Bronchopulmonary Dysplasia

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Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common morbidities of prematurity. It is a disease characterized by abnormal continued development and repair after premature birth and exposure to oxygen, mechanical ventilation, and inflammation. Outcomes reported from the National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) over the last 20 years have shown modest but significant decreases in mortality and many major morbidities for even the smallest infants [1]. However, the incidence of BPD remains at approximately 50% for the smallest infants, which has remained steady or slightly increased over the previous two decades [1]. This trend has been seen across the country and across the world [2]. Infants with BPD continue to have lung disease into childhood with higher rates of viral infections, need for respiratory support, and increased risk for asthma [3–5]. They also are at higher risk for growth failure and neurodevelopmental impairment [4].

Definition of BPD

BPD was first described in 1967, but the definition has changed several times over the last few decades. An early definition of BPD was the requirement for supplemental oxygen at 28 days following the diagnosis of hyaline membrane disease in premature infants [6]. This original form of BPD was characterized by extensive inflammatory changes with fibrosis created in the setting of aggressive mechanical ventilation and exposure to high oxygen concentrations [7, 8]. When this definition was first accepted, the majority of infants diagnosed with BPD were born at over 32 weeks' gestational age. Over time, the term BPD has evolved to describe a very different disease. In more recent years, the infants diagnosed with BPD are born at much younger gestational ages, typically below 26 weeks' gestation. They have less severe initial respiratory distress syndrome (RDS) and exposure to less iatrogenic injury. These infants, born in the exogenous surfactant era, do not have the same extensive lung scarring that was seen in previous generations. In the modern era, some infants who develop BPD never had RDS or had only mild disease. The "new BPD" can be characterized as abnormal development in the setting of extremely preterm birth. The lungs of these infants, born just at the transition of canalicular to saccular stages of lung development, do not reach the ultimate branching complexity as is seen in the term newborn lung, leading to fewer and larger alveolae [7, 8]. The newer definition of BPD was defined as oxygen use at 36 weeks post-menstrual age.

The current NIH consensus definition was established in 2000. It defines BPD as lung disease in infants born at less than 32 weeks' gestation and requiring oxygen for at least 28 days and defines its severity based on level of oxygen requirement at 36 weeks post-menstrual age (PMA) (Table 45.1).

Table 45.1 Classic definition of BPD based on NIH consensus guideline published in 2001

Mild BPD	Infants who are breathing room air at 36 weeks' PMA or discharge, whichever comes first
Moderate BPD	Infants who are on less than 30% oxygen at 36 weeks' PMA or discharge
Severe BPD	Infants who require greater than 30% oxygen or positive pressure at 36 weeks' PMA

Data from Jobe and Bancalari [106]

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New Directions: New Definition, New Studies

Work continues as clinicians and researchers continue to improve the respiratory care of the smallest infants. A new definition of BPD is being discussed at this time which acknowledges the degrees of respiratory support which may be required at 36 weeks. It also provides a mechanism to compare the severity of BPD which infants may have. A common concern is that the definition of requiring oxygen at 36 weeks does not allow for variation in severity or allow a reasonable comparison of later pulmonary outcomes. Initial studies evaluating this new classification system were also able to predict later death and serious morbidity.

New BPD Definition (Table 45.2)

Pathophysiology

The original description of BPD was of moderately preterm infants who had severe respiratory failure due to hyaline membrane disease and required long-term ventilatory support [6]. The injury in these infants was due to mechanical trauma from the pressure needed to open these non-compliant lungs and from oxygen toxicity. Although the infants now diagnosed tend to be much younger and smaller, these same mechanisms remain important.

Inflammation

In the modern era of prenatal steroids and exogenous surfactant administration, inflammation from ventilation and oxygen toxicity continues to be seen despite lower amounts of both being used. How much of this inflammatory damage happens prenatally vs postnatally remains unclear. Higher concentrations of inflammatory cytokines have been found in the amniotic fluid of women whose infants went on to develop BPD; elevated IL1B, IL 6, and IL 8 in the amniotic fluid predicted the development of BPD in those infants [9, 10]. Increased levels of inflammatory cytokines, as well as increased inflammatory cells, have also been seen in the tracheal aspirates of infants who progress to development of BPD [11–17]. Experimental models have also shown that elevated cytokine expression, specifically increased IL 6 and TNF-alpha, cause an arrest of alveolar septation leading to larger alveolae with increased fibrosis [18].

