respiratory distress syndrome: why does it matter?

Studies in the last year have demonstrated why defining ARDS in a less resource-dependent manner matters: paucity of data and feasibility of intervention.

Paucity of data

Other than our Rwandan single-site estimate, no data on ARDS incidence or outcomes from any low-income country exist. The most recent effort to look at ARDS epidemiology, treatment, and outcomes across the globe impressively includes 50 countries on five continents; however, it includes no low-income countries [11**]. This same study found that patients with clinician-recognized ARDS had statistically higher rates of higher PEEP levels, prone positioning, and neuromuscular blockade. Interestingly, however, clinician recognition was not associated with low tidal volume ventilation.

Interventions that may be feasible in resource constrained settings

Low tidal volume ventilation [13] for all ARDS and to a lesser extent neuromuscular blockade [14] and prone positioning [15] for severe ARDS are all potentially feasible in low resource settings [16*].

In the last year, other interventions that might be feasible in low resource settings have also been studied. Amato et al. [17*] retrospectively analyzed the impact of driving pressure on survival in ARDS and concluded that minimizing driving pressure may be more effective than targeting tidal volume. Even the older ventilators often available in resource poor settings are capable of volume and pressure modes, so if this finding is confirmed in prospective trials, it can be applied.

Grissom et al. [18**] retrospectively analyzed ARDS patients who received the Fluid and Catheter Treatment Trial Lite (FACTT Lite') protocol for conservative fluid management, a much-simplified version of the FACTT protocol, and found the same benefits of fewer ventilator-days and ICU-days. Although the protocol still uses a central venous pressure (CVP) measurement that will not be available everywhere, the PROCESS trial showed no difference in septic shock outcomes using CVP measurements versus clinical indicators of fluid status [19], and other research describes passive leg raise and ultrasound to be the best predictors of fluid responsiveness [20]. Taken together, these studies raise the possibility that a conservative fluid protocol in ARDS without CVP measurements may yield benefit.

Chawla et al. [21*] performed a prospective observational study of 170 ARDS admissions in an Indian medical ICU and described outcomes for patients initially supported with noninvasive positive pressure (NIPPV). They caution against use of NIPPV in moderate and severe ARDS, but nonetheless describe a cohort in which, of the 96 patients with ARDS initially managed with NIPPV, 54 (56.3%) improved without intubation. Conversely, a study of hypoxemic patients (a large majority of whom met criteria for ARDS), compared high-flow oxygen with regular oxygen via facemask and NIPPV, and showed improved 90-day mortality with high-flow oxygen [22*]. Although neither NIPPV nor high-flow oxygen is consistently available in resource constrained settings, either or both of these may be attractive alternatives to invasive ventilation in these settings.
Prevention of ARDS is another area of study that may be applicable to resource poor settings. A study this year found that aspirin was ineffective in preventing ARDS [23*], but it is worth noting that only two of the 22 variables used in the Lung Injury Prediction Score (LIPS) (hypoaalbuminemia and acidosis) require laboratory values. The identification of patients at high risk for ARDS with subsequent efforts at prevention is within reach.

Although many interventions may be feasible in resource constrained settings, study is needed to determine the real-world impact they might have in practice. Dondorp et al. [24*] describe the ‘almost untouched’ research agenda examining the translation of critical care practices developed in resource rich settings to resource constrained settings.

**THE KIGALI MODIFICATION: IS IT VALID?**

We screened every adult patient in a Rwandan referral hospital for 6 weeks, then collected clinical data and performed lung ultrasound on all hypoxemic patients [12**]. To estimate ARDS, we did not require a minimum PEEP, replaced the PaO₂/FiO₂ ratio with a SpO₂/FiO₂ ratio, and allowed lung ultrasound in place of chest radiograph (Table 1) [25**–27**,28,29,30**,31,32**,33,34**,35**]. We found 4.0% of all adult hospital admissions met the modified criteria for ARDS, with a hospital mortality rate of 50.0%. Our modifications were based on prior studies demonstrating variable impact of PEEP [3,4,36], correlation of PaO₂/FiO₂ with SpO₂/FiO₂ [37,38], and ultrasound as a more accurate imaging mode for alveolar filling than chest radiograph [39]. Recent studies have further supported the use of the modifications.

**Exclusion of the requirement for positive end expiratory pressure**

Whether to include a requirement for minimal PEEP has been controversial [3,4]; it is worth noting that only seven of the original 12 patients described as having ARDS were receiving PEEP [1].

