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Are we ready to accept the Berlin Definition of ARDS for use in Children?

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In this issue of Critical Care Medicine [1], members of the Brazilian Pediatric ARDS Study Group present a prospective validation of the Berlin Definition of ARDS [2] using an observational cohort from eight pediatric intensive care units in Brazil. Much like a previous validation of the Berlin Definition for younger children [3], the authors found that stratification into mild, moderate and severe categories of ARDS based on PF ratio better classified mortality than the AECC classification, and, like the previous pediatric validation, mortality did not differ between mild and moderate ARDS, but the severe group had significantly higher mortality. This validation is important for clinical care and research as it provides pediatric specific data regarding the performance of the Berlin Definition. However, it is important to consider this validation in the context of the broader picture of pediatric ARDS, and whether ultimately the Berlin Definition is the most appropriate definition to use for pediatric ARDS [4, 5]. The methodology and choices made by the investigators in this study highlight important ambiguities and practice pattern differences between adult and pediatric providers, which may have large implications for diagnosing pediatric ARDS.

First, the authors chose in this validation to select the worst PF ratio the patient attained at any point during their ICU stay to stratify risk. This is a salient, and often overlooked issue with regards to ARDS severity stratification. The main goal of different risk severity groups in the Berlin Definition surrounds potential risk benefit profiles of therapeutic interventions. Therefore, the “timing” of when ARDS severity is assessed becomes crucial. A PF ratio of < 100 several days into the course of mechanical ventilation may have substantially different implications than a PF ratio < 100 within the first 24 hours of ventilation [6-9]. The PF ratio several days into the course of mechanical ventilation, or several days after the initial diagnosis of ARDS, may be a marker of adequacy (or inadequacy) of response to therapy,

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and variability in ventilator management. Given the multi-center nature of this cohort study, and the lack of completely standardized approaches to ventilator management (including PEEP, FiO₂, Recruitment Maneuvers), it becomes even more crucial to use early values of PF ratio (i.e. within the first 24 hours of ventilation) to stratify risk. These issues will not be unique to these 8 centers; there is significant variability in ventilator or other management across pediatric centers, which may directly influence the PF ratio, particularly several days into the course of ventilation [10, 11]. Some of these issues can be overcome by using a measure of hypoxemia less subject to variability in practice, such as oxygenation index (OI), to stratify risk [12]. To that end, a pediatric specific definition of ARDS has been proposed by the Pediatric Acute Lung Injury Consensus Conference [13], in which OI is used as the primary metric for ARDS diagnosis and risk stratification for mechanically ventilated children. Moreover, PALICC recommends that epidemiologic studies report the performance of this risk stratification method using data from the first 24 hours of ARDS diagnosis, to minimize the potential effect of practice pattern variability [13]. Ultimately, a later measure of hypoxemia (beyond the first day) may be important for therapies considered for patients who are not “initial responders,” and this study highlights that hypoxemia severity beyond the first day of ARDS diagnosis has important prognostic implications.

A second important issue surrounds practice patterns with regards to arterial blood gasses. In this study, daily arterial blood gas (ABG) measurement was routine for all mechanically ventilated patients in these 8 intensive care units. However, pediatric and adult data suggest that the increased use of noninvasive mechanical ventilation in and outside of ICUs in combination with infrequent ABG sampling results in under recognition of ARDS in children and adults [11, 14-17]. Although routine, daily ABG sampling in this study helps to avoid this problem, the ABG data is acquired at discrete, arbitrary time points that may not reflect the condition of the patient throughout the day. Second, some centers reserve ABGs or arterial catheters for patients with significant hemodynamic compromise, rather than simply hypoxemia [18]. Therefore, there is an inherent selection bias regarding ABGs for ARDS diagnosis which may be related to disease severity or may not reflect the condition of the patient throughout the day. This may, in part, explain the lower number of patients identified with mild or moderate hypoxemia, and the minimal differences in risk of mortality between those with mild or moderate hypoxemia, as these deaths may be from cardiovascular causes. However, for generalizability it becomes imperative that the diagnosis of ARDS not be dependent on clinician behavior regarding a procedure (such as an ABG). For this reason, PALICC recommendations for diagnosis of ARDS allow for pulse-oximetry based criteria (Oxygen Saturation Index (OSI) and SpO₂/FiO₂ (SF) Ratio) to be substituted when an ABG is not available [13].

Third, the study investigators should be applauded on their attempt to standardize interpretation of bilateral infiltrates on chest radiograph for the purposes of this study. It appears as if their common training exercise between the study investigators and a radiologist resulted in good agreement regarding the presence of pulmonary edema and bilateral infiltrates. This is one of the first pediatric studies to demonstrate that such a method could result in similar, reproducible interpretation of bilateral infiltrates [3, 19].

However, it is still unclear just how necessary bilateral infiltrates are in the definition of ARDS. While bilateral infiltrates are meant to distinguish lobar processes like pneumonia from the diffuse injury seen in ARDS, chest radiographs demonstrate only modest sensitivity and specificity to detect areas of inflammation or infiltrate [20] [21-24]. Moreover, there are conflicting data whether presence or absence of bilateral infiltrates on CXR adds any prognostic value after controlling for the degree of hypoxemia [7, 25-29]. For this reason, the PALICC recommendations for diagnosis of ARDS have simplified radiographic criteria to patients with pulmonary parenchymal disease, in an attempt to improve disease recognition. However, PALICC continues to recommend tracking bilateral infiltrates, to determine the relevance on outcome [13]. If bilateral infiltrates are important for the definition, we must determine optimal methods for standardization of interpretation, which can be used both for clinical care and research. It is possible we can learn from the investigators of this study, to mimic their methodology and apply it on a broader scale.

Finally, this manuscript highlights the potential differences and ambiguities in “lung protective” ventilator settings and modes of ventilation between adult and pediatric practice. As highlighted in this study, pressure control (PC) and pressure regulated volume control (PRVC) modes of ventilation are used much more commonly in pediatrics [11, 30]. Adult data regarding settings to minimize VILI are based on the square wave flow pattern of volume control ventilation, rather than the decelerating flow of PC or PRVC [31]. Hence extrapolation of tidal volume (which is frequently the response variable) targets become difficult, particularly with a lack of pediatric data to support that tidal volume has a significant association with mortality when decelerating flow patterns are used [32]. Driving pressure may be the more relevant metric for pediatric ARDS, but there is paucity of data in pediatrics to suggest what these pressure targets should be. To that end, the concept of plateau pressure (as compared to peak pressure) has less meaning with the decelerating flow patterns of PC or PRVC, and it is unclear whether the inspiratory hold maneuvers to measure plateau pressure are done universally across institutions. The same issues are highlighted with compliance measurements, where variability in methods of assessment of tidal volume (location of measurement, circuit compensation, predicted versus actual body weight), as well as which pressure is used (peak versus plateau) influence the reproducibility and generalizability of compliance measurements in studies [33]. To this end, the PALICC group has recommended future research into reproducible and reliable methods to report compliance, tidal volume, and pressure in clinical studies, to enable direct comparison [13].

Ultimately, the authors should be applauded for providing this first pediatric specific prospective validation of the Berlin Definition, highlighting the potential for successful application of pieces of the Berlin Definition to pediatric ARDS. However, pediatric specific practice patterns and the pathophysiology of pediatric ARDS warrant a pediatric specific definition of ARDS, which can be applied universally for children taken care of across the world [13].

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