Oxygen is essential for life and aerobic metabolism, but when delivered at high concentration can be toxic due to free radical production and subsequent injury. Discussion of the damage created by oxygen toxicity has continued since the first descriptions of BPD [6, 19, 20]. The toxicity of oxygen is associated with the formation of reactive oxygen species such as OH*, NO, H_2O_2, O_2^-, and LOOH [21]. It has been shown that premature infants have lower levels of antioxidants than adults or term infants, making them particularly sensitive to the damaging effects of oxygen. It is the imbalance of oxidant versus antioxidant species which has been proposed to be the cause of oxygen toxicity.

At the same time infections (both prenatal and postnatal) are both significantly associated with the development of BPD. Inflammation has therefore been hypothesized to be a primary actor by some investigators, but merely an associated mediator by others.

Infection

Infection and inflammation leading to BPD can begin prenatally. In mothers with both clinical and subclinical chorioamnionitis, the infants have an elevated risk of BPD. The inflammatory injury within the fetal lung either can be triggered by feedback from inflammatory cytokines from the placenta and fetal membranes or can take place in the setting of aspiration of infected fluid and direct injury [18]. Many clinical reports have determined that maternal colonization by ureaplasma urealyticum and other atypical bacteria increase the risk of BPD [22, 23]. Atypical bacteria such as ureaplasma urealyticum and ureaplasma parvum are commensal bacteria which colonize the genital tract and have been isolated in the placenta as well as in premature neonatal secretions (gastric, tracheal, etc.) [24]. Studies have demonstrated that, in premature animals injected with ureaplasma urealyticum and exposed to mechanical ventilation, those who were unable to clear the bacterial were more likely to have chronic inflammation and develop chronic lung disease [24]. In contrast exposure to these pathogens was associated with decreased severity of RDS and early lung maturation [18, 25–27]. This supports the theory that the exposure to atypical bacteria may predispose to abnormal lung develop-

Table 45.2 New proposed definition of BPD based on work by Eric Jensen et al. (2019)

No BPD	Grade 1		Grade 2			Grade 3	
Room Air	Nasal Canula <2 L/min		NC > 2 L/min		nCPAPA/NiPPV	Invasive PPV	
	<30%	>30%	<30%	>30%	Any FiO2	<30%	>30%

Data from Jensen et al. [107]

ment or may alter the way that the lung tissue responds to other pathogens. Other researchers were able to show that chronic ureaplasma infection in fetal sheep is associated with altered innate immune responses [28]. Despite an abundance of research into the association of infection or colonization with atypical bacteria, no study has been able to demonstrate causation. In addition, clinical studies looking at use of macrolides to treat ureaplasma infection have failed to demonstrate improvement in the rate of BPD [24, 29, 30].

Other studies have looked at colonization or infection after birth as contributing to the development of BPD. In one study evaluating tracheal aspirates taken in VLBW found an association of gram-negative rods in those infants who developed BPD [31]. It is likely that an interplay between exposures contributes to BPD.

Immaturity

A critical component to the development of BPD is the immaturity of the premature lung. The vast majority of infants who develop BPD are born at less than 26 weeks' gestation. At that developmental stage, the developing lungs remain in the "saccular" stage of development. The development of the lungs follows a staged process, and the transition from canalicular to saccular stages happens at approximately 22–23 weeks. Pathological studies in both animals and humans have shown that exposure to both oxygen and pressure causes arrest and atypical lung development with decreased septation – with fewer and larger alveolae [32–35]. In examining pathological samples, extremely premature infants have lower radial alveolar counts than control infants [32]. In the setting of extreme prematurity, exposure to oxygen and mechanical ventilation can adversely affect lung development and alter cellular differentiation [36–38]. A key to survival is rapid maturation and the ability of the premature lungs to function for gas exchange. However, it is possible that in that process, those early maturational changes lead to scarring which contributes to the development of BPD.

