



Editorial: Bronchopulmonary Dysplasia: Past, Current and Future Pathophysiologic Concepts and Their Contribution to Understanding Lung Disease

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Editorial on the Research Topic

Bronchopulmonary Dysplasia: Past, Current and Future Pathophysiologic Concepts and Their Contribution to Understanding Lung Disease

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Pulmonary disease arising from both pre- and immediate postnatal adverse events affecting the developing lung was first described around 50 years ago by Northway and colleagues (1). By today's standards, the disease termed "bronchopulmonary dysplasia" (BPD) was seen in relatively mature babies weighing over 2 kg at birth, who were ventilated with higher pressures and at slower rates than would be acceptable today. Much has happened since then.

Whereas, the initial or so called "old" BPD (Northway) was characterized by a pronounced effect on the airways, albeit with an element of failure of alveolar development, BPD today ("new" BPD) is characterized by lung hypoplasia driven by dysregulated growth factor signaling (2) in the context of extensive matrix remodeling and a pronounced inflammatory response (3, 4). This picture arises because neonatologists worldwide now salvaging babies weighing <500 g at birth.

Despite improved perinatal care, and most likely reflecting the changing picture of structural and functional consequences of lung injury in this patient cohort, the overall rates of chronic lung disease in the preterm infant have not decreased significantly and BPD remains the most common morbidity of prematurity (5–7). Adding another level of complexity, the validity and utility of commonly used BPD definitions have been questioned and most prediction models for BPD only hold limited value for clinical use (8–10). Likewise, contemporary changes in the perinatal management of infants, such as the use of high-flow nasal cannula and less aggressive neonatal resuscitation, limit the application of prior definitions, and may result in further misclassification of the disease (11).

Unresolved as of today is the presumptive presence of different disease endotypes with variable contributions of airway pathology, matrix remodeling and pulmonary vascular disease, all covered by the umbrella term BPD.

As clinical understanding of the ever-changing picture of BPD is limited, conceptual insights derived from careful clinical observations and validated scientific findings in human babies

and preclinical animal models were and are needed to improve clinical standards. As a consequence, the use of antenatal steroids and postnatal surfactant have become routine and resuscitation has become gentler, especially with the previous imperative to get the baby fully oxygenated immediately after birth having been removed. The use of supplemental oxygen to maintain oxygen saturation in an evidence based low-normal range (12)—depending on lung vascular and extrapulmonary complications—is now known to be important as is the avoidance of unnecessarily high oxygen concentrations even for short periods of time. In addition to the reduction or prevention of oxygen toxicity, ventilation regimens have been profoundly revised with lower ventilation pressures and higher ventilation rates than were applied in the early years of neonatology (13, 14).

As important for minimizing the risk of sustained lung injury is the controlling of postnatal infections and the optimization of fluid balance (15, 16) and nutrition while preventing fluid overload and normalizing somatic growth. Prenatal risk factors including intra-amniotic infections and growth retardation are known to contribute to disease development in the structurally and functionally immature lung, but are—despite improved treatment regimen to initially support lung function and potentially maturation (17, 18)—still poorly controlled as of today and long-term benefits of existing therapies remain unclear.

Identification of the risk factors outlined above has helped to inform concepts of pre- and postnatal management although many challenges are only partially understood and therefore still unmet. Inevitable risks for BPD development remain including the higher risk for males. As both experimental and clinical studies revealed, other genetically determined risk factors are important, and an initial report has highlighted the involvement of a multitude of genes implicated in BPD (19).

Similarly challenging, new therapeutic developments that have been and will be highly beneficial for babies and their families, but are—as is well-known—accompanied by iatrogenic complications and change the pattern of disease in survivors. Two examples are the use of systemic corticosteroids in pre- and postnatal treatment regimens (17, 20, 21) and the careful consideration of potentially longer periods of oxygen exposure (22) as a tradeoff for a reduced period of invasive ventilation.

Nonetheless, even if neonatal practice was perfect, being born preterm is enough to lead to long term respiratory consequences, independent of any iatrogenic complications (23, 24).

