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Long term outcomes in chronic lung disease requiring tracheostomy and chronic mechanical ventilation

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is the most common serious complication associated with preterm birth. Infants with severe BPD often require prolonged and intensive pulmonary care. Among those with the most severe lung disease, this care may include tracheostomy and long-term invasive mechanical ventilation. Although there is a plethora of data on long term respiratory and developmental outcomes of BPD survivors, relevant information on BPD survivors requiring chronic respiratory failure are limited. When compared to those born at term gestation, infants with BPD requiring chronic ventilation are at increased risk of hospitalizations and develop more frequent lower respiratory infections. In childhood and young adulthood, spirometry often shows an obstructive flow pattern. From a neurodevelopmental standpoint, the short-term outcomes appear optimistic, with improvement in growth and increased participation in development-promoting activities. Nonetheless, children born prematurely are vulnerable for long term cognitive, educational and behavioral impairments. BPD is an additional risk factor which exacerbates these deficits, thus contributing to lifelong neurodevelopmental impairments of prematurity.

1. Introduction

Bronchopulmonary dysplasia (BPD) is one of the most significant and serious complications of prematurity. It is estimated to affect 25% of newborns with a birth weight under 1000 gr, and 70% of those born between 22 and 26 weeks of gestation [1]. Despite paramount advances in the management of BPD such as administration of antenatal corticosteroids, surfactant replacement and effective modes of invasive and noninvasive ventilatory support, the prevalence of BPD has plateaued over the past decades.

BPD was originally described as the respiratory condition affecting preterm infants typically born at or after 32 weeks exposed to aggressive ventilation and high concentrations of inspired oxygen [2]. However, the term 'new BPD' has been established, and is characterized mainly by alveolar simplification and abnormal pulmonary vascularization [2]. The current BPD definition as proposed by the National Institute of Child Health and Human Development (NICHD), includes the treatment with supplemental oxygen for at least 28 days, and categorizes its severity into mild, moderate and severe according to the level of respiratory support required near to term. Infants with severe BPD requiring positive pressure ventilation at 36 weeks' postmenstrual age are more likely to transition into prolonged mechanical ventilation via tracheostomy while in the neonatal intensive care unit. While the exact prevalence of children with severe BPD necessitating positive pressure ventilation at home is unknown, it is estimated that the number of patients with BPD requiring tracheostomy and prolonged mechanical ventilation has been increasing significantly from 0.7 to 2 per 100.000 to 6.3 per 100.000 children, over the past decades [3–5].

Most tracheostomies in children are performed in infants less than 12 months of age [6]. In addition to the need for prolonged mechanical ventilation, other indications include significant airway abnormalities such as severe tracheomalacia, bronchomalacia, and subglottic stenosis. The optimal timing of tracheostomy placement is unknown. Studies have shown that early tracheostomy placement reduces the risk of subglottic stenosis, decreases the need for sedation, improves comfort and most importantly, promotes cognitive and physical growth by facilitating the transition to homecare [5,7].

Both the presence and severity of BPD are independently associated with cognitive impairment [8,9]. Although there are emerging data on long term pulmonary and neurodevelopmental outcomes in infants with BPD, there is limited information on the subgroup of patients who require prolonged mechanical ventilation. Our aim is to review the literature and provide data on the respiratory and neurodevelopmental outcomes in children with severe BPD who are supported by long term

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mechanical ventilation through tracheostomy.

2. Respiratory outcomes

2.1. Rehospitalization

Hospital readmission rates for respiratory illness in children with BPD range between 43% up to 63% during the first 2 years of life [10–12]. Hospitalization rates for BDP infants are not only higher than those of the general population, but are also higher than those of very low birth weight infants without lung disease [10,12]. The most common causes for rehospitalization in this population are respiratory diseases including reactive airway disease, pneumonia and respiratory syncytial virus infection, which account for 65% of readmissions in the first year, and 81% in the second year.