Ventilator Injury Pressure/Volume

The initial descriptions of BPD described the relationship of mechanical ventilation with BPD. Further research has shown that even a few breaths of positive pressure can cause damage leading to increased risk of BPD [39]. Cyclic stretch and overdistension of the lung tissue cause direct inflammation and injury. This promotes further inflammation and inhibits normal lung growth and differentiation. Great debate exists on whether the mechanical injury is more from the direct effect of pressure or whether it is the changes in volume, from the pressure that caused the primary injury. In experimental animal models exposed to high levels of positive inspiratory pressure, either with or without a rigid external chest wall cast (to limit pressure changes), the pressure alone, without changes in lung volume, resulted in significantly fewer cases of BPD. Given concern about the injury caused by volume changes, newer ventilation strategies have emerged.

Avoiding mechanical ventilation is associated with lower rates of BPD. Multiple large, multicenter studies have shown the benefit of avoiding mechanical ventilation to decrease development of BPD [40–45]. Applying noninvasive positive pressure rather than intubation and mechanical ventilation decreases the rate of BPD [41, 42, 44].

In some cases, intubation and mechanical ventilation cannot be avoided. In those cases, exogenous surfactant should be given to decrease the damage from positive pressure ventilation. Providing early selective surfactant (within 2 hours of delivery) to infants with worsening respiratory distress syndrome decreases the risk of air leaks and neonatal morbidity and chronic lung disease [46–48] (Fig. 45.1).

Current Management Strategies

As our understanding of the pathophysiology of BPD has increased, strategies have been adopted to try to decrease the incidence of BPD. Central to this is the early respiratory management of extremely premature infants. To successfully accomplish transition from fetal life to extrauterine breathing, the lungs must rapidly expand, clear themselves of fluid, and begin gas exchange. This requires the establishment of functional residual capacity (FRC). Surfactant is a naturally occurring substance which decreases the surface tension in the lungs, increases compliance, facilitates gas exchange, and allows the maintenance of FRC. Prophylactic and selective surfactant administration decreases both mortality and pulmonary air leaks when administered in the first hours of life. Prophylactic surfactant is defined as giving surfactant to all infants at risk of RDS, typically defined by a specified birth gestational age or birth weight criteria, in the delivery room, typically within 30 minutes of birth or ideally prior to positive pressure ventilation. The clinical practice of selective surfactant administration involves placing at-risk infants on noninvasive positive pressure in the delivery room and then intubating and giving surfactant only if certain clinical criteria are met. Over the last decade, further studies have evaluated different delivery room strategies, particularly comparing these two approaches. Use of early nasal CPAP with selective surfactant administration if certain oxygen needs or hypercarbia limits were met resulted in decreased BPD [40, 41, 44]. A meta-analysis of several of these trials showed that prophylactic intubation and surfactant adminis-