In parallel with the change in the nature of BPD, tools for investigation and monitoring have become increasingly sophisticated. These include infant and pre-school lung function, including sensitive tests such as multi-breath washout, and imaging, initially with high-resolution computed tomography, and now increasingly with magnetic resonance imaging. Next to the need for further refinement of structural assessment using advanced imaging technologies while avoiding radiation exposure or general anesthesia, unmet challenges include the lack of biomarkers allowing for early disease detection and subsequent monitoring of progression. Here, multiomic technologies and systems

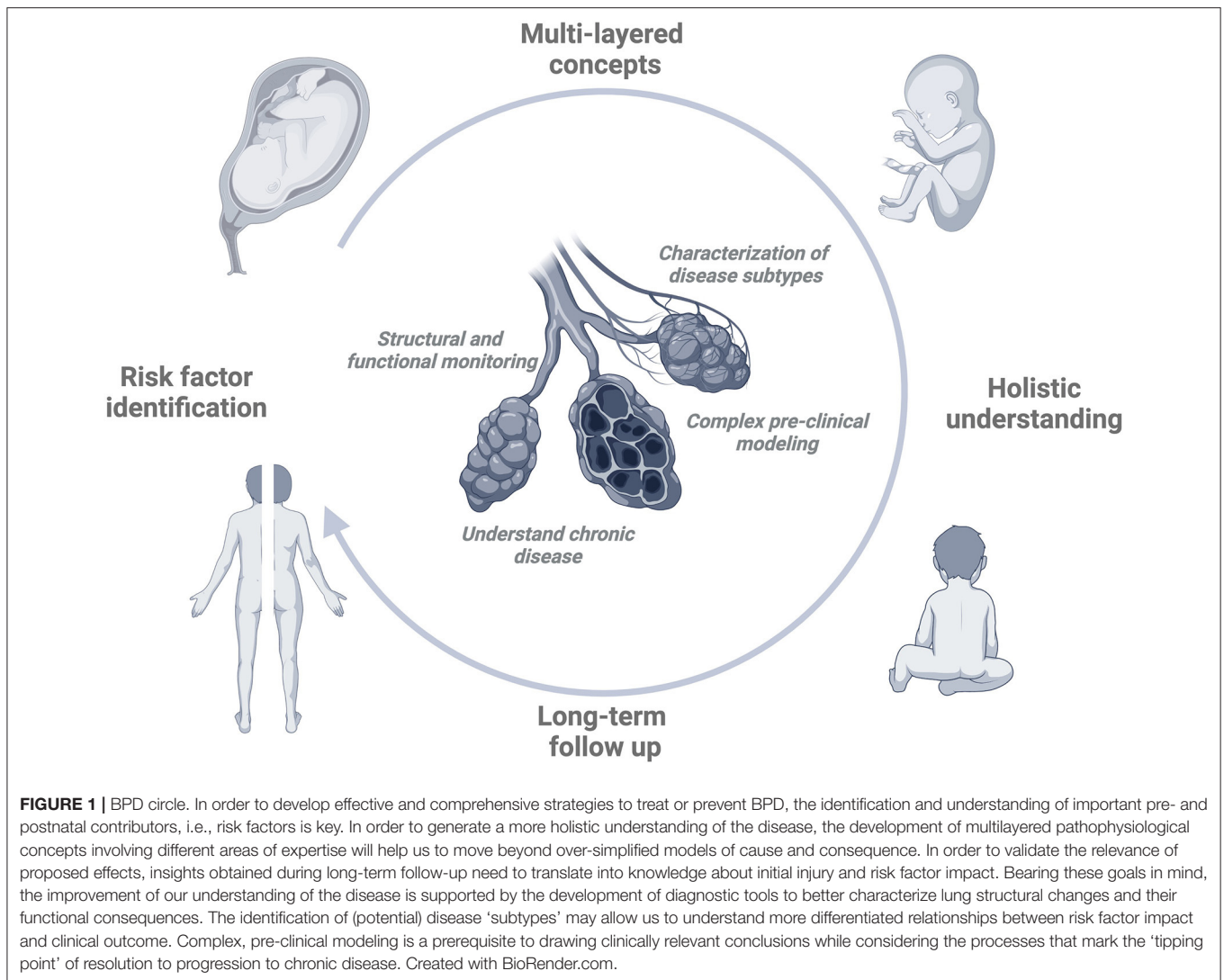
biology may be of help including further sophisticated probing of potential BPD endotypes, that could allow individualized and maybe pathway specific treatment and monitoring approaches.