The severity of BPD has been associated with longer hospitalization, but there are limited data specifically regarding ventilator-dependent patients. A retrospective cohort study by Kun et al. [13] on newly discharged pediatric patients on home mechanical ventilation, reported a 40% 12- month incidence of non-elective hospitalizations, with close to half of these hospitalizations occurring during the first 3 months after their initial discharge. Pneumonia and tracheitis were the most common causes of readmission. In another retrospective cohort study conducted by Cristea [14] et al. which included 102 patients with severe BPD and ventilator dependence followed over the course of a total of 871 person-years, the readmission rate was impressive with a total number of 675 events. The incidence of rehospitalization was significantly higher before decannulation (554 vs. 121 events, $p < 0.0001$). The decrease in the patients' readmission rate after decannulation could be attributed to removal of tracheostomy, improvement of BPD, or both. After 4–5 years of age, hospitalizations for respiratory problems tend to decrease [15,16]. Nonetheless, chronic respiratory symptoms continue to be reported in greater frequency among patients with BPD than those born at term without lung disease in most studies.

2.2. Asthma-like signs and symptoms

There have been numerous studies describing the increased incidence of asthma-like symptoms in BPD patients. In a systematic review and meta-analysis of preterm birth and childhood wheezing disorders, researchers identified 30 studies undertaken between 1995 and 2013 which is a time spam chosen to allow for changes in the management of prematurity, and investigated the association between prematurity and asthma/wheezing in more than 1.5 million children. Preterm birth was associated with an increased risk of wheezing, and the risk was particularly high among children born very preterm (< 32 weeks gestational age). The population attributable risk of prematurity for childhood wheezing disorders was more than 3.1%, which means that if there were no premature births, then there would have been more than 3.1% of reduction in wheezing disorders in childhood [17]. While evidence shows that prematurity increases the risk of asthma, it has been emphasized that the pathogenesis of those symptoms may significantly differ.

In the EPICure study [18], a population based study including extremely premature infants, born between 22 and 26 weeks' gestational age, children born prematurely had significantly more chest deformities and respiratory symptoms at age 11 years compared to age-, sex-, ethnicity-matched peers. Specifically, twice as many had a diagnosis of asthma (25% vs. 13%, $p < 0.01$). In this study, three quarters of the cohort were described as moderate to severe BPD, but there were no technology dependent children included.

A study from a Danish collaborative group reported that of 508 19-year old adults born prematurely, those who had BPD had a higher prevalence of respiratory symptoms, and females were more likely to be affected than males [19]. Northway et al. [20], followed twenty six BPD survivors with a mean age of 18.3 years, and reported that 25% of adolescents with BPD had significant pulmonary symptoms including higher number of wheezing episodes, pneumonias, and use of long-term medications, compared with age-matched controls who were also born prematurely but did not require mechanical ventilation, as well as compared to a group born at full term.

In summary, extreme prematurity is associated with increased respiratory morbidity which persists into middle childhood and young adulthood. This is particularly accentuated in patients with BPD.

2.3. Pulmonary function

It has been well described that children with BPD demonstrate an obstructive pattern of lung disease which is confirmed by functional respiratory tests [21,22]. Fakhoury et al., [23] studied forty-four children with moderate and severe BPD and mean gestational age of 25.6 weeks with serial measurements of lung function at 6, 12 and 24 months after initial discharge from the neonatal care unit. Their results showed that children with BPD had low partial expiratory airflow measured by V(max)FRC compared with normative data, with mean z score (+or –SD) of −1.92 (+or – 1.04), - 1.79 (+or −1.5), and −1.67 (+or – 1.5) at 6, 12 and 24 months respectively. There was no significant improvement in z scores ($P = 0.66$), and 45% of the patients had a z score value of less than 2 SDs below the mean at the end of the study. In summary, children with mostly moderate to severe BPD continued to show significant abnormalities with airflow limitation based on lung function testing during the first 3 years of life.

