The Impact of Bronchopulmonary Dysplasia on Childhood Outcomes

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KEYWORDS

• Bronchopulmonary dysplasia • Chronic lung disease • Prematurity • Development • Outcomes

KEY POINTS

- As mortality rates after extremely premature birth decrease, rates of survival with bronchopulmonary dysplasia (BPD) are increasing.
- BPD is associated with adverse health outcomes throughout early childhood and until school age; these include rehospitalizations, respiratory symptoms, and poor lung function.
- Preterm-born children with BPD have worse developmental outcomes in early childhood than both preterm-born and full-term peers. At school age, they often have lower intelligence quotient and worse performance on tests of academic achievement.
- Many interventions to decrease BPD and the sequelae of BPD have been studied; few to date have been proven to decrease both BPD and later disability.

INTRODUCTION

Worldwide, 5% to 18% of infants are born early (before 37 weeks) and, despite a slight decline in recent years, 10% of infants born in the United States each year are premature.[1,2] Modern practices have led to improved survival to discharge for preterm infants throughout the world, with the most significant improvements among the smallest and most immature infants. Mortality and both the incidence and severity of morbidities of prematurity increase with decreasing gestational age.[3] Lung diseases, namely respriatory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD), remain leading causes of mortality among premature infants. Although

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historically BPD was caused by a combination of barotrauma and oxygen toxicity, BPD in modern neonatology refers primarily to an arrest of lung development that is unique to the most extremely prematurely born children.[4] Although the optimal definition of BPD is under debate, it is most commonly defined as a need for supplemental oxygen at 36 weeks postmenstrual age (PMA) (**Fig. 1**).[5] The literature suggests that mortality from BPD and RDS in the United States has fallen in recent years, from 83 deaths per 1000 live births 22 to 28 6/7 weeks in 2000 to 2003 to 68 per 1000 live births in 2008 to 2011 (P = .002).[6] However, this also corresponds with significantly increasing rates of BPD among the same immature infants, from 32% in 1993 to 47% in 2012 (**Fig. 2**).[3] This trend reflects, at least in part, improved survival of the most extremely premature infants.[3] This article explores what is currently known about the effects of survival with BPD on respiratory and developmental outcomes during early and middle childhood. The article then discusses the impact of efforts to reduce BPD on these outcomes. Lastly, the article briefly presents an agenda for future research to improve the outcomes of infants and children in this high-risk population.

THE IMPACT OF BRONCHOPULMONARY DYSPLASIA ON MEDICAL OUTCOMES IN EARLY CHILDHOOD

In the early years, after discharge from the hospital, BPD is associated with increased hospital readmissions as well as increased utilization of medical resources.[7–9] Smith and colleagues[7] demonstrated that among infants born less than 33 weeks and discharged from 6 level 3 neonatal intensive care units in Northern California, 49% of those with BPD and 23% of those without BPD were rehospitalized in the first year of life. In addition, children with BPD had significantly more and longer rehospitalizations.[7] The inverse is also true. Extremely preterm infants who were rehospitalized between initial discharge and 18 to 22 months were more likely to have BPD, were more likely to have received postnatal steroids for prevention or treatment of BPD, and had a longer average duration of mechanical ventilation and supplemental oxygen exposure while in the hospital.[10] Furthermore, infants who were rehospitalized were more likely to have been discharged on supplemental oxygen or diuretics.[10] Importantly, excess hospitalizations among infants with BPD are not exclusively due to

