Equipoise and Acumen in Pediatric Acute Respiratory Distress Syndrome Research

Severe lung injury in children manifests as pediatric acute respiratory distress syndrome (PARDS) and is associated with a mortality of up to 35% (1). Management in the pediatric ICU is based on supportive care and prevention of secondary ventilator-induced lung injury (2–4). Studies in adult patients have reported additional benefit from adjunctive therapies, including the early use of continuous neuromuscular blockade and prone positioning (5, 6). Other adult studies investigated alternative modes of support, including extracorporeal membrane oxygenation (ECMO) and high-frequency oscillatory ventilation (HFOV), finding equivocal benefits and potential harm, respectively (7–10). Unfortunately, studies in PARDS have not demonstrated a benefit from continuous neuromuscular blockade or prone positioning similar to that observed in adults, and neither HFOV nor ECMO has been shown to confer an advantage over conventional therapy (11–14). In fact, pediatric ICU physicians are bereft of proven therapies or management strategies to turn to for patients who cannot be supported with conventional mechanical ventilation. As such, there is an urgent need for additional well-designed clinical trials for the management of PARDS.

In this issue of the *Journal*, Rowan and colleagues (pp. 1389–1397) present their substudy of a prospective, international, cross-sectional observational study from 100 centers treating children with PARDS (15). They investigated the use of six adjunctive therapies during the first 72 hours of illness: continuous neuromuscular blockade, corticosteroids, inhaled nitric oxide, prone positioning, HFOV, and ECMO. Their aim was to gather contemporary data on the early use of these therapies to facilitate future investigations. Unbiased randomized controlled trials require clinical equipoise. By capturing the early management of PARDS in centers across the world, the authors provide future investigators insight into international and regional practices. In aggregate, there appears to be equipoise about the use of adjunctive therapies: 55% of the centers did not use any of the six therapies studied within the first 72 hours, and the rest used between one and five.

Absent evidence-based guidelines, clinicians are likely to deploy adjunctive therapies as disease severity increases, particularly because there is an underlying pathophysiologic rationale for this approach. In fact, the investigators found a positive correlation between the use of these therapies and the oxygenation index. In severe PARDS, patients may receive mechanical ventilation for several weeks (13). Thus, although an understanding of the early management of PARDS is important, it would also be valuable to know what therapies were added over the entire treatment course in this study. Indeed, data are lacking to guide a determination of whether a given approach is a success or failure. For example, patients placed on ECMO are often first placed on HFOV, and many will initiate ECMO later in the disease course (beyond the first 3 d of illness) (13). But there is no evidence to guide decisions regarding the transition from conventional ventilation to HFOV or ECMO. Instead, clinicians determine on an individual basis when a given approach has failed, and adjunctive therapies often represent rescue efforts.

Fundamentally, the goal of support in critical care medicine is to maintain adequate oxygen delivery and end-organ function. Clinical signs of end-organ dysfunction or other markers of inadequate oxygen delivery likely contribute to clinicians' decisions to add adjunctive therapies or to change modes of support in the case of severe PARDS that is not responding to conventional therapy. However, few studies are designed in a manner aimed at informing these decisions. The NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network conducted an important study evaluating management guided by a pulmonary artery catheter, with serial determinations of cardiac index and pulmonary artery occlusion pressure, compared with standard therapy using central venous pressures (16). They found that pulmonary artery catheter–guided therapy did not improve outcomes and was associated with more complications. However, the protocolized management did not incorporate lactate levels, the rate of oxygen delivery, or mixed venous and superior vena cava oxygen saturations. Furthermore, none of these data were used to determine treatment failure that would result in initiation of an adjunctive therapy or the transition to an alternate form of support.

Crossover studies are designed to help account for these problems. Although well-conducted studies should help answer questions related to sequencing of the therapies being studied, protocols to determine the failure of one arm and the timing of transition to another are based on the expert opinion of the individuals designing the trials. For example, in a study comparing early ECMO with conventional ventilation, Combes and colleagues allowed control patients to transition to ECMO if they developed refractory hypoxia, defined as Sa_{O_2} <80 persisting for ⩾6 hours (7), whereas the study protocol for the ongoing PROSpect (Prone and Oscillation Pediatric Clinical Trial; ClinicalTrials.gov Identifier: NCT03896763) trial defines failure of conventional ventilation as Sa_{O_2} <85 persisting for ⩾4 hours. Although both of these definitions are clinically sound, there is no doubt that the ramifications of these parameters for individual patients in terms of the adequacy of oxygen delivery and end-organ function would be quite variable.

Novel approaches to the management of PARDS are needed to further reduce mortality. It is remarkable that the landmark trial that demonstrated a survival benefit with low V_T ventilation in adults was published two decades ago and yet remains the cornerstone of pediatric management. Rowan and colleagues have contributed to

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this effort by determining the initial approach that clinicians take to manage PARDS around the world. We must seek to better understand these clinicians' decision-making process, as surely there are important lessons that can be derived from their collective bedside acumen. Perhaps the next leap forward will come from innovative study designs that capture the impact of PARDS on the adequacy of individual patients' oxygen delivery and utilization, and the ability of existing and future therapies to mitigate these effects. ■

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Disease Phenotyping of Infants with Severe Bronchopulmonary Dysplasia

The most common complication of preterm birth is bronchopulmonary dysplasia (BPD) (1), widely referred to as the chronic lung disease of prematurity. This disease was first described over 50 years ago in moderately preterm infants (~34-wk gestation). At the time, the most cutting-edge therapies were supplemental oxygen and nascent mechanical ventilation techniques used to treat respiratory distress syndrome—for which the mortality rate was >50% (2). Since this initial report by Northway and colleagues in 1967 (2), extensive efforts by basic and translational researchers have dramatically changed the BPD landscape. Today, as we enter the sixth decade since the initial BPD description, over 90% of preterm infants survive their neonatal ICU course with the use of antenatal corticosteroids, improved delivery room

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