In the EPICure cohort [24], the peak expiratory flow (PEF) measurements obtained in extremely preterm children at 6 years of age, were on average 39 l/min (95% CI 30 to 47) lower than in the comparison group. BPD was the only independent associate of PEF. In the same population study, the assessed respiratory function at 11 years in children with BPD showed an abnormally low baseline lung function; forced expiratory volume at 1 s FEV1, FEV1/FVC, and forced expiratory flow at 25–75% of vital capacity, FEF 25–75. There was a statistically significant increase in the FEV1 after administration of bronchodilators. Interestingly, other studies suggest that obstructive lung disease symptoms in BPD are less responsive to bronchodilators and inhaled corticosteroids which could be explained by an irreversible airflow limitation [25]. Doyle et al. [26], studied 33 BPD survivors who were born during 1977–1982 and had mean age of 18.9 years at the time of the pulmonary function testing. This study demonstrated significantly low (< 75%) FEV1/FVC ratio in adults with BPD compared to controls as well as a gradual deterioration between 8 and 18 years.

While there is abundance of data on impaired pulmonary function in children and adolescents with history of BPD, limited information exists regarding the spirometric values in patients with severe BPD requiring chronic ventilatory support. In one study by Cristea et al. [27], 19 patients with severe BPD who were previously ventilator dependent at home underwent spirometry once they were able to follow commands. The median age of first reproducible spirometry measurement was 6.6 years, and the results showed evidence of severe airflow obstruction as reflected by z scores. More so, serial spirometric measurements' slopes revealed that the airway obstruction remained static over time.

Given that airway function tracks through life [28], those with reduced lung function in childhood are likely to retain this position through to adulthood and are thus likely to be among the first to reach a critical threshold for the onset of chronic obstructive pulmonary disease (COPD) with subsequent ageing. It appears that pulmonary function impairment in survivors of BPD who had chronic ventilation at home predisposes to a COPD phenotype later in life. This situation is likely to be exacerbated by the high prevalence of active smoking [29] and reduced exercise capacity which has been reported in ex-preterm adolescents and adults [30].

2.4. Exercise testing

There are several studies that have examined exercise capacity in BPD survivors and concerns have been raised about impaired physical activity persisting through adulthood [31]. The proposed mechanisms are exercise induced bronchoconstriction, decreased lean muscle mass and strength, compromised ventilatory response, and impaired lung function. In a longitudinal follow up study [18,32], 11 year old children born prior to 25 weeks' gestational age (71% with BPD) were matched with controls. Participants performed apart from spirometry, body plethysmography, gas transfer testing and a peak exercise testing on a cycle ergometer. The investigators concluded that children born extremely premature had lower z-scores in FEV1 and RV (residual volume), significant reduction in peak oxygen consumption and employed greater breathing frequencies and lower tidal volumes during exercise. However, no differences in physical activity were observed between the two groups. Unfortunately, there are no data on exercise capacity in children with BPD who were previously ventilatory dependent, or even stratified results based on severity of BPD.

2.5. Pulmonary arterial hypertension

Several factors may contribute to significant reduction in cross-sectional area of the pulmonary vascular bed, such as altered vascular development and vascular remodeling with smooth muscle cell proliferation. These give rise to an increase in pulmonary vascular resistance, which in turn leads to the onset of pulmonary arterial hypertension. This has often been associated with higher morbidity and mortality in BPD infants, especially in the first 6 months after the initial diagnosis [33]. This diagnosis is thus important not only for prognostic purposes but also to ensure appropriate treatment [34]. It is not currently known how long the pulmonary vascular effects of BPD persist into later life. Nonetheless, it is speculated that pulmonary vascular reactivity to hypoxia, and the negative effects of BPD on the global cardiac performance of both ventricles and on pulmonary arterial pressure may persist even into adulthood. Although technically difficult, future non-invasive studies could assess pulmonary vascular function in adolescent and/or adult survivors of preterm birth.

Liberation from mechanical ventilation and decannulation.