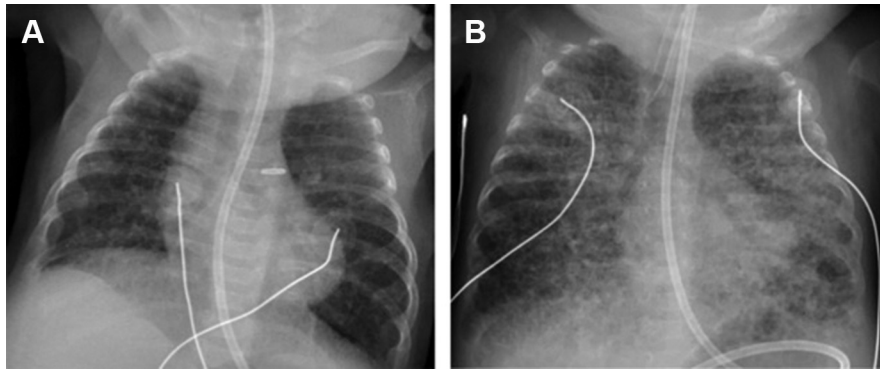

Fig. 1. Chest radiographs of infants born at 23 weeks gestation (*A*) and 26 weeks gestation (*B*), both obtained at 36 weeks PMA. Infant A remained on noninvasive positive pressure ventilation and less than 30% Fio_2, whereas infant B remained intubated with 40% to 50% Fio_2. Therefore, both met criteria for severe BPD. (*Data from* Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723–9.)

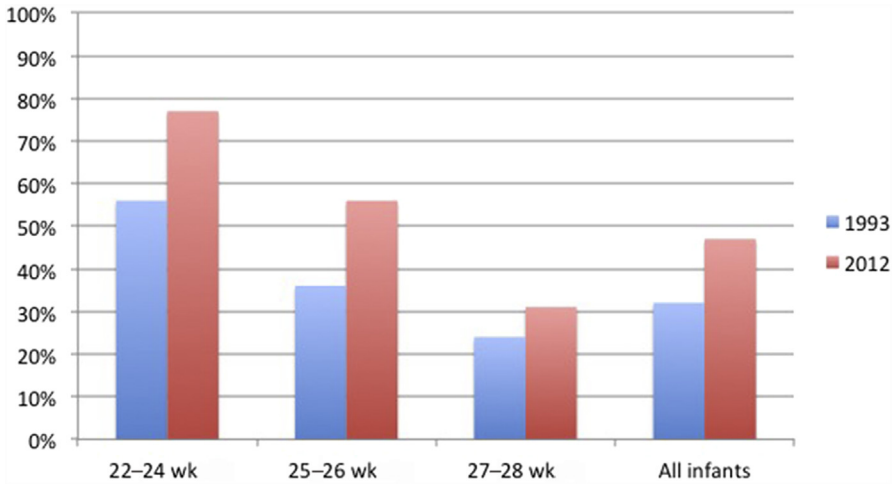

Fig. 2. BPD rates in infants who were born at 22 to 28 6/7 weeks of gestation and survived to 36 weeks postmenstrual age in 1993 and 2012. (*Data from* Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314(10):1039–51.)

respiratory causes, highlighting the fact that children with BPD suffer from chronic illness that may affect many body systems.

Beyond hospitalizations, parents of children with BPD are far more likely to endorse respiratory symptoms and bring their children to the emergency room or doctor for these symptoms during the first 2 years of life. In the Breathing Outcomes Study conducted by the NICHD Neonatal Research Network, 48% of 918 extreme low birth weight (ELBW) study participants experienced wheezing more than twice per week during at least one 2-week period and 31% experienced more than 3 days of coughing without a cold before 18 to 22 months of age.[11] In the same cohort, 26% used inhaled steroids, 9% used systemic steroids, 63% went to the doctor, 47% went to the emergency room, and 31% were hospitalized for breathing problems.[11] Nearly all of these outcomes were significantly more common among children with BPD than among those without BPD. Furthermore, families of children with BPD were more likely to have to alter plans because of the child's breathing problems (41% vs 32%, $P<.05$).[11]

Lastly, growth failure is common among infants with BPD. This failure is concerning because both developmental outcomes and lung recovery are correlated with growth in extremely preterm infants.[12,13] Importantly, the cohort of infants with BPD who require supplemental oxygen after discharge may be at highest risk for poor growth after discharge and the associated sequelae.[9]

