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EDITORIAL

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Evaluating the Berlin Definition in pediatric ARDS

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Since its original description in 1967 [1], there have been various attempts to use clinical criteria to define the acute respiratory distress syndrome (ARDS). The 1994 American European Consensus Conference (AECC) [2] established diagnostic criteria that became widely used, also in pediatrics, despite virtually no studies evaluating its use in children. Twenty years later, ARDS diagnostic criteria have been revised using a combination of consensus opinion and empirical evaluation, resulting in the Berlin Definition [3, 4]. This definition provides limited changes from the AECC definition, although some may have fundamental importance, with uncertain implications for pediatric critical care [5].

In this issue of *Intensive Care Medicine*, investigators from the European Society for Pediatric and Neonatal Intensive Care (ESPNIC) report an observational study evaluating the Berlin Definition in children [6]. The authors found that stratification into mild, moderate and severe categories for ARDS based on oxygenation better classified mortality or need for extracorporeal membrane oxygenation than the AECC classification. Interestingly, mortality was found not to differ between mild and moderate ARDS, as was reported in adults, but the severe group did have significantly higher mortality.

These investigators should be applauded for their attempt to validate the Berlin Definition in children. They tackle a number of unique issues pertaining to pediatric ARDS through consensus opinion, namely risk factors and age criteria not addressed in the original report. Moreover, they have established a set of pediatric training X-rays to complement those from adults [3]. The study, however, has limitations. First, as in the adult validation, the investigators began with patients already coded as having ARDS by the AECC definition, thereby introducing a selection bias. As such, they can only evaluate elements of the Berlin Definition that are more restrictive than the AECC definition. For example, the impact of the

change in how one excludes heart failure as the primary cause of respiratory failure remains uncertain. A preferred approach in future studies in both adults and children would be to start with a broader population of patients with acute respiratory failure. Similarly, because only patients with hypoxemia documented on arterial blood gas were included and because arterial lines are used less frequently in children, the investigators may have missed a significant proportion of potentially eligible patients [7–10]. This selection bias may partly explain similar mortalities which were found for mild and moderate ARDS, as arterial lines are more likely placed in a subset of children with mild ARDS who are more systemically ill. The investigators noted that all patients met the minimum positive end-expiratory pressure (PEEP) requirement of 5 cm of water. While the use of a PEEP of <5 has dramatically declined in adults in recent years [11], corresponding data suggest that a lower PEEP may still be used more frequently in pediatric practice, and with more variability [7, 12]. Again, however, the authors of the ESPNIC study were unable to evaluate the impact of this phenomenon.

There are some unique aspects of pediatric ARDS which this group has attempted to address by consensus opinion. First, the authors hypothesized that risk factors for ARDS in children are different than those in adults and created a ranked list based upon perceived importance and prevalence. This is interesting methodology and begs further validation. It would have been helpful had the authors specifically evaluated the incidence and significance of each of these perceived risk factors on both diagnosis and mortality.

The age limits in this evaluation are also important. The authors presumably excluded children aged <30 days to avoid lung disease related to prematurity or birth events. The upper limit of age for inclusion in the study limits the evaluation to mostly infants, and presumably there are further differences in lung maturation, development, risk factors, and outcomes for toddlers, young children and adolescents [13]. Given the stated intent, however, it was reasonable to focus on this population for this study. Future investigation into potential differences in the pathobiology of ARDS as a function of age, and whether definitions should be modified for age, is warranted.

As in the initial Berlin evaluation, the authors of this study evaluated whether corrected minute ventilation (VE_{corr}), a surrogate for dead space, further discriminated the risk of mortality. They came to the conclusion that this parameter was of limited value. Pediatric data suggest that a measure of dead space improves risk stratification when added to degree of hypoxemia in pediatric ARDS [14]. VE_{corr} may be an even more imprecise surrogate for dead space in children than in adults because of the need to correct for differences in body weight and because minute ventilation measurements can be inaccurate with air leak around uncuffed endotracheal tubes [15].

