Acute Respiratory Distress Syndrome in the Global Context

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a clinically defined syndrome of hypoxia and bilateral pulmonary infiltrates due to inflammatory pathways triggered by pulmonary and nonpulmonary insults, and ARDS is pathologically correlated with diffuse alveolar damage. Estimates of ARDS's impact in the developed world vary widely, with some of the discrepancies attributed to marked differences in the availability of intensive care beds and mechanical ventilation. Almost nothing is known about the epidemiology of ARDS in the developing world, in part due to a clinical definition requiring positive pressure ventilation, arterial blood gases, and chest radiography. Current frameworks for comparing the epidemiology of death and disability across the world including the GBD (Global Burden of Disease Study) 2010 are ill-suited to quantifying critical illness syndromes including ARDS. Modifications to the definition of ARDS to allow a provision for environments without the capacity for positive pressure ventilation, and to allow for alternate diagnostic techniques including pulse oximetry and ultrasound, may make it possible to quantify and describe the impact of ARDS in the global context.

In 1967, Ashbaugh et al. [1] described 12 patients receiving respiratory support who were noted to have bilateral infiltrates on chest radiograph; decreased lung compliance; hyperemia, engorged vessels, and hyaline membranes on pathology; and who "did not respond to usual methods of therapy." From this remarkable set of observations, the acute respiratory distress syndrome (ARDS) was born. Its definition was first operationalized by the 1994 American European Consensus Conference (AECC) [2]. ARDS was defined as a syndrome of acute onset, oxygenation impairment of partial arterial oxygen tension/fractional concentration of oxygen in inspired gas (PaO_2/FiO_2) <200 mm Hg regardless of positive end-expiratory pressure (PEEP) level, bilateral infiltrates on frontal chest radiograph, and pulmonary artery wedge pressure ≤18 mm Hg or no clinical evidence of left atrial hypertension. Acute lung injury carried the same definition except that oxygenation was less impaired: PaO_2/FiO_2 <300 mm Hg. Mechanical ventilation was excluded as a requirement with the explicit recognition that its use varies by resource availability and practice patterns. In addition, whereas PEEP was known to have a profound effect on oxygenation, it was thought to have too inconsistent an effect to include in the definition. Also explicitly noted were the fact that even mild infiltrates would meet criteria, and that infectious causes of the syndrome (bilateral pneumonia) would not be excluded.

The next redefining of the syndrome occurred in 2012, with the Berlin definition [3]. This consensus statement sought to correct deficiencies in feasibility, reliability, and validity of the 1994 definition. The Berlin definition of ARDS requires:

- onset within 1 week of a known clinical insult;
- bilateral opacities on chest radiograph or computed tomography scan not fully explained by effusions, lobar/lung collapse, or nodules;
- respiratory failure not fully explained by cardiac failure or fluid overload (objective assessment needed with echocardiography only if no clear risk factor present); and
- oxygenation of PaO_2/FiO_2 ≤300 mm Hg with PEEP of at least 5 cm H_2O.

With the Berlin definition, acute lung injury is no longer a category, and severity of ARDS is divided by PaO_2/FiO_2 ratio (≤300 cm H_2O mild, ≤200 cm H_2O moderate, ≤100 cm H_2O severe.)

The inclusion of a minimum PEEP of 5 cm H_2O as a requirement in the Berlin definition was on the basis of evidence that PEEP can have a large effect on the PaO_2/FiO_2 ratio [4]. The Berlin panel made this addition on the basis of its "face validity," without specific testing of the effect of various PEEP levels. The earlier AECC panel also explicitly noted the effect of PEEP on the PaO_2/FiO_2 ratio, but did not include a particular PEEP level as a requirement given PEEP's inconsistent effect on the PaO_2/FiO_2 ratio, as well as differences in the availability of mechanical ventilation in different areas of the world.

The current ARDS definition is an improvement over the 1994 definition, enabling better comparisons for trials designed to test interventions. However, it is difficult to apply in resource-poor settings. As noted in the editorial accompanying the publication of the Berlin definition, "the latest definition, by specifying PEEP requirements when measuring the PaO_2/FiO_2 ratio, has essentially excluded ARDS as a possible diagnosis in patients without ventilation. Around the world, many individuals develop critical illness far from the modern intensive care unit (ICU). Hopefully, this new Berlin definition for ARDS will not inadvertently compromise efforts to develop and disseminate strategies for the care of such patients through unintended mislabeling" [5].