THE IMPACT OF BRONCHOPULMONARY DYSPLASIA ON DEVELOPMENTAL OUTCOMES IN EARLY CHILDHOOD

Several large trials and cohort studies have demonstrated increased risk for delays in development during early childhood in preterm-born children with BPD, when compared with preterms without BPD.[13–18] In a single-center cohort of ELBW infants born in the mid-1990s, Hack and colleagues[16] reported that BPD significantly increased odds of both scoring less than 70 (2 standard deviations below the

expected population mean of 100) on the Bayley Scales of Infant Development: 2nd Edition Mental Development Index (MDI) (adjusted odds ratio [aOR] 2.18) and being diagnosed with a neurologic abnormality (aOR 2.46) at 20 months corrected age. In a multicenter cohort from the same era, Vohr reported that BPD was an independent risk factor for Bayley MDI less than 70, Bayley Psychomotor Development Index (PDI) <70, failure to walk independently, and failure to feed independently by 18 to 22 months corrected age.[17] In a large cohort of 3-year-olds with and without BPD, BPD was significantly associated with increased risk for both mild and severe neurodevelopmental disability.[13] In a longitudinal study, Singer and colleagues[18] compared preterm-born children with BPD to very low birth weight (VLBW) and full-term controls at 8, 12, 24, and 36 months. At all time points, the children with BPD had lower MDI and PDI scores than both control groups. In multivariable models, BPD was strongly and independently predictive of motor development (PDI) at 3 years.[18] Furthermore, in 2 separate multicenter trial cohorts, Schmidt demonstrated that BPD is independently predictive of death or developmental impairment at both 18 to 21 months corrected age and 5 years.[19,20] In these studies, the impact of BPD is similar in magnitude to, and independent of, the impact of severe brain injury or severe retinopathy of prematurity on neurodevelopmental impairment.

However, the consistency of results across these studies of early childhood assessments belies the complexity of the relationship between lung disease and outcomes. Not all infants with "BPD" have the same severity of respiratory illness or the same risk for adverse developmental outcomes over time; in fact, not all infants with BPD have poor outcomes. To date, no one characteristic or combination of characteristics have yet been identified that are sufficient to predict with certainty which infants with BPD will go on to have developmental problems. Two studies have demonstrated that infants with BPD who are discharged on supplemental oxygen do not have a specific developmental disadvantage at 1.5 to 3 years when compared with infants with BPD who are not discharged on oxygen.[13,21] On the other hand, the adjusted odds of death or developmental impairment at 18 to 22 months in preterm infants with tracheostomies are 3.3 (95% confidence interval [CI] 2.4–4.6) times higher than in those without tracheostomies.[22]

Nearly all prior studies define BPD as a dichotomous outcome, diagnosed after either 28 days of oxygen exposure or supplemental oxygen use at greater than 36 weeks postmenstrual age. Few have used more nuanced approaches to categorize children based on severity of lung disease. One study compared developmental quotient among preterm-born children with less than 28 days of oxygen, more than 28 days of oxygen, and oxygen until older than 36 weeks postmenstrual age.[23] Although there were no differences between groups based on these categorical outcomes, duration of mechanical ventilation (in days) was strongly and independently correlated with developmental quotient. Similarly, using observational data from the NICHD Neonatal Research Network, Walsh and colleagues[14] found that total duration of invasive respiratory support was correlated with risk for death or developmental impairment at 2 years in ELBW infants (**Fig. 3**). Thus, as compared with dichotomous outcomes, use of more detailed categorization schemes may allow for improved understanding of the impact of severity of neonatal lung disease on longer-term outcomes.

Given the frequency of BPD among preterm infants and the clear impact of lung disease on over the first few years of life, it is essential to also describe the longer-term impact of BPD as children grow. School age assessments are critical for understanding how medical status evolves over time. In addition, many cognitive and functional outcomes cannot be assessed until early school age.

