Editorial

Disappointing results: a call to action

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We read with a great deal of enthusiasm and interest the recent article by Doyle *et al.* entitled "Ventilation in extremely preterm infants and respiratory function at 8 years of age" recently published in the New England Journal of Medicine (1). This well designed, cohort study examined respiratory outcomes at 8 years of age in children born extremely preterm in 3 different time periods (cohorts): 1991–1992, 1997, and 2005. The authors hypothesized that respiratory outcomes would improve from the earliest time period to the last time period, with less oxygen dependence at 36 weeks post-menstrual age (PMA) and improved lung function at 8 years of age. The authors examined supplemental oxygen dependence at 36 weeks PMA, because in extremely preterm infants it is often used to define bronchopulmonary dysplasia or BPD (2). Much to the disappointment of nearly the entire field of neonatology, the authors found no improvement over time in respiratory outcomes despite an increase in the use of nasal continuous positive airway pressure (nCPAP) and a decrease in the use of invasive positive-pressure ventilation (IPPV) in extremely preterm infants. These results in the clinical setting are disappointing for the field of neonatology because based on previous randomized controlled trials (RCTs) we have long assumed that in the neonatal intensive care unit (NICU) setting that minimizing exposure to IPPV by increasing the use of nCPAP leads to lower rates of respiratory morbidities following extremely preterm birth (3). The authors should be commended on a well-designed study in a defined regional setting with standardized approaches to the clinical care of the extremely preterm infants. Furthermore, the study had an enviable follow-up rate at 8 years of age. The limitations of the study were well documented by the authors and included that some children were unable to undergo lung function testing at 8 years of age due to disabilities, that the results may not be widely applicable outside of their region in Australia, and that data on hospitalizations or need for respiratory medications were not available on all of the patients. Although the results from this cohort study should not be used to change current practice, it is extremely thought provoking for practitioners that care for these highly vulnerable patients.

Perhaps the first thing to consider is just what constitutes a poor respiratory outcome following extremely preterm birth? For most practitioners a poor respiratory outcome is defined as the development of BPD. BPD was described by Northway and colleagues in 1967 (4) and is diagnosed during the stay in the NICU. The diagnosis is based on the definition of BPD, which has varied since it was first described and the most frequently used definition of BPD currently is a requirement for supplemental oxygen at 36 weeks PMA in infants born at less than 32 weeks gestation. Unfortunately, using a therapy-based definition that is not specific to the disease (i.e., there are other indications for supplemental oxygen use in neonates besides BPD) may result in the inclusion of disease states that are not related to the abnormal lung development following preterm birth that underlies BPD. Furthermore, there is no currently accepted standard in neonatology for the optimal target range of oxygen saturation as measured by pulse oximetry (SpO_2). Thus the clinical use of supplemental oxygen in the NICU setting including the dose given varies from center to

center and even from practitioner to practitioner within the same center (5). Another potential issue related to changes over time, which Doyle and colleagues (1) point out, is that continuous SpO_2 monitoring is now the standard of care in most NICUs and that was not always the case in the 1990s. The authors suggested that with closer monitoring of continuous SpO_2, oxygen administration may be more aggressive, leading to higher rates of supplemental oxygen use at 36 weeks PMA. Additionally, the authors emphasize the critical point that for patients breathing room air, the fraction of inspired oxygen (FiO_2) can only be turned up, leading to a potential bias towards treatment. Thus, the definition and therefore the incidence of BPD potentially vary from center to center, as well as from epoch to epoch. Furthermore, the current definitions of BPD are all short-term definitions (i.e., while the patients are hospitalized in the NICU) and do not take into account the likely far more relevant long-term respiratory outcomes (6). Finally, we know that even preterm infants who did not receive the diagnosis of BPD may have abnormal respiratory outcomes later in life (7). We are concerned, therefore, that efforts to "prevent BPD" are doomed to failure when applied to clinical care in the absence of: (I) an accurate, reliable definition of BPD; (II) a consensus standard for target SpO_2; and (III) an acknowledgement that extreme preterm birth itself, even in the absence of a diagnosis of BPD, is associated with long-term respiratory morbidities.

There continues to be accepted and marked variations in our approach to the extremely preterm infant, which result in marked variation in outcomes (8,9). The clinical approach to respiratory management in extremely preterm infants is also highly variable (10). Similar to Doyle and colleagues (1), the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development recently reported that the incidence of BPD has increased in extremely preterm infants despite an increase in the percent of infants never treated with IPPV (11). Compared to our adult counterparts, extreme preterm birth and BPD are rare, and therefore multi-center trials are required to have adequate numbers enrolled. But since the approach to care varies from center-to-center, and even provider-to-provider, why then do we continue to expect that one intervention studied in a multi-center RCT will be able to demonstrate prevention of an ill-defined disease when adopted into clinical use? That is to say, given a complete lack of standardized protocols and guidelines, our field's highly varied approach to care will likely confound any outcome of even the best designed RCTs when adapted for clinical care. Furthermore, it is also difficult to design clinically relevant RCTs in neonatology due to our widely variable approach to clinical care. When we bring together multiple centers in the design stages of an RCT, given the lack of standardization of care, we often sacrifice stringent protocols in an effort to keep all centers involved in the study. This softening of protocols is felt to be necessary to assemble enough subjects to create a well powered study for statistical analysis. An example of such protocol softening that would be expected to confound results might be allowing "clinical care" to dictate extubation readiness in an RCT studying the effects of post-natal steroids on time to extubation. In this example, it would be easier to have many centers agree to participate and thereby have adequate numbers of subjects for statistical analysis, but any specific results likely would be impacted by center bias. Therefore to prevent BPD, we need to follow the many examples in adult medicine and pediatric oncology and develop evidenced-based, standardized approaches to the extremely preterm infant that will minimize inter-center and inter-provider variability. Such a standardized approach to the extremely preterm infant would not only improve our ability to perform meaningful RCTs but it would also facilitate the successful incorporation of RCT results into routine clinical practice. Thereby, significantly increasing the likelihood that result of RCTs will be translated into routine clinical care and successfully impact outcomes of all NICU patients.

