Walter and Reyfman that because our bulk approach did not capture the relative contributions that specific AM subtypes made to the overall transcriptional signal, our ability to detect differentially expressed genes may have been weakened. Despite this limitation, our bulk transcriptomic approach has advanced our understanding of AM function in ARDS by identifying AM-specific genetic programs that were associated with good versus poor outcomes. Future work is needed to identify the AM subtypes that might be responsible for the bulk transcriptional signatures we identified in our clinical cohort.

We believe that “lumping” and “splitting” approaches are complementary in furthering our understanding of the pathobiology of syndromes such as ARDS and sepsis. Analytical approaches such as cellular deconvolution (7) may be able to bridge bulk transcriptomic datasets and clinical cohorts like ours with highly granular single-cell datasets to fully leverage the strengths of both lumping and splitting approaches to understand the mechanisms of complex human syndromes.

References

1. Morrell ED, Bhatraju PK, Mikacenic CR, Radella II F, Manicone AM, Stapleton RD, et al. Alveolar macrophage transcriptional programs are associated with outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med 2019;200:732–741.
2. Morrell ED, Wiedeman A, Long SA, Gharib SA, West TE, Skerrett SJ, et al. Cytometry TOF identifies alveolar macrophage subtypes in acute respiratory distress syndrome. JCI Insight 2018;3:99281.
3. Mould KJ, Jackson ND, Henson PM, Seibold M, Janssen WJ. Single cell RNA sequencing identifies unique inflammatory airspace macrophage subsets. JCI Insight 2019;4:126556.
4. Riemondy KA, Jansing NL, Jiang P, Redente EF, Gillen AE, Fu R, et al. Single cell RNA sequencing identifies TGFβ as a key regenerative cue following LPS-induced lung injury. JCI Insight 2019;5:123637.
5. Kiselev VY, Andrews TS, Hemberg M. Challenges in unsupervised clustering of single-cell RNA-seq data. Nat Rev Genet 2019;20:273–282.
6. Ziegenhain C, Vieth B, Parekh S, Reinius B, Guillaume-Adkins A, Smets M, et al. Comparative analysis of single-cell RNA sequencing methods. Mol Cell 2017;65:631–643, e4.
7. Wang X, Park J, Susztak K, Zhang NR, Li M. Bulk tissue cell type deconvolution with multi-subject single-cell expression reference. Nat Commun 2019;10:380.

Copyright © 2019 by the American Thoracic Society

Diagnostic Classification of Bronchopulmonary Dysplasia: A Compromise between Defining Lung Disease versus Long-Term Outcome Prediction

To the Editor:

There are important limitations to current bronchopulmonary dysplasia (BPD) definitions, and many groups are working to come up with diagnostic criteria that are better adapted to current clinical presentation and treatment modalities and can also predict long-term outcomes.

Jensen and colleagues analyzed data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network to explore 18 different combinations of respiratory support and identify the definition that best predicts death or poor long-term respiratory and neurological outcomes (1). The authors concluded that a definition that includes nasal cannula flow, nasal continuous positive airway pressure, and mechanical ventilation at 36 weeks corrected age offers the best prediction for these composite outcomes. Surprisingly, many of the combinations of respiratory support tested in this study showed very similar accuracy for predicting long-term outcomes.

Although the proposed definition is appealing because of its simplicity and ability to predict outcomes and was validated in a large, multicenter population, it may not accurately reflect the severity of lung disease. This analysis assumes that the use of respiratory support in preterm infants is driven mainly by parenchymal lung disease. In reality, the use of respiratory support in this population can be related to many different respiratory and nonrespiratory problems, and indications for such support are subjective and vary considerably among institutions. Therefore, many patients may be inappropriately labeled as having BPD when in fact they are receiving respiratory support for indications other than lung disease.

More surprisingly, and in contrast to previous evidence (2–4), the authors concluded that inspired oxygen administered at 36 weeks postmenstrual age did not add strength to the prediction models. Oxygen administration may vary among centers, but in most instances, oxygen is titrated to maintain a narrow range of SaO₂. In the absence of extrapulmonary shunts, inspired oxygen is the simplest and most sensitive single indicator of the severity of
respiratory failure and parenchymal lung disease. Few clinicians would question the fact that an infant who requires 50% oxygen has worse lung function than one who is receiving 25% oxygen to maintain normal arterial oxygenation. Before concluding that the need for oxygen at 36 weeks postmenstrual age is not informative about the severity of lung disease or long-term morbidities, we need to thoroughly evaluate the association between different fractions of inspired oxygen and long-term respiratory or neurologic outcomes while adjusting for other confounding factors.

