The Challenges of Identifying an Oxygenation Index Threshold for Increased Mortality in Pediatric Acute Respiratory Failure

The Pediatric Acute Lung Injury Consensus Conference (PALICC) recognizes oxygenation index (OI), a measure of oxygenation based on level of respiratory support, as the primary metric of lung disease severity in defining pediatric ARDS.¹ Traditionally, OI has been used to guide escalation of respiratory support to high-frequency ventilation (OI > 20) and extracorporeal membrane oxygenation (OI > 40).^{2,3} In this issue of *RESPIRATORY CARE*, Hammond et al⁴ report a retrospective, single-center study evaluating the association between mortality and maximum OI during mechanical ventilation among subjects 1 month to 20 y of age who were mechanically ventilated for > 24 h. The authors identify mortality of 6–7% among those with maximum OI ≤ 17 compared with 18% among those with a maximum OI > 17.

Consistent with recent literature, Hammond et al⁴ challenge historic OI cut points used for escalation of respiratory support or initiation of extracorporeal support.^{5,6} A 2015 analysis of 397 mechanically ventilated children with acute lung injury identified a near doubling in mortality for each step up: OI < 4 (at risk for pediatric ARDS), 4–8 (mild pediatric ARDS), 8–16 (moderate pediatric ARDS), and > 16 (severe pediatric ARDS).¹ Although data aggregated from 6 other studies reveal a stepwise increase in mortality with pediatric ARDS classifications, OI demonstrates poor sensitivity for prospective mortality predictions.^{1,7} In an analysis of 511 subjects with pediatric ARDS, a peak OI > 16 in the first 3 d of mechanical ventilation predicted mortality in only 40% of subjects.¹

Several potential reasons for the poor predictive ability of OI for mortality among children with pediatric ARDS exist, many of which are well demonstrated in the report by Hammond et al.⁴ First, we must acknowledge the presence of competing risks, or events that preclude the occurrence of the primary event of interest.⁸ For example, critically ill children are at risk of death from a variety of causes, including death from brain injury, but a child who dies from brain injury has no chance of later death due to respiratory failure nor any chance of surviving respiratory

failure. According to Table 1 in Hammond et al,⁴ no non-survivors had a primary diagnosis of acute respiratory failure; however, brain injury was either the primary or secondary diagnosis in all 6 non-survivors. Typically, a child

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who dies from brain injury has a lower maximum OI than a child who dies from respiratory failure.^{9,10} Consequently, deaths from brain injury lower the OI associated with mortality, although advanced respiratory support or extracorporeal membrane oxygenation would not have saved such patients. Statistically, this problem can be solved by stratifying the analysis: excluding all children with a non-respiratory diagnosis or a non-respiratory cause of death and evaluating OI versus death from respiratory failure alone. The limited sample size in Hammond et al⁴ prevents such stratification and broader subsequent conclusions about the OI threshold for mortality.

Second, there is good evidence to suggest that a patient's trajectory early in the course of illness may predict outcome, potentially accounting for a patient's response, or lack thereof, to interventions.^{7,11,12} Although Hammond et al⁴ account for this fact by limiting their included population to those mechanically ventilated for > 24 h, mixed models and other statistical methods that accommodate multiple measures over time may improve the predictive capabilities of OI while slightly diminishing the issue of limited sample size.

Third, confounders of the relationship between OI and mortality among children with pediatric ARDS can lead to poor sensitivity of OI for mortality predictions. Several studies report an increased risk of mortality in infants < 1 y of age^{1,13} and in African American and Hispanic patients.^{14,15} Other potential confounders include a primary diagnosis of non-pulmonary sepsis, immunodeficiency, and multi-organ system failure.^{6,15,16} Immunodeficiency in pediatric ARDS is associated with a mortality of up to 95% for those with a history of bone marrow transplantation or hematologic malignancy,^{17–19} and mortality increases by almost 60% with 3 organ failures compared with a single organ failure in children with pediatric ARDS.²⁰ Hammond et al⁴ used traditional multivariable logistic regression to account for the potential confounding bias of days of mechanical ventilation, length of hospital stay, and subject age. However, in traditional logistic regression, accuracy and pre-

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cision of regression coefficients decrease with < 10 outcomes per variable.²¹ Hammond et al⁴ reported only 6 outcomes (subject deaths). In addition to the high likelihood of unmeasured confounders, this limited number of outcomes prevents us from relying on the results of the regression, particularly as they relate to effecting clinical practice change.

We are fortunate to have low mortality rates in pediatrics, ranging from 2 to 3% nationwide in the ICU.²² Undoubtedly, Hammond et al⁴ have taken on an arduous and extremely important task of identifying the point at which escalation of therapy may save additional lives to further decrease mortality in pediatric acute respiratory failure. Although challenges exist in developing large sample sizes, we should remember when conducting analyses of pediatric mortality that there is strength in numbers. Collaboration among centers to obtain adequate sample sizes for prospective and retrospective studies will improve latitude and clinical utility of studies in pediatric critical care medicine. Further, robust statistical analysis of samples both large and small serves to enhance study validity and applicability.

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