Caironi et al. [30**] compared classification of 139 ARDS patients as mild, moderate, and severe ARDS by Berlin PaO₂/FiO₂ ratio at three different PEEPs: clinically set PEEP (mean ± SD, 11 ± 3 cm H₂O), 5 cm H₂O, and 15 cm H₂O. They also looked at potentially recruitable lung on computed tomography (CT) scan. They found that lung recruitability was linearly associated with severity classification only at 5 cm H₂O PEEP, and that lung recruitability was independently associated with mortality. Fifty-four percent of patients classified

<table>
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<tr>
<td><strong>Timing</strong></td>
<td>Within 1 week of a known</td>
<td>Within 1 week of a known clinical insult or new or worsening respiratory symptoms</td>
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<tr>
<td><strong>Oxygenation</strong></td>
<td>PaO₂/FiO₂ ≤ 300</td>
<td>SpO₂/FiO₂ ≤ 315</td>
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<td><strong>PEEP requirement</strong></td>
<td>Minimum 5 cm H₂O PEEP required by invasive mechanical ventilation (noninvasive acceptable for mild ARDS)</td>
<td>No PEEP requirement</td>
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<td><strong>Chest imaging</strong></td>
<td>Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or CT</td>
<td>Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or ultrasound</td>
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<td><strong>Origin of edema</strong></td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload [need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present]</td>
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ARDS, acute respiratory distress syndrome; PEEP, positive end expiratory pressure.
as mild ARDS at clinical PEEP became either moderate or severe ARDS when receiving 5 cm H$_2$O of PEEP. The study does not answer the question of whether a minimum PEEP level should be required in defining ARDS, but it demonstrates the variability of hypoxemia with different levels of PEEP and points to hypoxemia at lower PEEP levels as potentially more predictive of mortality.

**Using SpO$_2$/FiO$_2$ as an alternative to PaO$_2$/FiO$_2$**

We based our initial ARDS cutoff of SpO$_2$/FiO$_2 \leq 315$ (with a requirement of SpO$_2 < 97\%$) on a study that found this value to correspond to $\text{PaO}_2/\text{FiO}_2 \leq 300$ [38]. We also did sensitivity analyses, using PaO$_2$ estimated from SpO$_2$ based on a table used in a prior study [40] and SpO$_2$/FiO$_2 \leq 370$ based on another study [37].

The ability to use SpO$_2$/FiO$_2$ rather than PaO$_2$/FiO$_2$ in defining the hypoxemia cutoff and severity of ARDS has been further confirmed in the past year. Brown et al. [25**] compared the performance of the aforementioned linear [38] and log-linear [37] equations used in our study with a nonlinear equation. The latter equation gave a superior imputation of PaO$_2$/FiO$_2$ from SpO$_2$/FiO$_2$, with correlation between measured and imputed PaO$_2$/FiO$_2$ of $r = 0.84$ overall, and $r = 0.90$ when SpO$_2$ less than 96%.

Another study this year compared the nonlinear and linear equations, but among emergency room patients with pneumonia [26**]. Because this was not an ARDS cohort, it applied to varying levels of oxygenation, and for patients not on mechanical ventilation. Both linear and nonlinear equations performed reasonably well though the nonlinear equation again outperformed the linear equation. In this nonventilated population, the nonlinear equation predicted PaO$_2$/FiO$_2$ less than 300 (hypoxemia cutoff for mild ARDS) accurately in 80% of patients and PaO$_2$/FiO$_2$ less than 200 (hypoxemia cutoff for moderate ARDS) in 92% of patients.

Another study pointed to the relevance of these findings to patients in resource rich settings. In a study of a medical ICU in the United States, one-third of patients received a diagnosis of ARDS using a cutoff of SpO$_2$/FiO$_2 \leq 315$, and had no PaO$_2$ available [27**]. Patients diagnosed by SpO$_2$/FiO$_2$ and by PaO$_2$/FiO$_2$ were not statistically different in duration of mechanical ventilation, duration of ICU stay, and hospital mortality. Recent pediatric literature points to an even greater proportion of critically ill hypoxemic patients without arterial blood gases [28].