Another limitation of the proposed definition is that it is based on a one-time assessment. In this situation, a preterm infant who exhibits acute respiratory deterioration at approximately 36 weeks and needs mechanical ventilation would be labeled as having severe BPD even if his or her lungs were normal. This limitation can be easily avoided by including an indicator of the chronicity of the parenchymal lung disease. Although the proposed definition may work in a large population base and predict long-term outcomes, it will not always reflect the severity of lung disease and therefore will not be appropriate for research or benchmarking focused on pulmonary outcomes.

Although most clinicians would agree that more contemporary definitions of BPD are necessary, these definitions must be based on the premise that BPD is secondary to chronic parenchymal lung disease. Therefore, any definition of BPD, whether based on diagnostic or therapeutic criteria, should reflect the severity of lung disease and exclude nonpulmonary indications for respiratory support. The proposed definition, though marginally better at predicting outcomes, will not consistently meet the challenge of defining BPD.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Eduardo Bancalari, M.D.*
Nelson Claure, Ph.D.
Deepak Jain, M.D.
University of Miami Miller School of Medicine
Miami, Florida

*Corresponding author (e-mail: ebancalari@miami.edu).

References

1. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence-based approach. Am J Respir Crit Care Med 2019; 200:751–759.

2. Ehrenkranz RA, Walsh MC, Vohr BR, Jope AH, Wright LL, Fanaroff AA, et al.; National Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 2005;116:1353–1360.

3. Isayama T, Lee SK, Yang J, Lee D, Daspal S, Dunn M, et al.; Canadian Neonatal Network and Canadian Neonatal Follow-Up Network Investigators. Revisiting the definition of bronchopulmonary dysplasia: effect of changing panoply of respiratory support for preterm neonates. JAMA Pediatr 2017;171:271–279.

4. Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. Thorax 2013;68:760–766.

Copyright © 2019 by the American Thoracic Society

Need for an International Consensus on the Definition of Bronchopulmonary Dysplasia

To the Editor:

The definition and diagnosis of bronchopulmonary dysplasia (BPD) are widely debated topics in neonatology (1). The half-century-long history of different definitions highlights the changing paradigm for managing pulmonary immaturity (2). Jensen and colleagues compared 18 BPD definitions based on levels of supplemental oxygen and respiratory support provided at 36 weeks postmenstrual age (PMA) (3). They reported categorizations of BPD severity that predicted serious respiratory morbidities or mortality at 18–26 months corrected age. This study is a useful addition to the literature; however, it inherently accepts a fundamental misconception that 36 weeks PMA is somehow a “magic” postnatal age when preterm infants are mature enough to be off respiratory support. There is no physiological or clinical basis for using 36 weeks PMA as a cutoff.

The authors assessed various categorizations of BPD severity only at 36 weeks PMA and did not consider other PMA timings because of data limitations. It is well known that BPD at 36 weeks PMA is not a robust marker for predicting long-term outcomes (1). Physiological and developmental considerations have led investigators to suggest using a PMA closer to the expected due date, because even late-preterm and early-term infants of 34–38 weeks gestation have a higher risk of developing respiratory issues than infants of 39–41 weeks gestation (4). Although using a later PMA may increase missed assessments due to transfer of infants to step-down units or discharge home before assessment, obtaining such information from step-down units or families is not impossible. Shennan and colleagues chose 36 weeks PMA as a cutoff for BPD based on a compromise between sensitivity and specificity; however, in the 30 years since their work was published, there have been marked changes in the relevant population (with gestational ages as low as 22 wk), approaches, and technology available to provide respiratory support (both invasive and noninvasive) (5). Thus, applying a cutoff without any physiological basis seems to represent a halt in progress. Moreover, the first 12 BPD definitions assessed by Jensen and colleagues had similar predictive abilities, with a difference in area-under-the-curve values of 0.01. A recent study reported that the ability to predict long-term respiratory morbidities improved as the timing to define or diagnose BPD increased from 36 to 40 weeks PMA, indicating that 40 weeks PMA is the best time for...