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PATHOPHYSIOLOGY

ARDS is thought to begin with lung injury precipitated by any of a large number of "clinical insults" [3]. The usual categories are shock, sepsis, pneumonia, aspiration, pancreatitis, blood transfusion, drug overdose, high-risk surgery, high-risk trauma, and "other" [6,7]. These are often divided into "direct" or pulmonary causes versus "indirect" or nonpulmonary causes, though no consistent difference in mortality has been demonstrated on the basis of a direct versus indirect cause [8–10]. Beyond these predisposing conditions, additional patient characteristics, or "risk modifiers," have been identified that increase the probability that a given patient will develop ARDS: history of alcohol abuse; obesity; hypoalbuminemia; chemotherapy; initial FiO_2 >0.35; respiratory rate >30 breaths per minute; functional oxygen saturation (SpO_2) <95%, arterial pH <7.35; and presence of diabetes mellitus [6].

Alveolar injury in ARDS results in the release of proinflammatory cytokines leading to damage to the vascular endothelium and alveolar epithelium [11]. ARDS progresses through 3 definite phases, though not all patients experience all phases. The first phase is the acute or exudative phase, which is characterized by inflammation, pulmonary edema, and capillary leak, resulting in refractory hypoxemia and decreased lung compliance. The abnormalities are heterogeneous, with greater consolidation usually found in dependent portions of the lungs. In some patients, the acute phase is followed by the second phase of fibrosing alveolitis characterized by continued hypoxemia, worsening pulmonary compliance, and pulmonary hypertension. Pulmonary hypertension is likely caused by a combination of factors including airway collapse, microthrombi in pulmonary vessels, vascular compression from positive pressure mechanical ventilation, and vasoconstriction due to hypoxemia, hypercarbia, and the release of vasoconstrictive substances [12]. The recovery phase involves gradual improvement in hypoxemia, with full resolution of radiologic abnormalities and return of normal pulmonary function for many survivors [11].

The pathologic correlate in the acute phase of ARDS is diffuse alveolar damage (DAD) consisting of hyaline membranes with edema, cell necrosis, and/or fibrosis; however, in an autopsy study of 356 patients who met the clinical definition for ARDS at the time of death, only 45% of patients met criteria for DAD on autopsy [13]. The clinically defined syndrome is heterogeneous, comprising patients with DAD, pneumonia, pulmonary hemorrhage, pulmonary edema, cancer, tuberculosis, abscess, fibrosis, pulmonary embolism, emphysema, and even some without a pulmonary lesion [13]. However, the specificity of the clinical definition to its pathologic correlate of DAD increases considerably when confined to "severe" ARDS as defined by the Berlin definition. In addition, it is reassuring that even with this heterogeneity of pathologic findings, clinical trials have identified interventions that decrease mortality for ARDS patients as defined by clinical, not pathologic, criteria [14,15].

EPIDEMIOLOGY

The global impact of ARDS is difficult to estimate. The GBD (Global Burden of Diseases, Injuries, and Risk Factors Study) 2010 sought to estimate causes of death for the populations of 187 countries categorized into 21 regions of the world with 235 causes [16]. It separated causes of death into 3 broad categories: 1) communicable, maternal, neonatal, and nutritional disorders; 2) noncommunicable diseases; and 3) injuries. Although this study represents an impressive analysis of global disease incidences and trends, it offers little insight into the epidemiology of ARDS, which can result from and accompany disorders in all 3 categories [17].

Adhikari et al. [18] note that defining the burden of critical illness including ARDS is also difficult due to changing definitions, requirement of multiple clinical data points, brief periods of illness that decrease prevalent cases at a given point in time relative to chronic diseases, and the fact that most studies are confined to ICUs, with ICU capacity varying widely between countries. They estimate the burden of ARDS by World Bank region using population estimates and applying ARDS incidences from developed countries, but they note that the estimates necessarily rely on the assumption that population structure, underlying risk factors, and critical care capacity are similar between the developed world and developing world.