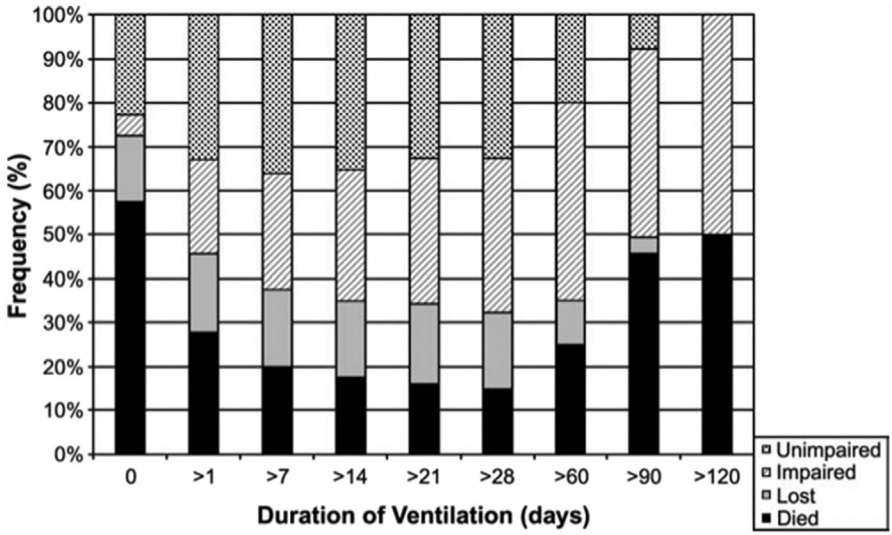

Fig. 3. Distribution of survival to 18 to 22 months corrected age with and without impairment, defined as Bayley-2 MDI less than 70, PDI less than 70, moderate or severe cerebral palsy, bilateral blindness, or deafness, among 3782 infants in the NICHD Neonatal Research Network. (*From* Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. J Pediatr 2005;146(6):801; with permission.)

THE IMPACT OF BRONCHOPULMONARY DYSPLASIA ON MEDICAL OUTCOMES AT SCHOOL AGE

BPD increases risk for rehospitalization during childhood. In a recent Israeli population-based study, VLBW children with BPD had significantly increased risk of rehospitalization at least through age 10 years, when compared with VLBW children without BPD.[24] In a population-based study in Washington State, teens (aged 12–20 years) with history of low or very low birth weight had increased risk of respiratory rehospitalizations; this was mediated in part by history of BPD.[25] School-age children with a history of BPD also continue to have frequent doctor visits and at least a quarter still require frequent use of bronchodilators to prevent or relieve cough or wheeze.[26,27]

School-age children with a history of prematurity have worse lung function on spirometry than term comparisons; these outcomes are even worse in the preterm-born children with BPD.[27–31] For example, in a regional follow-up study of school-age children born in Australia in the early 1990s, full-term/normal birth weight children (n = 208) had FEV_1 97.9 ± 11.8; ELBW or very preterm infants without BPD (n = 151) had FEV_1 87.1 ± 11.5; and ELBW/very preterm infants with BPD (n = 89) had FEV_1 81.1 ± 13.7.[29] Several subsequent studies have demonstrated findings consistent with these results.[27,30,31] In a systematic review of 59 studies that reported $\%FEV_1$ during childhood for preterm-born children, those who received supplemental oxygen at 36 weeks PMA had $\%FEV_1$ 18.9% lower than term-born controls.[32] These abnormal pulmonary mechanics translate into more frequent respiratory symptoms and more frequent need for respiratory medication at school age.[27] In the EPICure cohort of infants born before 26 weeks gestational age, 25% carried a diagnosis of asthma at 11 years.[27]

