Can We Define Bronchopulmonary Dysplasia?

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The progression from severe respiratory distress syndrome (RDS) to lung injury was carefully described and named bronchopulmonary dysplasia (BPD) by Northway et al 50 years ago in a seminal report.[1] The context for that report was very high mortality of moderately preterm infants from RDS because supplemental oxygen was the only effective therapy available in the late 1960s. Several neonatal services were trying to ventilate infants with RDS with minimal success until Gregory et al described the use of continuous positive airway pressure in 1971.[2] Ventilation strategies then incorporated positive end expiratory pressure and were more successful. Although surfactant deficiency had been identified by Avery and Meade as the primary pathophysiologic abnormality in RDS in 1959, surfactant treatments were not available until 1990.[3] Thus, BPD was described as the adverse survival outcome of the initial attempts to ventilate preterm infants. The sequence from RDS to lung edema and then lung injury characterized by severe airway and parenchymal injury with emphysema and fibrosis was a radiologic and pathologic diagnosis as ascribed to high oxygen exposure and ventilator pressures (in retrospect without positive end expiratory pressure).

Changes in Disease and Diagnosis Over 50 Years

Hines et al recently reviewed the history of the changes in the diagnosis of BPD.[4] In 1967, neonatology was an emerging subspecialty focused on survival for relatively large preterm infants, and with minimal tools to improve outcomes. Most infants who survived ventilation were ventilated for short periods. Tooley defined BPD in 1979 as an infant who had lung radiologic changes and required supplemental oxygen at 30 days of age.[5] In the same year, Bancalari et al refined the diagnosis to require mechanical ventilation for ≥3 days in the first week of life, clinical and radiologic signs of respiratory disease, and an oxygen need for >28 days.[6] Variants of these diagnostic criteria were used for term and preterm ventilated newborns until Shennan et al proposed in 1988 a simple definition for BPD as the use of supplemental oxygen at 36 weeks of postmenstrual age (PMA) for infants with birth weights of <1500 g.[7] This definition emphasized the strong association of BPD with prematurity and with the increasing survival of smaller preterm infants in the 1980s.

The definition evolved again after recommendations of a National Heart, Lung, and Blood Institute workshop in 2000 that BPD for very preterm infants be defined separately from BPD in infants with gestations of >32 weeks of PMA.[8] For the preterm infant, BPD was defined as oxygen exposure for ≥28 days, although in practice, many practitioners remain uncertain whether the oxygen exposure must be continuous. BPD was then categorized as mild—room air at 36 weeks of PMA or at discharge before 36 weeks of PMA; moderate—supplemental oxygen at 36 weeks of PMA or at discharge at <36 weeks of PMA; or severe—supplemental oxygen ≥30% and/or positive pressure at 36 weeks of PMA. The definition was further refined to use of an oxygen challenge test for the moderate BPD group to verify if the infant was being treated with oxygen to maintain saturations of >90%.[9]

In practice, variants of the definition from Shennan et al (1988) are most frequently used today because of its simplicity.[7] The Vermont-Oxford Network uses the Shennan definition modified to accommodate discharges before 36 weeks of PMA. The National Institute of Child Health and Human Development neonatal network uses the Shennan definition for epidemiology and the workshop definition with an oxygen challenge test for trial outcomes. Beam et al reviewed in 2014 the definitions used for primary outcomes for therapeutic agents for BPD, and of 44 trials, 14 used oxygen at 28 days and 22 used oxygen at 36 weeks of PMA without categorization of severity of BPD or need for oxygen by an oxygen challenge test.[10]

Inadequacies in Definitions for BPD

Definitions vs Pathophysiology

The pathophysiology of BPD will be explored in a subsequent review in this series. From the perspective of definitions, the elements of all the definitions of BPD are simply management details of supplemental oxygen need and/or use of positive pressure support in preterm infants. Thus, the disease is defined by its treatments and not any specific aspects of pathophysiology or lung injury. Radiology was not included in the workshop definition, because there was no confidence in consistency of reading.[8] No laboratory tests are included, nor is histopathology. BPD is a lung injury syndrome that is unique because it occurs from interactions between antenatal exposures, postnatal oxygen and ventilation-mediated injury, and other injuries (eg, postnatal infection, inadequate nutrition) to an immature and developing lung where development,

BPD	Bronchopulmonary dysplasia
PMA	Postmenstrual age
RDS	Respiratory distress syndrome

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injury, and repair are superimposed.[11] Present definitions simply identify infants at a single point in time—28 days, 36 weeks, or 40 weeks. The progression from the fetal premature lung to 36 weeks of PMA is a rich period for the collection of extensive physiologic and nutritional information that could be used to define subtypes of the BPD syndrome. Laughon et al used oxygen exposure to 14 days to identify groups of infants with different risks of BPD.[12] Cumulative area under the curve evaluations for oxygen and pressure exposures may be improvements on definitions at a single point in time.[13] New imaging techniques using magnetic resonance imaging can define structural lung changes with remarkable resolution.[14] At least for research purposes, such techniques may provide new insight into the progression of BPD.