In infants with severe BPD, tracheostomy is generally considered if they are beyond 40 weeks postmenstrual age and anticipated to require high-level respiratory support (either invasive mechanical ventilation or high level non-invasive support) for a prolonged period of time. Often, this decision is driven by each institution's clinical practice and accounts for each patient's clinical status. As home assisted ventilation in children has evolved significantly over the last decade; hence more data are emerging on the outcome of pediatric patients with chronic respiratory failure and tracheostomy [5,7,35]. However, there is still limited information on the subgroup of BPD patients who require home ventilation.

Mandy et al. [36], reported a survival rate of 77% in 22 children who were placed on chronic mechanical ventilation due to BPD in a single institution. The causes of death were not always known in the aforementioned studies, but accidental decannulation and cardiorespiratory arrest were reported. In a single institution study by Com et al. [37], children with BPD without central nervous system insult were more likely to be decannulated within 5 years while in another center, the median age of decannulation was 38 months, almost 10 months after liberation from mechanical ventilation. Similarly, Cristea et al. [14] reviewed the medical charts of patients with severe BPD who were dependent on home mechanical ventilation and were enrolled over the course of 27 years. Of the evaluable 102 patients, 83 patients were alive with a survival rate of 81.4%. The median age at liberation from mechanical ventilation was 24 months (interquartile range, 19–33) and at decannulation was 37.5 months (interquartile range, 31.5–45), with a median interval between liberation from ventilation and decannulation of 11 months. Although extreme prematurity associated with severe BPD necessitating mechanical ventilation carries significant risks of morbidity and mortality, successful liberation from mechanical ventilation is likely to occur. Future prospective cohort studies are needed in order to further elucidate this topic.

2.6. Prematurity and neurodevelopmental outcomes

During 24–40 weeks of gestation, multiple complex events critical for brain development take place, including axonal and subplate growth, differentiation of premyelinating oligodendrocytes, and proliferation and migration of gamma-aminobutyric acid-ergic neurons [38]. These processes are highly vulnerable to pathogenic factors, such as hemorrhagic events, hypoxic-ischemic events, and inflammation, and may be further exacerbated by environmental factors, such as stress and malnutrition [39]. Neuropathology associated with prematurity includes both direct brain injury of which white matter lesions are most common and secondary neuronal abnormalities affecting gray matter. These disturbances in brain development are reflected in reduced overall brain volume in childhood and adolescence, with reductions being evident in both gray and white matter [40]. White matter abnormalities in particular have been associated with neurocognitive deficits.

Specifically, Bhutta et al. showed the detrimental effect of preterm birth on intelligence based on cohorts of children born before 1990 [41]. Similar findings were published in the meta-analysis based on 27 studies including preterm children born between 1975 and 2000 [42]. A meta-analysis of 71 studies [43] which included 7752 extremely or very low preterm and 5155 full term children, showed a large 0.86 standard deviation difference in intelligence between extremely or very preterm children and controls which corresponds to 13 points in intelligence scores (IQ). A difference in intelligence of almost 1 SD is likely to have important consequences for academic achievement and socioeconomic outcomes. Furthermore, this difference was stable over age (5–20 years) and birth year (1990–2008). This implies that despite medical advances, overall improvement of neurodevelopmental outcomes over the years seems to be marginal, therefore emphasizing the need to focus on improving long-term cognitive outcomes of premature infants.

2.7. BPD and neurodevelopmental outcomes

Previous studies showed a positive association between BPD and brain anomalies in preterm infants [44], but the mechanisms remain to be elucidated. Specifically, Short et al. sought to examine the effects of BPD and very low birth weight (VLBW) on the cognitive and academic achievement of a large sample of 8 year old children [45]. The BPD group demonstrated deficits compared with the VLBW group and the term children in intelligence, mathematics, and gross motor skills, as well as in need for special education services. After controlling for birth weight, and neurologic problems, BPD and/or duration of supplemental oxygen therapy predicted lower performance IQ, perceptual organization, full scale IQ, motor and attention skills, as well as special educational placement. In a meta-analysis including 71 studies (7752 extremely or very low preterm and 5155 full term children), BPD accounted for 65% of the variance in intelligence across studies. One factor implicated in the pathogenesis of both BPD and brain injury in preterm infants is oxidative stress, which is defined as an imbalance between the generation of free radicals and antioxidant defense, and free iron release [46]. Organ immaturity, hypoxia-ischemia, hyperoxia, inadequate nutrition, and mechanical ventilation further increase the risk for free radical-induced injury [47]. Animal studies have shown that hyperoxia results in both lung and brain injury, and that the severity of lung injury is positively related to the severity of brain injury. Another plausible explanation is that children with BPD have reduced pulmonary function, increased airway resistance and reactivity, and