ARDS epidemiology in the developed world

The estimates we have for ARDS incidence all originate in the developed world. In Table 1, we present the most recent population-based estimates representing various parts of the developed world. Estimates of ARDS (previously acute lung injury, PaO_2/FiO_2 <300 mm Hg) even in these studies vary from 10.1 to 86.2 cases per 100,000 person-years.

All of these studies are based on the screening of ICU patients, and all use a version of the 1994 AECC criteria. All but the Scandinavian study [19] require mechanical ventilation for inclusion, though mechanical ventilation was not required by the AECC definition. Explanations for the large variability in incidence estimates are many: true differences in underlying risk factors for ARDS including critical care interventions; the potential for seasonal variation not captured in studies of brief duration; misclassification due to varying chest radiograph interpretations; differences in methodology; true incidence changes over time; and differences in ICU bed availability and use (Table 2) [7,20].

ICU bed availability varies widely across global jurisdictions. Because only patients in ICUs were screened for ARDS in these studies, variability in ICU bed concentration will affect ARDS incidence estimates. In this way, we esti-

TABLE 1. Select studies reporting ARDS population incidence

Study, Year [Ref]	Population	Observation Period	Inclusion Criteria	Incidence (Per 100,000 Person-Yrs)	In-Hospital Mortality, % (95% CI)
Luhr et al., 1999 [19]	Scandinavia: Sweden, Denmark, and Iceland (132/150 ICUs)	2 months, October to November 1997	• Age ≥15 yrs • FiO_2 ≥40% by mask, or by invasive or noninvasive mechanical ventilation • Assessed for ARDS at 1 point: 24 h after meeting study inclusion criteria	• ALI: 17.9 • ARDS: 13.5	• ALI: 41.4* • ARDS: 41.2*
Bersten et al., 2002 [8]	Australia: all 21 adult ICUs in 3 states†	2 months, October to November 1999	• Age >15 yrs • Invasive or noninvasive mechanical ventilation	• ALI: 34 • ARDS: 28	• ALI: 32 (25—40)‡ • ARDS 34 (27—43)‡
Hughes et al., 2003 [9]	Scotland: 23/31 ICUs	8 months, May to December 1999	• Age >15 yrs • Mechanical ventilation (invasive or noninvasive not specified)	• ARDS: 16	• ARDS: 60.9 (55.9—65.9)
Rubenfeld et al., 2005 [7]	USA: King County, Washington	12 months, April 1999 to July 2000	• Age ≥15 yrs • Invasive mechanical ventilation	• ALI: 78.9 • (age-adjusted 86.2) • ARDS: 58.7 • (age-adjusted 64.0)	• ALI: 38.5 (34.9—42.2) • ARDS: 41.1 (36.7—45.4)
Li et al., 2011 [20]	USA: Olmsted County, Minnesota	8 yrs, 2001—2008	• Age ≥18 yrs • Invasive mechanical ventilation	• ARDS 2001: 82.4 (age and sex-adjusted 81.0) • ARDS 2008: 38.9 (age and sex-adjusted 38.3)	• ARDS: 34.8§
Caser et al., 2014 [26]	Brazil: 14 medical and surgical ICUs in 1 state (Espirito Santo)	15 months, October 2006 to December 2007	• Age 18—75 yrs • Invasive mechanical ventilation >24 h • PEEP ≥5 cm H_2O	• ALI: 10.1 • ARDS: 6.3	• ALI: 49.2 (40.6—57.8) • ARDS: 55.5 (44.7—66.4)

All studies are prospective cohort studies except Li et al. [20], which is a retrospective cohort study.
All studies used American European Consensus Conference (AECC) criteria to define ARDS and ALI. Caser et al. [26] also used the Berlin definition to compare incidence with each of these definitions.
We include ALI because the current Berlin definition of ARDS includes what was known as ALI under the AECC definition (PaO_2/FiO_2 <300 mm Hg).
ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; FiO_2, fractional concentration of oxygen in inspired gas; ICU, intensive care unit; PaO_2, partial arterial oxygen tension; PEEP, positive end-expiratory pressure.
*Ninety-day mortality.
†The 3 Australian states are South Australia, Western Australia, and Tasmania.
‡Twenty-eight-day mortality.
§Mortality on the basis of aggregating mortality rates from Table 2; mortality rates did not change significantly over the 8-year period of the study.