Classification Problems

BPD definitions now are dated relative to rapidly evolving respiratory treatment strategies and the changes in populations at risk. Although there was minimal change in the incidence of BPD between 1993 and 2012, the number and survival of the smallest and most preterm infants has increased.[15] Some of the infants not classifiable into the currently used definitions are accommodated by straightforward adaptions. For example, the Shennan definition (1988) did not account for infants discharged before 36 weeks of PMA. The Vermont-Oxford Network definition codes infants discharged at 34-36 weeks of PMA on supplemental oxygen as having BPD, whereas those on no oxygen have no BPD.[16] They have no adjudication for infants discharged at <34 weeks of PMA, probably because discharge on home oxygen is rare in that setting. The recently collected Prematurity and Respiratory Outcome Program (PROP) cohort of 765 surviving infants of <29 weeks' of gestation illustrates the problems caused by changing respiratory care practices.[17] Traditionally, invasive ventilatory support with an endothelial tube or nasal continuous positive airway pressure was considered positive pressure. Recently, a variety of nasal cannula flow systems have been widely adopted that will deliver some but highly variable pressure or dead space washout support. For the PROP cohort, 359 of 765 infants were being treated with nasal cannula flow at 36 weeks of PMA, and 95 infants were on flow with no oxygen. The other extreme was the 34 infants on <0.1-L flow with 100% oxygen. Although some clinicians have developed equations to estimate the fraction of inspired oxygen delivered by low-flow cannulas, there are presently no firm rules to adjudicate how much flow qualifies as respiratory support.[18] Similarly, 100% oxygen use equals severe BPD by the workshop definition, but very low flows need to be tested by flow reduction to adequately classify an infant. Variations of these BPD definitions are frequently used as quality measures to assess individual performance in the neonatal intensive care unit. However, in practice, there is substantial variability in individual practice regarding the use of oxygen and flow, and oxygen need testing is not performed consistently outside the context of research.

Clinicians and industry have an interest in a better definition of severe BPD, because the workshop definition groups infants who are receiving only 31% oxygen by nasal cannula with infants on high ventilator settings receiving drugs for pulmonary hypertension and who may not survive. These cases of the most severe BPD need to be identified as early as possible in their clinical course (ie, 1 or 2 weeks of age) as a very high-risk group for experimental therapies. Occasionally, infants may be on ventilatory support but on room air. Their primary problems likely are related to airway instability or control of breathing, and they do not have substantial lung parenchymal injury. They should not be classified as having BPD.

Infants Who Should Be Classified as Having BPD

A problem with the current definitions is that the diagnosis of BPD is made at a single point in time, generally 36 weeks of PMA. It is instructive to evaluate how clinicians assign cause of death from RDS or BPD for infants before 36 weeks of PMA. RDS is a disease of limited duration, particularly in the era of surfactant treatment.[19] A reasonable approach is to assign a death to RDS if it occurs owing to persistent respiratory failure from birth up to 7 days. Technically, severe BPD cannot be diagnosed by today's definitions until 36 weeks of PMA, even if babies die of respiratory failure before that time point. Patel et al reported that about 30% of the mortality for infants born at 22-28 weeks of gestation between 8 and 60 days was from RDS and about 15% of the mortality before 36 weeks of PMA was from BPD.[20] We roughly estimate, based on the mortality data from Patel et al, that about 1900 infants die before 36 weeks of PMA in the US each year of severe respiratory failure progressing toward BPD. In the PROP cohort, 25 of 35 deaths between 2 weeks of age and 36 weeks of PMA were adjudicated to be primarily from respiratory failure that perhaps should be defined as severe early BPD.[21] Further, 2 of the 3 deaths between 36 and 40 weeks of age were from BPD. In many clinical trials, death is considered a competing outcome to BPD. We suggest that in the context of trials, severe early and lethal BPD should be counted as BPD and not a competing outcome.

BPD as a Predictor of Longer Term Pulmonary Outcomes

For most diseases, a diagnosis is an end unto itself. However, a major consideration for BPD is how that diagnosis can predict longer term respiratory outcomes. There are numerous cohort and epidemiologic reports indicating that BPD is associated with adverse pulmonary outcomes in the early years of childhood relative to infants without BPD using a variety of BPD definitions.[22] Although true, it is important to recognize that the lung function of virtually all extremely low birth weight infants without BPD will be abnormal and that those infants also are at increased risk of adverse respiratory outcomes.[23] Environmental factors such as maternal smoking may cause long-term changes in lung function, which further complicate the predictive value of a BPD diagnosis at 36 weeks of PMA.[24]