It has recently become apparent that adult survivors of BPD have limited exercise tolerance and increased sedentary behavior when compared with healthy adults.[33–35] Far less is known about how BPD affects functional respiratory outcomes such as exercise tolerance, health-related quality of life, and age-appropriate participation at school age. However, abnormal respiratory mechanics and frequent respiratory symptoms are likely to have important functional impact on school-age children. In a cohort of 126 10-year-old children with a history of preterm birth compared with 34 controls, the preterm-born children had significantly worse performance on some (but not all) measures of exercise capacity in addition to significantly worse lung function on spirometry.[36] Exercise capacity was reduced by more than half in the 20-meter shuttle run, although submaximal exercise capacity as measured by the 6-minute walk test was not significantly decreased in the children with BPD. Children with BPD had lower predicted peak oxygen consumption than preterms without BPD; however, similar to data from spirometry, even "healthy" preterms had predicted peak oxygen consumption far below normative data for their age. More recently, in a cohort of Canadian children born extremely preterm with and without BPD, the children with moderate or severe BPD again had significantly lower oxygen uptake during exercise capacity testing.[31] In a study of 18 children aged 8 to 9 years with a history of BPD, pulmonary function testing, 6-minute walk test distance, and quadriceps strength were significantly lower and exercise heart rate was significantly higher than full-term controls.[37] Yet, not all studies have demonstrated the same association.[38,39] Among 38 children born less than 25 weeks in the United Kingdom and Ireland and matched controls, the preterm infants had lower peak oxygen consumption.[39] In addition, the preterm-born children perceived that physical activity was harder and that they had more difficulty with breathing during exercise when compared with their friends. However, in this small sample with high rates of BPD (71% BPD), these outcomes were not different between preterm children with and without BPD. Because of the lingering uncertainties about the impact of BPD on exercise tolerance and participation at school age, future research focused on these patient-centered outcomes and, if appropriate, strategies to mitigate these effects are essential.

THE IMPACT OF BRONCHOPULMONARY DYSPLASIA ON COGNITIVE AND FUNCTIONAL OUTCOMES AT SCHOOL AGE

Adjusted odds of death or survival with disability at 5 years are 2.3 (95% CI 1.8–3.0) times higher among children with BPD than among those without BPD.[20] Understanding this association, it is critical to look beyond composite outcomes of disability to evaluate the relationships between BPD and specific aspects of development and then to assess the functional impact of these outcomes on the child and family at school age.

BPD is likely to have significant impact on school-age motor outcomes, which may have important functional implications.[40–42] For example, developmental coordination disorder (DCD) is an impairment of fine and gross motor coordination abilities that significantly interferes with performance of daily activities or academic achievement. DCD generally cannot be diagnosed until children are at least 5 years old, and the most severe form is recognized in about 25% of 5- to 14-year-old former very preterm or VLBW children.[43] BPD is a strong predictor of poor performance on the Movement-ABC assessment, the test which is most commonly used to diagnose DCD.[40] Similarly, in a small (n = 27) study of infants with severe BPD and matched preterm-born controls without BPD at 10 years, infants with BPD had significantly increased

rates of abnormal neurologic outcomes, including both fine and gross motor skills, postural stability, and behavioral problems.[42]

Reports of cognitive outcomes at school age are conflicting, and many are from smaller and older cohorts with varying definitions of BPD. However, most suggest that BPD is associated with decreased intelligence quotient (IQ) when compared with both preterm controls without BPD and full-term controls (**Table 1**).[41,44–48] In a 2003 study, Short reported that 8-year-old children with BPD had worse motor, academic, attention, and cognitive skills than both preterm peers without BPD and full-term controls.[41] Furthermore, even when only children without severe neurologic injury were evaluated, both BPD and severity of BPD were associated with worse outcomes across domains and more need for therapy.[41]

On the other hand, a study of 31 infants with BPD and matched preterm controls in North Carolina reported no difference in IQ at 4 to 5 years.[49] Another study of cognitive development and visual-motor skills among 60 very preterm-born children with and without BPD reported no differences when all children with lung disease were grouped together.[50] However, those with the most severe lung disease had the worst developmental outcomes at 5.5 years. Similarly, in a small follow-up study of 11-year-old preterm-born children with and without BPD and full-term controls, Vohr and colleagues[47] reported no difference in full-scale IQ (see **Table 1**), but some children with BPD could not be tested and were therefore excluded from the analyses. They also reported significant increase in need for special assistance in the classroom and abnormal neurologic examination among the children with a history of BPD. Thus, definitions of BPD and classification of children who cannot be tested or scored have significant impact on the results of studies of school-age children with BPD.