**Lung ultrasound versus chest radiograph or computed tomography**

Our Kigali modification used evidence from previous studies that ultrasound is accurate in identifying alveolar filling and consolidation in general [41,42], and in ARDS in particular [39]. Studies in the past year have confirmed the utility of ultrasound for diagnosing ARDS and potentially even for guiding treatment.

Ma et al. [31] compared lung ultrasound and chest CT scan in 30 rats, and found a Spearman rank correlation of 0.758 with kappa of 0.737; they concluded that ultrasound could be used for assessing ARDS in rat models. Lichtenstein [32] found that 86% of ARDS cases have an ultrasound profile matching their previously defined pneumonia profiles. In a review with other authors, Lichtenstein also presented unpublished data, with 74% of 100 patients with early ARDS being identified as having an ARDS-consistent profile [33]. Ye et al. [34**] conducted a meta-analysis of ultrasound and chest radiograph detection of community acquired pneumonia as compared with gold standard CT scan. They found a pooled sensitivity of 0.95 (0.93–0.97) and a specificity of 0.90 (0.86–0.94) for lung ultrasound whereas chest radiography had a pooled sensitivity of only 0.77 (0.73–0.80) and a specificity of 0.91 (0.87–0.94). Shah et al. [35*] demonstrated the feasibility of lung ultrasound in a resource constrained setting. They implemented a 10-h didactic plus 20-h bedside practice training on cardiopulmonary ultrasound for Haitian physicians; the trainees then performed ultrasounds on 117 patients presenting with dyspnea. With expert interpretation of ultrasound as the reference standard, the trainee physicians' interpretation of B lines (alveolar edema pattern) had a sensitivity of 92.7% and specificity of 97.9%.

Small preliminary studies in the last year went beyond data suggesting the accuracy of lung ultrasound for diagnosing ARDS, to explore ultrasound as a means of prognosticating and monitoring response to treatment in ARDS. Zhao et al. [43] looked at the ultrasound patterns of 21 ARDS patients and found these to be predictive of mortality. Prat et al. [44] examined 19 patients with severe ARDS and found that normal aeration of the bilateral anterobasal segments of the lung prior to proning was predictive of oxygenation response to proning. Haddam et al. [45] performed a similar study in 51 patients, but did not find any of the ultrasound patterns prior to proning to be predictive of oxygenation response.

**SpO$_2$/FiO$_2$ and ultrasound**

Only one study in the past year evaluated two portions of the Kigali modification at the same time.
Bass et al. [29] examined consecutive mechanically ventilated ICU patients at a single hospital in the United States to test the sensitivity and specificity of using SpO₂/FiO₂ and ultrasound to define ARDS in comparison to PaO₂/FiO₂ and chest radiograph. The study showed only modest correlation, with sensitivity of 83% and specificity of 62% for ARDS overall and sensitivity of 64% and specificity of 86% for moderate or severe ARDS. However, the study was a small pilot with some methodologic constraints, so its results should be viewed with caution. Because of the requirement for oxygen saturation ≤97%, only 33 patients were included in the final analysis. The study physician had only 4 h of ultrasound training prior to the study, and only three zones per side were examined (half of what is usually examined) [39]. Patients were not moved for examination, so that posterior lung regions were usually not examined, a particular issue since ARDS tends to be a posterior-predominant disease. They only considered B lines to be consistent with opacities, but ‘tissue patterns’ of consolidation on ultrasound would also result in opacity on chest radiograph. Chest radiograph was treated as the ‘gold standard’ even though prior studies have shown ultrasound to be superior to chest radiograph when CT scan is considered to be the reference standard [39]. And finally, the comparison of SpO₂/FiO₂ to PaO₂/FiO₂ used the linear equation which has now been found to be less accurate than the nonlinear equation [25**]. For these reasons, the study is not adequate for drawing conclusions about the use of pulse oximetry and ultrasound for the diagnosis of ARDS; it serves as an excellent pilot that points to multiple improvements to be used in future studies.

CONCLUSION
The Kigali modification of the Berlin definition of ARDS is an initial attempt to redefine an important syndrome with fewer resource requirements. This is important for quantifying and treating ARDS in resource constrained settings, but studies in the past year have also suggested implications for resource rich settings as well. Removing the requirement for PEEP would make it possible to recognize ARDS outside of the ICU. Using pulse oximetry rather than arterial blood gases would allow diagnosis without arterial samples or arterial lines. Lung ultrasound is an imaging technique that can be done at the bedside, without the need to transport critically ill patients to CT scanners and without radiation.