TABLE 2. Proposed reasons for variability in ARDS population incidence estimates [7]

Differences in the epidemiology of risk factors for ARDS in different populations
Differences in ventilation and other care that may prevent or predispose to ARDS
Seasonal variation
Misclassification on the basis of chest radiograph interpretation
Differences in methodology, for example:
Inclusion of all ventilated patients versus only invasively ventilated patients
Whether screening for ARDS criteria occurs daily or at one point in time
True trends toward lower ARDS incidence over time [20]
Differences in ICU bed availability
Differences in ICU bed use and end of life decision making

Abbreviations as in Table 1.

mate "treated incidence" not actual incidence [21,22]. This is a fundamental challenge in comparing incidence across locations in the developed world and much more so in the developing world. However, it is important to note that variability in ICU resources do not explain all differences. For example, the estimated 20 ICU beds per 100,000 population in the United States compared with the 8 per 100,000 in Australia [18], may help explain the approximately 2-fold higher incidence of ARDS in a study of an American county [7] versus 3 states in Australia [8] (Table 1). However, it does not explain why a Scandinavian study demonstrated one-half the incidence of Australia [19] when Sweden has 8.7 beds per 100,000 population, which is very similar to Australia's ratio [18].

The issue of changing incidence over time is another reason for variability and may be associated with improvements in critical care. Li et al. [20] make a convincing argument that the incidence of ARDS in 1 American county decreased from 82.4 to 38.9 per 100,000, all in hospital-acquired ARDS and during a period of multiple improvements in critical care interventions.

ARDS epidemiology in the developing world

Understanding the epidemiology of ARDS in the developing world is difficult for the same reasons as in the developed world, with some additional challenges. The definition of ARDS relies on a ratio of PaO_2 to FiO_2, with the former requiring capability of performing blood gases and the latter requiring administration of oxygen in a manner that can be precisely calculated. Both are challenging in resource-poor settings. Even chest radiographs to determine bilateral opacities may be inconsistently available. One survey of the 44 district and referral hospitals in Rwanda found that only 75% of hospitals had radiography machines [23], and our experience is that the actual day-to-day capacity for chest radiography is more limited. The Berlin definition's requirement for mechanical ventilation with PEEP $\geq$5 cm H_2O means that patients in settings without ventilation capacity cannot meet the definition of ARDS. As noted, the definition of ARDS leads to an estimation of "treated incidence" that will vary with the availability of resources including arterial blood gases, radiographs, and medical ventilation.

To our knowledge, no study of ARDS incidence has been published from a lower-middle-income or low-income country. However, 3 recent studies from upper-middle-income countries begin to offer insight into the epidemiology of ARDS outside high-income countries. Azevedo et al. [24] studied admissions requiring mechanical ventilation to 45 ICUs in Brazil for 2 months and found that 31% of the 773 patients included met the Berlin criteria for ARDS. Although this suggests a high rate of ARDS, it is difficult to interpret its significance because more than one-half of the ventilated ICU patients initially considered were excluded due to short length of ventilation, lack of consent, withdrawal of care, and other reasons [24]. Estenssoro et al. [25] looked at the 3,050 adult patients admitted to 4 Argentine ICUs over a 15-month period; 1,193 (39%) of these received mechanical ventilation, and 235 of these (7.7% of all ICU patients and 19.7% of all ventilated patients) met AECC criteria for ARDS. Neither of these studies provides a population-based estimate of ARDS, making comparison to the developed world studies difficult.

Only one study from a non-high-income country provides population estimates. Caser et al. [26] performed a prospective observational study of 14 medical and surgical ICUs in one region of Brazil, including all of the 7,133 adults admitted to the ICU and ventilated $\geq$24 h over a 15-month period. They found ARDS by Berlin criteria in only 1.8% of all patients and estimated a population incidence of 10.1 per 100,000 person years (Table 1). Although this very low incidence may reflect a real difference in incidence from those of the developed world studies, some methodologic issues may also contribute [17]. The study excluded patients with chronic obstructive pulmonary disease, lung cancer, chronic renal disease, and chronic liver disease. In addition, the study mentions 2 very different approximate populations for the region and does not comment on whether patients might feasibly seek care outside the hospitals included in the study. Therefore, it is not clear that the population estimates are comparable to those of other studies.