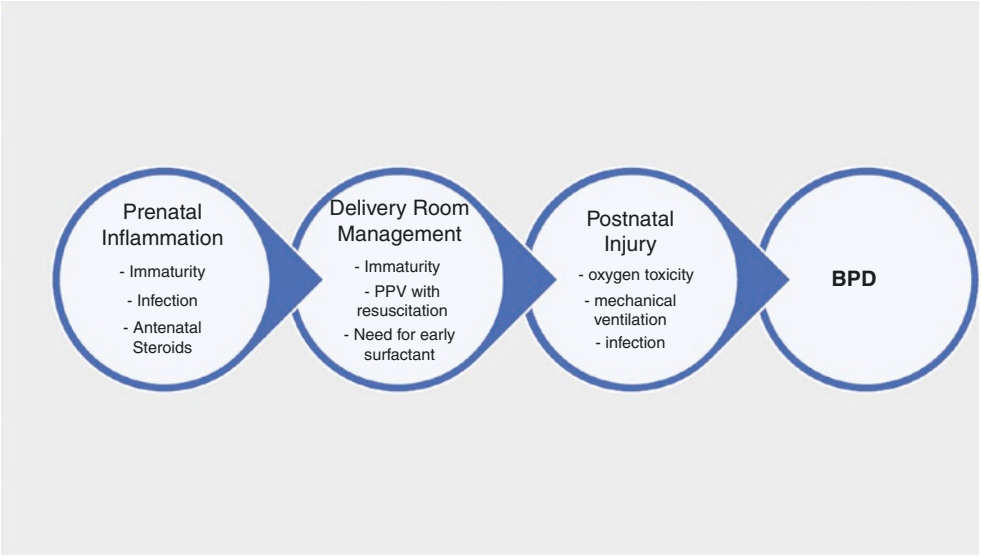

Fig. 45.1 Conceptual model of pathogenesis of BPD

tration with extubation to CPAP resulted in increased risk of death or BPD (RR 1.12 with number needed to harm 17). If intubation and mechanical ventilation is needed, earlier surfactant (i.e., within 2 hours of delivery) is preferable to delayed administration [48–50].

If intubation and mechanical ventilation is needed, a gentle ventilation strategy with permissive hypercapnia decreases the rate of BPD without increasing other morbidities. Permissive hypercapnia (targeting CO2 > 52 compared to <48) was evaluated in a multicenter trial by the Neonatal Network. In this trial permissive hypercapnia resulted in decreased need for ventilation at 46 weeks from 16% to 1% [51]. However another study comparing even more permissive hypercapnia up to 75 mmHg on day 7–14 did not show any benefit [52]. Some animal research suggests that CO2 may have direct benefit on the lung. However, much of the benefit appears to come from a more conservative approach to intubation and a more aggressive attitude toward extubation [43]. A more permissive attitude toward CO2 also allows a gentler approach to ventilation, with lower minute ventilation typically through lower inspiratory pressures.

Traditional pressure-controlled ventilation risks change in volume and resulting volutrauma. Rapid changes in compliance may be caused by clearance of fetal lung fluid and/or surfactant administration and other changes in the first hours of life. As a result, newer forms of mechanical ventilation have come to be favored which target a specific volume and decrease both volutrauma and atelectrauma. Several trials have evaluated volume-targeted ventilation of premature infants who require mechanical ventilation. A meta-analysis of these showed decreased BPD and mortality in the use of volume-targeted strategies [53, 54]. Other studies have evaluated the effectiveness of high-frequency ventilation to decrease BPD. There are two modes of high-frequency ventilation – the high-frequency oscillator (HFOV) and the high-frequency jet ventilator (JET) which are widely available in the United States and have been extensively studied. Both rely on an open lung strategy with high mean airway pressure to maximize oxygenation. The trials of these ventilators have shown mixed results regarding decreasing mortality or BPD [53, 55–57].

Management Strategies to Reduce Lung Injury and Development of BPD

Currently best recommendations based on the available evidence:

- Provide nasal CPAP to establish FRC in the delivery room.
- Provide selective surfactant within 2 hours of birth if needed.
- Extubate to nasal CPAP as soon as possible.
- If continued intubation and mechanical ventilation is necessary, use gentle ventilation with an open lung strategy and volume-targeted approach which minimized volutrauma and atelectrauma.

Medications

Despite extensive research over many years, few medications have been identified which impact BPD. The most important of these is caffeine. Caffeine is a methylxanthine, commonly used to decrease apnea of prematurity. In the Caffeine for Apnea of Prematurity (CAP) trial, over 2000 infants with birth weights between 500 g and 1250 g were assigned to caffeine versus placebo. The infants who received

caffeine had a significantly lower rate of BPD, were able to come off positive pressure on average 1 week earlier, and had improved neurodevelopmental outcomes [58, 59]. Additional research has shown that earlier caffeine is associated with improved rates of BPD compared with later administration. In post hoc analyses of the CAP trial, infants who started on caffeine before 3 days were less likely to develop BPD compared to those who started later [60–62]. In a large retrospective study of more than 62,000 infants, the rate of BPD was significantly lower in infants who received early caffeine. They were also exposed to significantly less mechanical ventilation [62].

