Editorial

Bronchopulmonary dysplasia (BPD): a change in perspective

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About 50 years ago, Northway was first to describe the entity of bronchopulmonary dysplasia (BPD) (1). His description of a syndromic disease of neonates below 2 kg of birthweight, who develop pulmonary fibrosis and pulmonary emphysema caused by severe respiratory distress treated with conventional ventilation and 100% oxygen, is today considered as "old" BPD. BPD together with asthma and cystic fibrosis represents the three most common entities of chronic lung disease of infants in the western world that continue into adulthood. For asthma and BPD incidences are increasing, for BPD—at least in the most immature infants—severity is increasing, too. Another interesting common fact is that both, BPD and asthma, may be defined as phenotypes induced by different etiologies. For BPD, several corner stones changing in neonatal medical care caused an increase in incidence and severity. Improved survival of tiny premature neonates; the establishment of specialized care to enable spontaneous ventilation supported by continuous positive airway pressure (CPAP); the reduction of perinatal inflammation and infection of mothers and fetus/infant by the use of antibiotics and anti-inflammatory drugs (e.g., steroids). For steroids in turn, a new role was invented which was the induction of fetal lung maturation by prenatal treatment of mothers. Finally, the ability to treat the immature surfactant deficient lung with intratracheal pulmonary surfactant was a significant step that additionally improved perinatal care and reduced morbidity and mortality of preterm neonates, including a reduction of the (old) BPD originally described by Northway. Today millions of premature infants have been treated with surfactant since the first medical report of Fujiwara 1980 (2).

However, BPD did not disappear, rather was changed in definition (3,4). Thus, a new phenotype of BPD of more premature infants born below 28 weeks of postmenstrual age appeared. Husain *et al.* characterized this new BPD pathologically by a partial or total arrest of alveolar development (5). The pathophysiology of BPD includes several non-physiologic hits on the developing premature lung whose function is launched prematurely (6) (*Figure 1*).

The "new BPD" phenotype develops during interference with the continuing lung development induced by inflammation, oxidative stress, ventilator induced damage, "microbiologic stress" and genetic predisposition. Since these hits may be at different time points with regard to development stages, of different (I) severity, e.g., sepsis or pneumonia, and (II) quality, e.g., ventilation trauma, bacterial, viral or fungal infection, the "multiple hit" etiology hypothesis makes clear that there will be no simple solutions ("no silver bullet for prevention of BPD"). In addition, prenatal and genetic causes of BPD are described as modifiers of the disease (8). Together, these factors may lead to sustained disrupted alveolar and microvascular development (9), and finally, to disability to achieve the full airway growth potential in adulthood (10). Follow-up studies could show progressive obstructive pulmonary disease after extreme prematurity even after introduction of surfactant treatment (11). Additional long-term observations suggest similarities of BPD in adulthood with chronic obstructive pulmonary disease (COPD) in