It is in fact difficult to predict how ARDS incidence in resource-poor settings will compare to that in resource-rich settings. For example, the higher proportion of traumatic and infectious illness in resource-poor settings could increase ARDS incidence [18]; however, the lack of critical care resources may mean that critically ill patients die before ARDS develops and are free from the iatrogenic contributions of mechanical ventilation [15].

TABLE 3. Potential modifications to methodology and the Berlin definition to estimate ARDS incidence [27,28] in resource-poor settings

Use validated SpO_2/FiO_2 ratios to estimate PaO_2/FiO_2 where blood gases are unavailable [28,29]
Waive the requirement for mechanical ventilation with PEEP $\geq$5 cm H_2O [2] in locations where ventilation capacity is low
Allow use of lung ultrasonography in addition to chest radiography to define bilateral opacities [30]
Validate alternate diagnostic modalities in resource-rich settings by comparison to gold standard modalities
Screen patients in all areas of the hospital, not just ICUs [27]

SpO_2, functional oxygen saturation; other abbreviations as in Table 1.

Improving our understanding of ARDS epidemiology in the developing world

What can be done to fill the gap in data? Modifications to the Berlin definition that allow for diagnosis in resource-limited settings must be incorporated: estimation of the PaO_2/FiO_2 ratio where arterial blood gases are unavailable; waiving the requirement for PEEP where mechanical ventilation access is poor; and ultrasonography for diagnosis of bilateral opacities [27–30] (Table 3).

Two studies have used the ARDSnet study [14] data to estimate corresponding PaO_2/FiO_2 ratios from SpO_2/FiO_2 ratios for ARDS, so that pulse oximetry can reasonably substitute for blood gas measurements [28,29]. Waiving the requirement for a minimum PEEP to meet ARDS criteria is a necessary concession in studying ARDS in resource-poor settings and is consistent with previous studies using the AECC definition [2].

Ultrasonography machines are often more accessible than radiographs in resource-poor settings, and almost always more accessible at the bedside. The bilateral opacities found in ARDS manifest in ultrasonography as 2 findings: 1) alveolar-interstitial filling indicated by "B lines," which are an artifact composed of >2 vertical lines arising from the pleural line and extending to the screen edge; and 2) alveolar consolidation seen as hypoechoic areas resembling tissue with hyperechoic punctiform lesions corresponding to air bronchograms [30]. Ultrasonography can also be used to exclude cardiac failure, thus fulfilling another portion of the ARDS criteria. Initial studies on the accuracy of ultrasonography in diagnosing pulmonary disease are encouraging. One study examined 384 lung regions in 32 patients with ARDS and found ultrasonography to significantly outperform chest radiography in diagnosis of the alveolar-interstitial syndrome (accuracy 95% vs. 72%) and alveolar consolidation (accuracy 97% vs. 75%) [30]. Another study of 260 patients with acute respiratory failure demonstrated a diagnostic accuracy of 90.5% with ultrasonography as compared to a gold standard combining chest computed tomography and other clinical information [31]. Another study of 78 patients with acute respiratory failure found that a combination of pulmonary and cardiac ultrasonography was more accurate than an initial diagnosis using chest radiography and clinical and laboratory data (83% vs. 63%) [32]. Given this preliminary data suggesting the superior accuracy of lung ultrasonography, it is possible that ultrasonogram techniques employed due to resource limitations could be found to be a superior method of diagnosis in all settings.

In addition to allowing these modifications to the Berlin definition, incidence studies in the developed world need to be performed using these modifications and including screening outside the ICU to allow more meaningful comparisons across different regions of the world (Table 3).