Two single-center studies (n <100 children in each) have evaluated the impact of BPD based on the NIH consensus definition of mild, moderate, and severe disease on school-age developmental outcomes, with conflicting results.[5,51,52] In the first, children with severe BPD performed more poorly on the Bayley-2 MDI and PDI at 3 years and had lower full-scale IQ on the Wechsler Intelligence Scale for Children, third edition (WISC-III) at 8 years than those with mild or moderate BPD.[51] A second study found no differences in cognitive, motor, or language outcomes of 3- to 6-year-olds based on severity of BPD.[52]

In parallel, children with BPD have been reported in multiple studies to have worse performance on tests of educational skills than both preterm and full-term controls.[41,44,45,48,53] Those with severe BPD may have the lowest performance on

Table 1
Full-scale intelligence quotient of school-age preterm-born children with and without BPD and full-term controls

First Author and Publication Year	Preterm or VLBW with BPD	Preterm or VLBW Without BPD	Full-Term Controls
Vohr et al,[47] 1991	n = 13 93 ± 21	n = 15 94 ± 13	n = 15 108 ± 11
Robertson et al,[44] 1992	n = 21[a] 88 ± 21	n = 21 97 ± 20	n = 21 115 ± 10
Hughes et al,[45] 1999	n = 95 86 ± 18	n = 311 96 ± 18	n = 188 100 ± 17
Short et al,[41] 2003	n = 98 87 ± 20	n = 75 95 ± 16	n = 99 102 ± 15

[a] Born less than 32 weeks gestation with oxygen dependence at 36 weeks postmenstrual age.

language tests and most measures of academic skills.[51] Children with BPD are more likely to require speech-language services and special assistance in the classroom.[41,47] Importantly, academic success depends on far more than IQ alone; children must integrate executive function, attention, memory, and visual-spatial perception skills. To date, few of these essential aspects of neurocognitive performance have been thoroughly evaluated in large populations of children with BPD.[53,54] Furthermore, it remains unknown how lower IQ and poor academic performance at school age translate into longer-term participation and functional outcomes such as wage earning, social competency, and quality of life in adolescents and adults with BPD.

STRATEGIES TO IMPROVE OUTCOMES

Countless randomized trials have attempted to rigorously evaluate interventions or strategies to decrease the incidence of BPD and thereby improve both short- and long-term outcomes of preterm infants. The international "Caffeine for Apnea of Prematurity" trial demonstrated that neonatal treatment with caffeine reduces BPD, improves developmental outcomes at 2 years, and is associated with improved respiratory mechanics and reduced risk of motor impairment at least until 11 years.[55–58] On the other hand, although treatment with vitamin A reduces BPD, it does not improve developmental outcomes at 2 years.[10] Similarly, surfactant therapy reduces mortality and early morbidities but does not seem to improve longer-term developmental outcomes.[59]

Corticosteroids have been used antenatally, immediately postnatally, and up to several weeks after preterm birth in an effort to reduce lung inflammation and injury. Antenatal steroids reduce mortality and early respiratory distress syndrome and improve developmental outcomes at least until 2 years.[60,61] This effect is evident even down to at least 23 weeks of gestation.[61] However, antenatal steroids do not seem to reduce rates of BPD, especially in the youngest infants. In fact, infants born at 22 to 25 weeks of gestation after antenatal steroid exposure are more likely to survive with BPD than unexposed infants.[61] Postnatal treatment with dexamethasone has been repeatedly demonstrated to reduce BPD; however, use in the first week is associated with increased risk for cerebral palsy and abnormal neurologic outcomes and is therefore not recommended.[62–64] Given these concerns, a recent trial of early prophylactic hydrocortisone demonstrated that this strategy reduced BPD without increasing rates of neurodevelopmental impairment at 2 years.[65,66] Unfortunately, the reduction in BPD also did not translate into improved outcomes at 2 years.