decreased exercise tolerance starting from preschool age, through early adolescence and into adulthood [45]. These respiratory problems may limit opportunities for these children to engage in the physical activities necessary to develop gross motor skills.

Finally, more BPD children may be enrolled in lower grades. This can be explained by several factors. Many parents of children with a history of BPD have indicated that they chose to delay school entry for a variety of reasons, including short stature, history of recurrent illness and hospitalizations, as well as perceptions of "increased vulnerability". In addition, given the multiplicity of difficulties experienced by both the child and the family during the early years of life, educational specialists may have advocated for delayed entry into formal education. In summary, both the presence and the severity of BPD strongly influence neurodevelopmental outcomes and a protracted course of mechanical ventilation is associated with increased neurodevelopmental disability in this population [9].

2.8. Postnatal corticosteroids and neurodevelopmental outcomes

Postnatal corticosteroids were widely used in the past to treat BPD, while later evidence showed substantial adverse consequences for neurodevelopment. Changes in neonatal practice such as the largely decreased use of postnatal corticosteroids, may have resulted in some improvement in cerebral palsy and neurosensory disability rates [48]. While results of a recent meta-analysis did not suggest that the strong association between BPD and intelligence was mainly attributed to postnatal corticosteroid use [43], future studies are needed to further elucidate the mechanisms underlying the association between BPD and neurodevelopment, taking into account the postnatal use of corticosteroids. Furthermore, based on recent evidence it seems that hydrocortisone may affect neurocognitive development to a lesser extent than dexamethasone [49].

2.9. Tracheostomy and neurodevelopmental outcomes

Singer et al. reported developmental outcomes at an average of 5 years in a cohort of 130 infants from 2 hospitals who received tracheostomies before 13 months of age during 1972–1982 [50]. Twenty-nine percent died before follow up and 45% of survivors were classified with mental retardation or some form of neurological deficit. In a single-center study of 41 infants with tracheostomies 97% had abnormal muscle tone, 36% had cerebral palsy, and 24% required hearing aids at a mean age of 27 months. Among those evaluated after 12 months of age, 68% had significant developmental delays. In a questionnaire –based study of functional status in former very preterm infants with tracheostomies, parents reported deterioration over time, especially in the areas of responsiveness, activity, and interpersonal functioning [51]. In a retrospect cohort study [52] from 16 centers of the NICHD Neonatal Network over 10 years (2001–2011), infants who survived to at least 36 weeks (N = 8, 683), including 304 infants with tracheostomies were studied. Tracheostomies were associated with adverse neurodevelopmental outcomes. Death or neurodevelopmental impairment (NDI) occurred in 83% of infants with tracheostomies compared to 40% of those without. [(odds ratio (OR) adjusted for center 7.0 (95% CI 5.2–9.5)]. After adjustment for potential cofounders, odds of death or NDI remained higher [OR 3.3% (95%CI, 2.4–4.6)]. Although tracheostomy might itself put children at risk for poor outcomes, such a causal relationship is less likely than a non-causal association between tracheostomy and significantly increased risk for poor outcome. It is likely that tracheostomy is a marker for risk of an adverse outcome. Clinicians considering tracheostomy placement for an individual patient could use these data to help parents grasp potential long term outcomes.