INTERVENTIONS AND OUTCOMES

Mortality from ARDS is high, approximately 30% to 40% in most studies (Table 1) [14,33]. Of individual interventions, only low tidal volume ventilation has convincingly been shown to reduce mortality in ARDS of all severity levels [14]. Conservative fluid management reduces duration of ICU stay and time receiving ventilation, though it does not appear to affect mortality [34]. Prone positioning reduces mortality in moderately severe ARDS (PaO_2/FiO_2 <150 mm Hg) [35]. Neuromuscular blockade may reduce mortality in moderately severe ARDS (PaO_2/FiO_2 <120 mm Hg), though confirmation of these results is warranted given the uncertain mechanism of benefit [36].

Higher PEEP, though improving oxygenation, has not been associated with a corresponding survival benefit [37], though 2 meta-analyses suggest that patients with moderate to severe ARDS (PaO_2/FiO_2 $\leq$200 mm Hg) may benefit from a high-PEEP strategy [38,39]. In addition, a study allowing higher PEEP, guided by use of esophageal pressures, suggests that targeting transpulmonary pressures may have benefit [40]. Whether using extracorporeal membrane oxygenation is beneficial in ARDS is still unknown, whereas referral for management in a center experienced with severe oxygenation failure and extracorporeal membrane oxygenation therapy does appear to improve survival [41]. Early [42] or late [43] treatment of patients with ARDS with corticosteroids, ketoconazole [44], and most recently early use of high-frequency oscillatory ventilation [45,46] have failed to improve survival among patients with ARDS.

These findings are relevant for resource-poor settings [11,35,47–54] (Table 4). Early recognition of ARDS and treatment of underlying conditions may improve outcomes [11]. Although central venous catheters to monitor intravascular filling pressures are not prevalent, the principle of conservative fluid management can be applied using clinical indicators of fluid status. The recent ProCESS (Protocolized Care for Early Septic Shock) trial for septic shock suggests that clinical indicators may be as effective as more invasive

TABLE 4. Interventions that may be implemented in resource-poor settings to improve outcomes for ARDS patients

Early recognition and diagnosis of ARDS [11]
Treatment of the underlying disorder [11]
Supportive care and reduction of iatrogenic harm applicable to all critically ill patients:
Nutritional support [47]
Moderate blood glucose control [48]
Prophylaxis for deep venous thrombosis [49]
Prophylaxis for gastric stress ulcers [50]
Conservative fluid management guided by clinical parameters [34,51]
Low tidal-volume ventilation (6 ml/kg) when ventilation available [14]
General ventilator care to reduce iatrogenic harm when ventilation available:
Protocols for daily sedation interruption and spontaneous breathing trials [52]
Oral decontamination with antiseptic such as chlorhexidine [53]
Semirecumbent body positioning [54]
Additional interventions to consider with appropriate training and monitoring:
Neuromuscular blockade for severe ARDS (PaO_2/FiO_2 <120 mm Hg) [36]
Prone positioning for severe ARDS (PaO_2/FiO_2 <150 mm Hg) [35]

Abbreviations as in Table 1.

measures [51]. In resource-poor countries, access to mechanical ventilation is limited, but where it is available, low tidal volume ventilation can be achieved on almost any ventilator. Prone positioning and paralysis are daunting prospects in many ICUs that lack a sufficient number of highly trained staff, but training specific to interventions associated with improved outcome is feasible and should be a focus of ongoing education. Other interventions that improve outcomes for ventilated patients and critically ill patients in general are also feasible, including prevention of thromboembolic disease, prevention of gastric stress ulceration, moderate glucose control, nutritional support, prevention of ventilator-associated pneumonia, and introduction of ventilator weaning protocols (Table 4). Recognition of ARDS in resource-poor settings may also encourage investigation of other interventions, such as early noninvasive positive pressure ventilation for less-severe ARDS, that might not otherwise be considered in resource-rich settings but could be of benefit in either.

SUMMARY

ARDS is a highly fatal inflammatory syndrome of critical illness arising from a variety of underlying causes. The clinical definition of ARDS makes the syndrome difficult to quantify in any setting but more difficult in resource-poor settings. Developing methods to identify and treat ARDS in the global context may require adaptation of the current Berlin definition, with validation of potential modifications. If ARDS cannot be diagnosed in resource-poor settings, we may lose the opportunity both to effectively treat patients with ARDS now and to discover new best practices that can be applied in all settings to improve outcomes in the future.

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