Vitamin A is another medication which has shown promise in decreasing BPD. In 1999, Tyson et al. published the results of their placebo-controlled randomized trial of prophylactic vitamin A. In this study, 807 infants with birth weights between 400 and 1000 g received either 12 IM injections of vitamin A or a sham procedure over the first 4 weeks of life. Use of vitamin A was associated with a significantly decreased rate of BPD; 55% of the infants receiving vitamin A developed BPD compared to 62% in the placebo group (NNT = 14–15 infants) [63]. Follow-up data at 18–22 months continued to show a mild but not statistically significant improvement for the infants in the vitamin A group, without evidence of harm [64, 65]. Despite initial interest in this treatment, the small benefit in risk of BPD must be balanced against the acceptability of the intervention, which required 12 intramuscular injections in the first weeks of life [66].

Inhaled corticosteroids are another therapeutic modality which has been evaluated as a potential preventative treatment of BPD. In a large multicenter randomized placebo-controlled trial of inhaled budesonide to prevent BPD, 863 infants were randomized to budesonide versus placebo. Budesonide was associated with a small but significant decrease in the primary outcome, the combined outcome of death, or bronchopulmonary dysplasia. However, this was due to a significant decrease in the rate of BPD (27.8% vs 38%) but a slight increase in mortality (16.9% vs 13.6%) [67]. Another trial using fluticasone showed similar results. In this trial 211 infants were randomized to inhaled fluticasone within the first 24 hours compared to placebo [68]. This study also showed a decrease in the incidence of BPD with an increase in the incidence of pre-discharge death. Based on these studies and a few other very small trials, inhaled steroids cannot yet be recommended for the prevention of BPD.

Steroids

Systemic corticosteroids have been used in the treatment and prevention of BPD for many years. Prenatal steroids are one of the most effective therapies in neonatal medicine. Prenatal steroids have been shown to decrease RDS, improve survival, and decrease intraventricular hemorrhage [69]. In the 1980s, clinicians observed that premature infants treated with corticosteroids had improved respiratory status. Use of dexamethasone was associated with decreased need for mechanical ventilation, decreased need for supplemental oxygen, and decreased BPD [70]. A review in 2010 found 20 studies involving 2860 infants treated with early (started at <7 days) to prevent BPD. These studies involved a range of doses and durations of therapy. Early dexamethasone treatment was associated with decreased rate of BPD, defined by need for oxygen or positive pressure at either 28 days or 36 weeks. It was also associated with earlier extubation and decreased severe retinopathy of prematurity. Importantly, dexamethasone was also associated with increased risk of several important adverse in hospital events including GI bleeding, GI perforation, hypertension, and hyperglycemia [71].

Later outcomes were reported in 7 of the studies involving 921 infants. Most significantly, the combined outcome of death or cerebral palsy was significantly increased in the infants exposed to dexamethasone [71]. Similar findings were seen in trials of later dexamethasone. Use of dexamethasone after the first week of life was associated with a decrease in the length of mechanical ventilation, decrease in infants failing extubation, and decrease in BPD. However, this was offset by an increase in cerebral palsy [72]. In a large study of dexamethasone in a 42-day tapering course, the rate of cerebral palsy was 25% in the treatment group compared with 7% in the placebo, and 45% of infants had an abnormal neurological exam compared to 16% [73]. These findings led to statements by the American Academy of Pediatrics and the Canadian Paediatric Society and the European Association of Perinatal Medicine recommending against the routine use of systemic dexamethasone for prevention or treatment of BPD [74]. These recommendations and the increased recognition of the adverse long-term neurological effects of postnatal steroids led to a dramatic decrease in their use. In a review of a national database, steroid use decreased from 23.5% to 11% between 1997 and 2004 [75]. This was also associated with an increase in BPD during the same period. As BPD is associated with worse neurological outcomes, independent of gestational age, some researchers and clinicians have speculated that, in a specific cohort of infants, there could be a balance where the benefit from steroids may outweigh the potential risks, particularly for later administration of steroids [4, 74, 76].