Unfortunately, even in the age of "big data", the field of neonatology doesn't widely share outcomes data in a transparent manner. As an example of complete and transparent data sharing, center A reports a BPD rate among extremely preterm infants of 20%, while center B reports a rate of BPD of 60%. Center A then touts their "success" in preventing BPD in a mailer to practicing neonatologists. We read the mailer with interest and remember that the more preterm a patient is born the higher the chances of developing BPD. We then discover that center A does not resuscitate 22- and 23-week gestation infants while center B routinely resuscitates all 22- and 23-week gestation infants. Thus, to effectively compare center A and center B we would need to look at BPD rates only for children born at 24 weeks gestation or greater. Furthermore, transparent data sharing would allow for rational comparative effectiveness research that could speed the rate of discovery for therapies aimed at BPD and/or long-term adverse pulmonary outcomes.

The article by Doyle and colleagues (1) should also make us consider how we adopt new therapies within

neonatology. Often well designed and powered RCTs are unavailable, due at least in large part to the relative rarity of extreme preterm birth. Because of limited numbers of patients and the time (many additional years) needed to get relevant long-term outcomes, the outcomes studied are those that are relatively easily and quickly measurable, i.e., days on IPPV, rates of BPD, length of stay, etc. Thus, in neonatology we are prone to adapting new therapies based on physiology or ease of application without well powered RCTs demonstrating long-term benefit. Doyle and colleagues (1) point out that recent RCTs related to newer modes of non-invasive ventilation usually show no benefit if the primary outcome is longer term respiratory morbidity, even if the short-term outcomes are improved. Schreiber and Marks (12) in a commentary on the article by Doyle *et al.* (1) emphasized that neonatology should not be in a rush to embrace newer, non-invasive approaches to respiratory support based on our belief that less is more.

The study by Doyle and colleagues (1) is a well-designed cohort study demonstrating in routine clinical care (i.e., outside of an RCT), that even though nCPAP use increased over time both the rate of BPD and the rate of abnormal pulmonary function at 8 years increased as well. This finding was contrary to the author's original hypothesis and quite surprising. Although this represents another disappointing result for the field of neonatology, this clinically relevant result should be viewed as a call to action: first to standardize care based on diagnosis and not location, and second to widely and transparently share data on outcomes and treatments. Once these have been done, only then can we develop clinically relevant RCTs that will optimize our ability to truly test novel approaches and therapies to prevent BPD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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References

1. Doyle LW, Carse E, Adams AM, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. N Engl J Med 2017;377:329-37.
2. Walsh MC, Wilson-Costello D, Zadell A, et al. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol 2003;23:451-6.
3. Owen LS, Manley B, Bhandari V, et al. Noninvasive ventilation for the prevention of bronchopulmonary dysplasia. In: Bhandari V. editor. Bronchopulmonary Dysplasia. Switzerland: Springer International Publishing, 2016:199-222.
4. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 1967;276:357-68.
5. Askie LM, Darlow BA, Davis PG, et al. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. Cochrane Database Syst Rev 2017;4:CD011190.
6. Isayama T, Lee SK, Yang J, et al. Revisiting the Definition of Bronchopulmonary Dysplasia: Effect of Changing Panoply of Respiratory Support for Preterm Neonates. JAMA Pediatr 2017;171:271-9.
7. Clemm HH, Engeseth M, Vollsaeter M, et al. Bronchial hyper-responsiveness after preterm birth. Paediatr Respir Rev 2017. [Epub ahead of print].
8. Helenius K, Sjörs G, Shah PS, et al. Survival in very preterm infants: an international comparison of 10 national neonatal networks. Pediatrics 2017;140.pii: e20171264.
9. Alleman BW, Bell EF, Li L, et al. Individual and center-level factors affecting mortality among extremely low birth weight infants. Pediatrics 2013;132:e175-84.
10. Parat S, Mhanna MJ. Respiratory management of extremely low birth weight infants: survey of neonatal specialists. World J Pediatr 2016;12:314-9.
11. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
12. Schreiber MD, Marks JD. Noninvasive ventilation in the premature newborn – is less always more? N Engl J Med 2017;377:386-8.