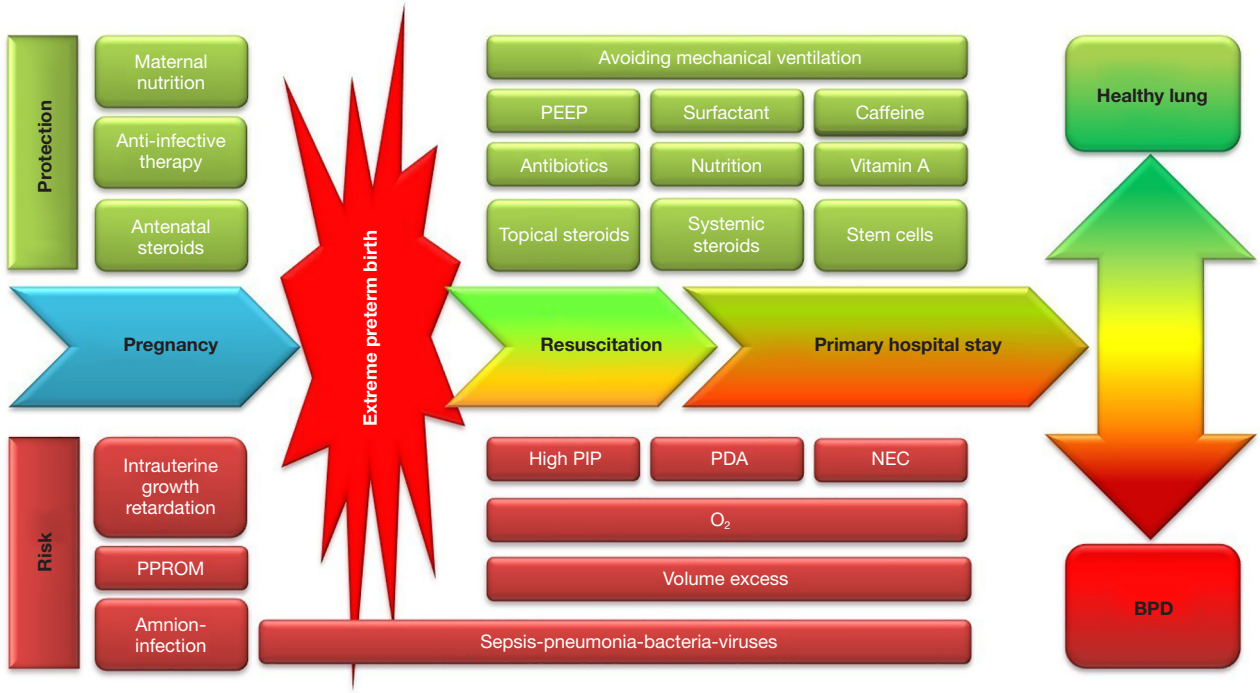

Figure 1 Contributors to risk or protection of BPD before birth during the periods of pregnancy, postnatal resuscitation and the primary hospital stay. Modified from (7). PEEP, positive end expiratory pressure; PPROM, preterm premature rupture of the membranes; PIP, peak insufflation pressure; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

adulthood (12,13).

Today, we haven't fully understood the pathophysiological mechanisms behind BPD; we have no chance to give a causal therapy to premature born infants and scarce possibilities to avoid preterm birth potentially resulting in BPD.

The course of the disease may be insidiously, showing improvement during the first years of life after a severe course during initial hospital stay. Yet, we have better understood, that previously extremely preterm infants with BPD develop progressive decreasing lung function during early adulthood (14). Recently, the European Respiratory Society suggested guidelines for long term follow-up of infants with BPD and contextualized it as a new group of COPD (15). Today's long-term follow-up of BPD is insufficient and multidisciplinary follow-up is needed since it is often accompanied by neurodevelopmental delay and/or cerebral palsy. While adult medicine gradually has to learn about role of premature birth for diseases later in life, neonatologists already understood important corner stones of BPD due to 50 years of experience: An early lung protective treatment strategy during the primary hospital stay and especially during the first days of life is of key importance to improve the outcome of the disease.

In their review in this journal, Verder *et al.* highlight the most recent pathophysiologic findings, early prediction and treatment strategies of BPD based upon papers published predominantly during the past 15 years (16), as since Northway's initial report, the understanding of BPD has expanded in terms of course of the disease and etiology. Considering this, e.g., new aspects as pulmonary microbiome or precise differentiation of etiologic factors that nowadays are known for contributing to the pathophysiology of BPD have to be taken into account for development of early diagnosis and early prevention and/or treatment strategies. Consequently, Verder and colleagues concentrate in their review on the first 28 days of live of premature neonates at risk. The authors develop the hypothesis that by early management and use of predictive tools early selective preventive treatments can be initiated. However, those patients remaining with BPD beyond the first 4 weeks of life also need to be counseled, since obstruction and avoidable factors like smoking contribute to the course of the disease (17). Early viral infections in

infancy like respiratory syncytial virus seem to be disease modifiers as well (18).

In conclusion, the perspective of BPD has changed and widened. Due to improved survival, the disease approaches the clinical field of adult pulmonologists with a new similar phenotype to COPD. And patients need to be counseled at each stage of life due to the chronic character of the disease. Thus, early reliable tools for BPD prediction may pave a promising way for early BPD-preventive treatments. Adult pulmonologists seeing patients with COPD like symptoms already in the 3rd decade of life will have to add the questions about gestational age and/or birth weight to their repertoire.

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