Adding to the complex disease picture, knowledge about co-morbidities is sparse but will—with increasing long-term survival—likely gain importance. The understanding of the late complications of BPD will inform neonatal practice, by analogy with cystic fibrosis, where long survival has led to the realization of the importance of detecting diabetes and bone disease in children and instituting preventive and treatment strategies. We have found out much about cardiovascular and metabolic morbidity and mortality in survivors; low first second forced expired volume (FEV₁) is a marker of increased risk in the normal term (25, 26), but also in BPD survivors (27, 28). Is our monitoring for diabetes and hyperlipidaemia adequate? These and other questions show that BPD is an illustration of the importance of not living in “developmental silos,” but taking a whole life course view of traditional “pediatric” diseases.

In light of these considerations, a further challenge is engaging adult thoracic physicians in following these children up to determine the long-term consequences of BPD. Unfortunately, and in contrast to the tremendous investment in intensive care and the immediate aftermath, by and large respiratory follow up has not happened, despite the known respiratory morbidity in survivors (29). The survivors are thus often likely to be given inappropriate therapy such as treatment with inhaled corticosteroids for “asthma-like” phenotypes in preterm infants, despite the compelling evidence of a non-inflammatory airway phenotype in most BPD survivors with wheeze. Many will not attain normal spirometric values and will thus be at risk for being diagnosed with chronic obstructive pulmonary disease (COPD) (30). In addition, adult patient care often neglects early life events (31), increasing the risk for survivors of prematurity to be falsely combined under the COPD umbrella together with chronic smokers, although they may have a very different endotype leading to the end stage of a reduced FEV₁/forced vital capacity (FEV₁/FVC) ratio. This knowledge—together with the exchange of insights into potentially common pathways in neonatal and adult lung disease and the contribution to regeneration strategies informed by specialists in lung development—should lead to a fruitful exchange between experts and care givers. But as the face of the disease is changing, so a new generation of problems is on the way.

In face of all these achievements and remaining challenges, it becomes increasingly clear, that BPD is a dynamic disease that will be changing with neonatal practice and it would be unwise to assume that there will not be further important developments in the years ahead.

Understanding BPD therefore requires novel concepts stemming from clinically relevant experimental and translational approaches that undergo holistic, multi-layered evaluation to determine their utility for disease understanding and clinical care (see **Figure 1**). Showcasing the complexity of events is the need to understand cellular crosstalk in the



developing alveolar niche while considering the impact of the surrounding scaffold to gain insight into repair and regeneration capacities as well as mechanisms of progression to chronic disease. Premature ageing and the implications of senescence are poorly understood but likely play an important role in determining the outcomes. Questions that concern e.g., the mechanisms behind a “switch off” of a specific cellular developmental capacity in lung development and their later “switch on” in adolescence or adulthood have yet to be explored.

In order to inspire the development of novel, broader concepts, a comprehensive overview over the state of knowledge in the BPD field is needed covering ongoing research and clinical developments.

We have been privileged to work with a stellar group of authors and commentators to put this “BPD Research Topic” together. The content includes a comprehensive overview about available (and feasible) animal models to unravel disease mechanisms and perform preclinical

studies (32, 33), insight into critical cell populations, the lung matrix and their complex interaction as determinators of the pulmonary landscape (2), and models of the nature and causation of lung injury reviewing the most critical pathophysiologic mechanisms (34, 35). Other manuscripts reflect on the role of new diagnostic and treatment concepts (36–39).

By combining specialist chapters with overview commentaries—often from authors who are experts in other fields of lung disease—we have furthermore aimed at giving a broader context to BPD with an “outside” view complementing the perspective from “within the NICU” (24).

We believe that the Research Topic on bronchopulmonary dysplasia provides a rounded and comprehensive picture of a disease that significantly determines quality of survival throughout the life course in one of the largest pediatric patient groups. It should paradigm for understating long-term consequences of early (multiple hit) injury.

AUTHOR CONTRIBUTIONS

AB and AH contributed as editors to the Research Topic on bronchopulmonary dysplasia by conceptualizing and supervising the content, inviting the contributing authors, and by writing the Editorial. Both authors contributed to the article and approved the submitted version.

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