Interestingly, death or NDI was lower in infants who received their tracheostomies, before, rather than after 120 days of life [adjusted OR 0.5 (95%CI, 0.3–0.9)]. These results suggest a possible association between earlier (< 120 days) vs. later (> 120 days) tracheostomy placement and better neurodevelopmental outcomes. These results support the work of several authors who have suggested that in older children and adults, tracheostomy placement should be performed as soon as possible [5]. Some plausible explanations are that while an infant awaits a tracheostomy placement, the medical focus is often on strategies to enable weaning and limit ventilator-associated lung injury. Following a tracheostomy placement, the focus may then shift to maximizing parent-infant interaction and developmental enrichment. In addition, there is often opportunity to wean off sedating medications, which may be associated with increased risk of NDI, after tracheostomy placement. In a retrospective analysis of a cohort of infants born < 32 weeks gestation or birth weights < 1500 g with severe BPD who underwent tracheostomy placement between 2010 and 2016 in a quaternary referral newborn and infant intensive care unit, tracheostomy placement was associated with improved proportional growth and increased participation in activities promoting development skills acquisition and reduced daily sedation requirements in preterm infants with severe BPD [53]. More importantly, severity of illness, indication for tracheostomy, anesthetic exposure, or other factors may influence either the timing of tracheostomy or developmental outcomes, leading to potential bias. Further research is needed to address the question of optimal timing for tracheostomy placement, prior to confidently counseling parents toward earlier decisions about tracheostomy placement.

2.10. Future directions

Given the projected global increases in children surviving preterm birth, there are strong economic incentives for secondary prevention of disability associated with preterm birth. Preventive measures should include minimizing lung injury before and after delivery, long term surveillance and appropriate treatment through childhood in order to minimize the prenatal and postnatal factors that affect the immature lung. Having failed to reach their optimal peak lung function in early adulthood, there are concerns of accelerated lung function decline in BPD survivors. Even if the rate of decline in lung function is normal, the threshold for respiratory symptoms will be crossed early. As the management of these subjects in adulthood is largely evidence free, continued surveillance of young adults with a history of BPD will be critical to understand the long term impact of neonatal lung injury on pulmonary maturation and aging. There are a number of clinical and research priorities to maximize the quality of life and lung health in the longer term in understanding the underlying mechanisms and optimizing treatment, rather than extrapolating from other airway diseases.

BPD is found to be a crucial factor for long-term neurodevelopmental and cognitive outcomes above and beyond the effects of prematurity. Despite advancing neonatal health care, studies show no indication of significant improvements in long-term neurodevelopmental outcomes. This suggests that reducing the incidence of BPD in premature children would be beneficial. This suggests that reducing the incidence of BPD in premature children would be beneficial. To our knowledge, there is no single prevention or intervention strategy proven to have a considerable influence on the incidence of BPD. The fact that multiple factors seem to be involved in the development of BPD and neonatal brain injury advocates a multifactorial approach for prevention and treatment. Potential strategies may include an optimal ventilation strategy and oxygen concentration, anti-inflammatory agents, antioxidant therapy, and adequate nutritional support.

Moreover, research has shown that impairments in executive function for preterm survivors extend into adulthood with greater deficits found in adults with BPD including difficulties with planning, initiating new tasks and monitoring the outcome of behaviors. Such deficits affect the day to day lives of these individuals and have consequences in their social functioning, educational attainment and quality of life. These findings imply that, children with BPD should be thoroughly assessed to

identify cognitive impairments, and allow early intervention aiming at ameliorating their effects.

Finally, we need to acknowledge that although there are emerging studies on long term pulmonary and neurodevelopmental outcomes in BPD, there is very limited data regarding patients with severe BPD necessitating chronic ventilatory support. Future studies are needed in order for health care providers and families to better understand how chronic ventilation can impact the respiratory outcomes and the long term development of infants with severe BPD. This will help establish evidence based clinical guidelines and strengthen the multidisciplinary approach needed in caring for these vulnerable patients across their life span, in order to reach their full potential.

Declaration of competing interest

The authors have no conflicts of interest.

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