The investigators also confirmed variability in the interpretation of bilateral infiltrates on chest radiograph [16]. Just how necessary bilateral infiltrates are in the definition of ARDS is controversial. Theoretically, bilateral infiltrates are meant to distinguish lobar processes such as pneumonia from the diffuse injury seen in ARDS. Chest radiographs, however, demonstrate only modest sensitivity and specificity to detect areas of inflammation or infiltrate compared to the computed tomography scan, lung ultrasound or metabolic scans [17–20]. Moreover, there are conflicting data on whether the presence or absence of bilateral infiltrates on chest X-ray adds any prognostic value after controlling for the degree of hypoxemia [21–24]. In future iterations of the definition, perhaps the pathophysiology of ARDS can be adequately captured without chest X-ray criterion; given the high variability in radiograph interpretation, this may improve disease recognition.

We are ultimately left with the question of whether the Berlin Definition helps us take better care of or learn more about children with ARDS. In Table 1 we summarize specific pediatric issues related to the ARDS definition. The investigators of the ESPNIC study have identified that the severe ARDS group in their cohort has 25 % mortality. The goal of stratification in ARDS is to identify patients whose risk benefit profile of certain interventions may be similar. For example, patients with severe disease may benefit from higher levels of PEEP than those with milder disease. While the Berlin Definition may provide a framework for future investigations and standardize definitions of disease severity, the known or suspected pathophysiologic interaction of the intervention and disease severity must ultimately guide interventions. It is likely that factors other than the severity of hypoxemia contribute to these individual risk benefit profiles.

The definition of ARDS may benefit from additional markers, including more precise measures of dead space, surrogates of intrapulmonary shunt less subject to variability in ventilator management (such as oxygenation index) or more specific measures of lung inflammation. Future work in both adults and pediatrics should evaluate the feasibility, reliability and validity impact of these and other markers.

The Berlin Definition may be an iterative improvement over the AECC definition, and this pediatric-specific evaluation is definitely welcome. While we can start with consensus, we need further pediatric-specific investigations to refine the definition to be most representative of the pathophysiology of pediatric ARDS, yet sufficiently pragmatic to be applied to children cared for in hospitals and intensive care units across the world [5].

Table 1 Pediatric considerations with the acute respiratory distress syndrome definition

Concept	Berlin definition	Pediatric considerations
Timing	Within 7 days of known clinical insult	Pediatric data consistent; most develop ARDS within 3 days
Risk factors	Defined, when not present rule out hydrostatic edema	Risk factors may be similar, but epidemiology of risk factors likely different
Chest imaging	Bilateral infiltrates, sample radiographs to decrease variability	Insufficient evidence regarding type and adequacy of common training to reduce variability Unclear if bilateral infiltrates needed to define disease given poor sensitivity, specificity, and uncertain prognostic relevance
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload	Similarly need to allow co-existence of ARDS and cardiac failure, although epidemiology of cardiac failure different
Oxygenation	Minimum PEEP of 5 cmH_2O Mild, moderate, severe based on PF ratio	Fewer arterial catheters, so may need SpO_2 based criteria as well Less and more variable use of PEEP, so minimum of five may be inadequate
Dead space	VE_{corr} considered for severe group, excluded because not helpful over hypoxemia	VE_{corr} subject to more bias in children because of endotracheal tube leaks and the need to correct for body weight Capnograph- based markers of dead space have prognostic relevance over hypoxemia
Age	Not addressed	May need age specific breakpoints given different epidemiology, lung maturation and possible pathophysiology of ARDS across childhood
Cyanotic heart disease	Not addressed	Need considerations to define ARDS in children with known intracardiac shunt
Chronic lung disease/ mechanical ventilation	Not addressed	Need considerations to define acute disease with significant pre-existing chronic disease

ARDS acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure, *PF* ratio PaO_2/FiO_2, VE_{corr} corrected minute ventilation, SpO_2 pulse oximeter oxygen saturation

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