Other investigators have looked at the role of other systemic corticosteroids, specifically hydrocortisone. Early prophylactic hydrocortisone was studied in a group of over 1000 ELBW infants between 24 and 28 weeks in the PREMILOC trial. This study showed a modest decrease in BPD in the intervention group without any difference in neurological outcomes at 18–22 months [77, 78]. Interestingly, this study

also looked at later respiratory outcomes in the infants at 18–22 months and did not find any difference. A pilot study evaluating stress dose hydrocortisone administered to ventilator-dependent ELBW infants between 10 and 21 days postnatal age with a tapering course over 7 days did not show any significant differences in either respiratory or neurological outcomes [79]. One study which is ongoing is the SToP BPD study which is a randomized controlled trial of hydrocortisone given over a 22-day tapering course [80]. Taken together there is some promise for the use of hydrocortisone to prevent or treat BPD, but its safety and efficacy remain uncertain.

Long-Term Implications

Despite improved neonatal care focused on prevention of BPD, the incidence of BPD, particularly among the smallest infants, continues to be significant [1]. These infants continue to exhibit respiratory symptoms long after discharge from the NICU [4, 5, 81]. Studies of former premature infants have shown that infants with BPD continue to have increased respiratory symptoms and increased need for respiratory medications for years [5, 82, 83]. Infants with BPD are more likely to be discharged home on oxygen and more likely to be rehospitalized within the first 2 years with a respiratory complication than premature infants without BPD [84–86]. In one series 73% of infants with BPD were rehospitalized within the first 2 years, and 27% had more than three readmissions [87]. Infants with BPD are more likely to be seen by both pediatric and specialty providers more often. They are more likely to be on chronic respiratory medications, such as inhalers [84, 86, 87]. When examining pulmonary function testing results, premature infants have significantly worse FEV_1 both in the pre-surfactant era and in the post-surfactant era [88]. Studies have also shown an increased risk of airway reactivity in former premature infants and a decreased exercise tolerance [88]. Both appear to improve over time but may not completely resolve.

Infants with BPD are more likely than age-matched premature infant controls to have neurological and developmental impairment. In one study of infants with severe BPD, they found that those infants had some neurological impairment in 71% of infants compared to 19% of control premature infants [89]. In larger cohort studies of the NICHD, BPD has been shown to be an independent risk factor for cerebral palsy [90, 91]. In more recent work, "severe BPD" as defined as the need for mechanical ventilation at 36 weeks was a predictor for cerebral palsy [92]. Infants with BPD had increased risk for multiple different types of neurological impairment. They were at increased risk for cerebral palsy, language delay, cognitive delays, and even attention and behavioral problems [4, 81, 90, 93]. These differences persist into school age. Infants with BPD continue to have increased academic challenges. Infants with BPD were more likely to have lower IQ scores, need increased special education services, and have poorer organizational and academic (mathematics and reading) skills compared to premature infants without BPD at 8 years of age [94].

Growth outcomes are also affected by BPD. Infants with BPD had significantly lower weights and head circumference at 18–22 months compared to premature age-matched controls [93]. Some studies have shown that linear growth is more affected than weight in infants with BPD [91, 95]. Growth can be improved in infants with BPD through use of oxygen supplementation as an outpatient. In studies where infants were compared between having oxygen with improved saturations compared to without oxygen, growth was significantly better [96].

Infants with BPD are frequently also affected by recurrent episodes of intermittent hypoxia. This can affect extremely premature infants both with and without BPD. Intermittent hypoxia is related to immature respiratory control and inconsistent stimulation from the respiratory control centers in the brain [97]. This is combined with immature and weaker musculature of the upper airway which combine to create apnea of prematurity, a form of apnea which has central and obstructive components [98]. Apnea of prematurity typically resolves between 36 and 40 weeks post-menstrual age. However, intermittent hypoxia and apnea frequently last even until 42 or 43 weeks, particularly in those extremely immature infants [99, 100]. Apnea of prematurity is typically treated with methylxanthines. Caffeine has been shown to be an effective treatment for apnea and has been shown to decrease BPD [59] and can also decrease intermittent hypoxia [99]. However, these alterations do not completely resolve as the infants mature. Studies have shown that sleep-disordered breathing may persist for many years. A study conducted in the United States found that premature infants were 3–5 times more likely than their term counterparts to have sleep-disordered breathing at 8–11 years of age [101]. In a Swedish cohort study, young adults who had been former low birth weight infants were twice as likely to have sleep-disordered breathing compared with those who had been born at term [102]. In addition, former premature infants who have sleep-disordered breathing later in life are more likely to experience more negative cognitive effects [103]. Infants who had been born premature are at higher risk of obstructive sleep apnea (OSA) during childhood [104, 105]. Where in the general population of children approximately 4% may have OSA, the rate is more than double that in former premature children [104]. They are also more likely to have other sleep disorders such as periodic limb movements of sleep compared with their term counterparts [104]. Given the high rate of exposure to methylxanthines, particularly caffeine which can affect sleep, researchers have