Although it is important to validate a definition of ARDS that can be used universally based on the current Berlin criteria, it should also be noted that current research is focusing on identifying patients with diffuse alveolar damage and inflammation, markers of what is thought to represent ‘true’ ARDS [5–9,33]. To the extent that tested biomarkers can include tests available in resource poor settings (erythrocyte sedimentation rate, for example) or subphenotypes can be defined by clinical variables, translation of new findings to resource constrained settings will be facilitated.

Studies in the last year have demonstrated the importance of defining ARDS with as few resources as possible, and have provided some additional evidence that ultrasound and pulse oximetry may be valid tools. What is needed now is a large and rigorous study in a resource rich setting that compares the Berlin definition to a modified definition. With a definition of ARDS that can be applied in all areas of the world, we could improve upon efforts to quantify the burden of disease, implement known best practices, and develop new treatment strategies worldwide.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
★ of special interest
★★ of outstanding interest

Diagnosing acute respiratory distress syndrome Riviello et al.


This study examined ARDS epidemiology, treatment, and outcomes in 50 countries on five continents. It included high-income and middle-income countries. It also looked at the connection between clinician recognition of ARDS and the use of various treatment modalities.


This study created and then used a modified definition of ARDS in a single referral hospital in Kigali, Rwanda. The modifications were: exclusion of PEEP requirement, use of SpO₂/FIO₂ in place of PaO₂/FIO₂, and use of ultrasound in place of chest radiograph. It found that 4.0% of all hospital admissions met the modified criteria for ARDS, with a mortality rate of 50.0%.


This review highlights the need for research on ARDS epidemiology and treatment, as well as educational initiatives, in resource-constrained settings.


This elegantly performed retrospective analysis suggests that driving pressure, rather than tidal volume, is a more relevant parameter to target in lung-protective ventilation. Further prospective work is needed to confirm this finding.


This retrospective analysis found that a simplified conservative fluid management protocol in ARDS, using only CVP and urine output, decreased ventilator-days and ICU-days without increasing complications.


This study suggested that a majority of patients with mild ARDS respond to NIPPV without the need for mechanical ventilation, whereas most patients with moderate or severe ARDS will require invasive mechanical ventilation.


This study examined what aspirin prevented the occurrence of ARDS in patients with high risk of developing ARDS (LIPS > 4). It found that aspirin did not prevent ARDS. It is important as the first use of LIPS in a trial. LIPS is a largely clinical score, with only two laboratory values needed.


This study used data from prior ARDS studies to compare the correlation between PaO₂/FIO₂ and SpO₂/FIO₂ derived from three different models. It found all models to work reasonably well, but the nonlinear model to have outstanding correlation. This suggests that oxygen saturations from pulse oximetry may reasonably be used in place of arterial blood gases for determining levels of hypoxemia in ARDS patients.


This study examined the correlation between PaO₂/FIO₂ and SpO₂/FIO₂ derived from two different models in nonventilated emergency room patients with pneumonia. It found the nonlinear equation to perform very well, suggesting that pulse oximetry could be used in place of arterial blood gas even in patients who are not mechanically ventilated.


This study found that one-third of hypoxic medical ICU patients in a center in the United States did not have arterial blood gas measurements. It also found that patients referred to have ARDS based on PaO₂/FIO₂ derived from SpO₂/FIO₂ had identical outcomes as those with Arterial blood gas measurements. This study also compared these stratifications to lung recruitability on chest CT. It finds that the lowest PEEP provides the stratification of hypoxemia that is most predictive of mortality.


This publication compares hypoxemia by PaO₂/FIO₂ ratio at three different PEEP levels, and also compares these stratifications to lung recruitability on chest CT. It finds that the lowest PEEP provides the stratification of hypoxemia that is most predictive of mortality.


This study found that 86% of ARDS cases had an ultrasound profile matching previously defined pneumonia profiles.


This is a meta-analysis examining the ability of lung ultrasound versus chest radiograph to identify community acquired pneumonia, with CT scan as the gold standard. As in prior studies, ultrasound outperformed chest radiograph.


This study demonstrated the practical feasibility and validity of using lung ultrasound in resource-constrained settings. The authors provided 90% of cardiopulmonary ultrasound training for Haitian physicians. These physicians then examined 117 patients with dyspnea. As compared with expert readers, the trainees performed very well in identifying B lines on lung ultrasound.


