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∂ Bronchopulmonary Dysplasia: A Continuum of Lung Disease from the Fetus to the Adult

The definitions of bronchopulmonary dysplasia (BPD), the lung injury that results from high oxygen exposure and mechanical ventilation of preterm infants, which was first described over 50 years ago by Northway and colleagues (1), have evolved to include very premature infants and changing care strategies (2). Each new definition was sequentially viewed as inadequate for the varied needs of epidemiology, clinical care, pathophysiology, and outcome predictions for evaluating new treatments. Dissatisfaction with Shennan and colleagues' 1988 definition of oxygen exposure at 36 weeks gestation and the 2000 NIH workshop definition of a graded severity of disease has resulted in a flurry of reports and editorials seeking to establish an ideal definition of BPD (2–5).

In a study presented in this issue of the *Journal*, Jensen and colleagues (pp. 751–759) used an evidence-based approach to determine which BPD definition best predicts respiratory and neurodevelopmental outcomes at 18–24 months (6). They parsed the elements of the NIH workshop definition and included newer care strategies that confound previous definitions. These elements included low- and high-flow nasal cannulas, levels of invasive respiratory support, and specified periods of oxygen support. They used a contemporary Eunice Kennedy Shriver National Institute of Child Health and Human Development neonatal research network data set of 2,677 infants to test the predictability of 18 definitions for death or serious respiratory morbidity (tracheostomy, initial hospitalization at >50 wk postmenstrual age, oxygen or respiratory support, or two or more respiratory hospitalizations) at follow-up at 18–26 months. The surprising result was that a graded severity of BPD based only on respiratory support at 36 weeks best predicted both respiratory and neurodevelopmental outcomes. This is surprising because oxygen use was the core variable for all previous definitions of BPD. The analysis has merit because of its statistical rigor resulting from the use of a large and relevant patient population. But the claim for the "best" definition with a C-statistic of 0.785 must be tempered by the five next best definitions with C-statistics of 0.784–0.780. The C-statistic for the worst definition was quite high at 0.741. Similarly predictive accuracy for neurodevelopmental impartment ranged narrowly from 0.747 to 0.725.

The cohort established as part of the Prematurity and Respiratory Outcomes Program has also been used to assess a composite measure of respiratory morbidity severity over the first year after very preterm birth with regard to outcome predictions (7). The aggregate of primarily nonpulmonary perinatal associations of male sex, intrauterine growth restriction, maternal smoking, race/ethnicity, intubation at birth, and public insurance was equivalent to BPD for the prediction of 1-year respiratory outcomes. When looked at from 36,000 feet, these attempts to predict outcomes for very preterm infants are all reasonably good, but not much different from each other. There are many pathways to BPD, including perinatal variables and postnatal adverse exposures that range from oxygen use and mechanical ventilation to necrotizing enterocolitis and sepsis. They all contribute to whatever BPD diagnosis one chooses and to adverse outcomes. The oxygen use and ventilatory support elements of a BPD diagnosis are simply linked fellow travelers—both physiologically and statistically.

A further consideration is the more recent realization that the lung injuries that result in BPD are not uniform. A recent report in the *Journal* by Tingay and colleagues (8) demonstrates that even gentle attempts to inflate the very preterm and surfactant-deficient lung cause nonuniform injury. Recent imaging studies using computed tomography or magnetic resonance imaging have demonstrated the extreme variability of parenchymal lung injury. Some infants have primarily emphysema and cysts, whereas others have fibrous interstitial opacities and mosaic lung attenuation or mixtures of abnormalities (9). Severe BPD also includes infants with glottic injury from endotracheal tubes, tracheal and bronchial malacia, control-of-breathing abnormalities, and pulmonary hypertension (10, 11).

A substantial criticism of all these definitions is that the elements of the definitions are simply therapies for BPD (12). In a recent report in the *Journal*, Svedenkrans and colleagues proposed the use of a measurement of gas exchange as a continuous indicator of disease severity (13). Oxygenation status is measured as oxygen saturation versus the oxygen pressure curve. Impaired oxygenation is indicated by a shift of the saturation curve from normal, by ventilation/perfusion, and by calculating shunt. For preterm infants with mild BPD, the complete test requires the use of oxygen concentrations of <21%, but a single measurement with a saturation of 86–95% at a known oxygen concentration may suffice. Of course, this test uses oxygenation only, with no assessment of ventilatory support.

Another criticism of current definitions that assess BPD at 36 weeks gestation is that the infant is still premature. However, Isayama and colleagues (14) demonstrated that an assessment at any week from 36 weeks to 44 weeks showed very similar risks for adverse respiratory or neurodevelopmental outcomes.

In their analysis, Jensen and colleagues point out that respiratory support variables alone are as good (or better) than oxygen variables. Keller and colleagues' report indicates that antenatal variables are also comparable (7). Conceptually, we like the physiologic approach of Svedenkrans and colleagues (13). An optimal research definition might include measurements of oxygenation, CO_2 elimination, and magnetic resonance imaging for the structural abnormalities that contribute to gas exchange abnormalities. For epidemiologic purposes, the definition does not seem to make much difference if it is consistently applied. For therapeutic studies, perhaps the outcome should be linked to the target of the therapy, such as parenchymal inflammation, airway injury, or pulmonary hypertension. ∎

Alan H. Jobe, M.D., Ph.D.
Cincinnati Children's Hospital
University of Cincinnati School of Medicine
Cincinnati, Ohio

Steven H. Abman, M.D.
Deptartment of Pediatrics
University of Colorado Denver Anschutz Medical Center
Aurora, Colorado

ORCID ID: 0000-0003-3632-4114 (A.H.J.).

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⊖ Loss of Microbial Topography Precedes Infection in Infants

Studies demonstrating that breastfeeding protected infants from respiratory infections began in the early 20th century. At the time, it was presumed that this was a result of nutritional

deficiencies in formula (1). In the mid-20th century, it became apparent that breast milk was more than a source of calories, but also a vehicle for the transmission of antibodies, immune cells, and oligosaccharides meant for microbial, rather than infant, nutrition (2). As a consequence, infant formulas now include substances meant to promote a healthy microbiome, yet formula-fed infants are still more susceptible to respiratory infections (3). Despite more than a century of data on the role of breast milk in protection from respiratory infections, we still do not know whether or how maternal antibodies help shape the composition of the upper respiratory tract microbiome, whether breast milk directly promotes the growth of some respiratory microbes over others, or whether protection from respiratory infections is primarily a consequence of immune maturation.