Based on clear observational data that exposure to mechanical ventilation is associated with risk for BPD and adverse outcomes, several trials attempted to decrease rates of intubation and use of mechanical ventilation after birth in extremely preterm infants. These individual trials have failed to demonstrate improved rates of death or BPD.[67,68] However, a meta-analysis of these trials reports a relative risk of death or BPD of 0.91 (95% CI 0.84–0.99) favoring CPAP over immediate intubation at birth for preterm infants less than 32 weeks of gestation.[69] With a 4% risk difference, this translates into a number-needed-to-treat of 25. In the SUPPORT trial, use of noninvasive support in the delivery room was associated with less use of postnatal steroids for treatment of BPD and shorter duration of ventilation during the neonatal hospitalization.[67] At 2 years, this was associated with fewer episodes of wheezing without a cold, respiratory illnesses, and physician or emergency room visits for breathing problems but no improvement in developmental outcomes.[11,70] In fact, recent work from the Victorian Infant Collaborative Study Group in Australia suggests that despite

decreasing use of noninvasive respiratory support over time, respiratory and developmental outcomes in school-age children who were born extremely premature may actually be getting worse.[71,72]

The optimal approach to management of children with BPD after discharge from the hospital is unknown. Little published data are available to guide clinical decision-making for those infants discharged on supplemental oxygen; therefore, oxygen saturation targets, rate of supplemental oxygen titration, and criteria for discontinuation vary widely.[73,74] Management of medication, including diuretics, bronchodilators, inhaled steroids, and many others, is at times performed by general practitioners, pediatricians, developmental follow-up clinics, or pulmonologists. Although early aggressive and goal-directed therapies are increasingly recognized as integral for children at risk for motor disorders, these have not yet been studied specifically in the context of BPD.[75]

Perhaps most importantly, pulmonary function and exercise capacity are linked with cognitive function throughout the lifespan.[76,77] Physical activity interventions improve outcomes of children with attention and behavior problems and improve executive functioning.[78–80] In parallel, increased sedentary behavior is negatively associated with some cognitive outcomes.[81] One study even reported an association between motor development during infancy and cognitive performance at an average age of 64 years.[82] Exercise training or rehabilitation programs improve quality of life and respiratory symptoms for adults with chronic obstructive pulmonary disease; whether the same is true for children with BPD is not known.[83]

SUMMARY AND FUTURE DIRECTIONS

BPD is associated with adverse developmental and medical outcomes both in early childhood and at least through school age. Therefore, BPD imposes a significant burden on infants and children, their families, and society. Whether and how strongly BPD influences trajectories of disease and health over the lifespan remains largely unexplored. Lung function worsens over the lifespan in normal, healthy people. It remains unknown whether lung function deteriorates more quickly in people with a history of BPD and whether this or even a normal trajectory of decline will position adult survivors of BPD for earlier onset of respiratory failure or even mortality.[84]

The current research predominantly uses dichotomous outcomes of "BPD," most recently leaning heavily on the National Institutes of Health consensus definition of supplemental oxygen use at 36 weeks postmenstrual age.[5] However, this definition has been questioned because it is not consistently predictive of longer-term clinically important outcomes and is based on treatment decisions rather than physiology.[85,86] As described earlier, duration of ventilation is independently predictive of developmental outcomes at least until 2 years. Such a graded relationship between severity of lung disease and outcomes has not yet been clearly demonstrated beyond 2 years. It is possible that in future research, more nuanced description of the spectrum of neonatal lung disease will allow investigators to draw stronger associations with specific adverse neurocognitive and respiratory outcomes.

Few therapies have definitively improved both BPD and the longer-term outcomes that are associated with BPD. In future work, it will be essential for neonatologists to continue to pursue therapies that limit damage to the preterm lung and reduce BPD as aggressively as possible. This must include evaluation of treatments and management strategies both in the neonatal intensive care unit and after discharge. Beneficial strategies may include not only modifications of current care such as different approaches to ventilation but also novel therapeutics in the neonatal period, including stem cell

therapy, liquid ventilation, and use of the artificial womb and aggressive pulmonary rehabilitation and exercise training for children with BPD. Long-term follow-up will be critical for understanding the influence of these new interventions on functional outcomes of children with BPD over the lifespan.

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