looked back at the infants who participated in the CAP trial and found no difference in sleep disorders between infants exposed to caffeine compared to placebo [104, 105]. This is still an area of active research as infants born premature are at risk for learning and behavior difficulties and sleep disorders is an additional risk.

Outpatient Management Strategies

Infants with BPD frequently continue to need significant care and management after discharge. As BPD is partly defined by the need for oxygen and respiratory support at 36 weeks, many of these infants are being discharged from the NICU on oxygen. The physiological need for this oxygen can come from a variety of causes. In some infants, it is related to poor diffusion across the alveolar capillary membrane resulting from the inflammation and scarring from earlier injury. While in others, the oxygen requirement may be related to the intermittent hypoxia from immature respiratory patterns. Pulmonary hypertension is another common diagnosis which complicates pulmonary outcomes for infants with BPD. Infants with BPD should be provided with supplemental oxygen to maintain saturations greater than 95% to support growth and improved neurodevelopment. Infants should be kept on pulse oximetry monitors to monitor oxygen saturations. Weaning off supplemental oxygen at home is a complicated problem, and currently there are not clear guidelines. Practice varies and may involve echocardiogram, blood gas, or polysomnography. Infants with BPD have increased nutritional needs and generally have increased caloric requirements. Ideally infants with BPD should be followed at a multidisciplinary clinic with expertise in the care of former premature infants. In this way these complicated and still vulnerable infants can be monitored and well supported in an outpatient setting. Critical components of this clinic would include pulmonary, nutritional, and developmental expertise.

References

1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA. 2015;314(10):1039–51.
2. Gortner L, Misselwitz B, Milligan D, Zeitlin J, Kollée L, Boerch K, Agostino R, Van Reempts P, Chabernaud J-L, Bréart G. Rates of bronchopulmonary dysplasia in very preterm neonates in Europe: results from the MOSAIC cohort. Neonatology. 2011;99(2):112–7.
3. Vom Hove M, Prenzel F, Uhlig HH, Robel-Tillig E. Pulmonary outcome in former preterm, very low birth weight children with bronchopulmonary dysplasia: a case-control follow-up at school age. J Pediatr. 2014;164(1):40–45.e44.
4. Doyle LW, Anderson PJ. Long-term outcomes of bronchopulmonary dysplasia. In: Seminars in fetal and neonatal medicine: 2009. Elsevier; 2009. p. 391–5.
5. Bhandari A, McGrath-Morrow S. Long-term pulmonary outcomes of patients with bronchopulmonary dysplasia. In: Seminars in perinatology: 2013. Elsevier; 2013. p. 132–7.
6. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med. 1967;276(7):357–68.
7. Bancalari E, Claure N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. In: Seminars in perinatology: 2006. Elsevier; 2006. p. 164–70.
8. Baraldi E, Carraro S, Filippone M. Bronchopulmonary dysplasia: definitions and long-term respiratory outcome. Early Hum Dev. 2009;85(10):S1–3.
9. Yoon BH, Romero R, Jun JK, Park KH, Park JD, Ghezzi F, Kim BI. Amniotic fluid cytokines (interleukin-6, tumor necrosis factor-α, interleukin-1β, and interleukin-8) and the risk for the development of bronchopulmonary dysplasia. Am J Obstet Gynecol. 1997;177(4):825–30.
10. Yoon BH, Romero R, Kim KS, Park JS, Ki SH, Kim BI, Jun JK. A systemic fetal inflammatory response and the development of bronchopulmonary dysplasia. Am J Obstet Gynecol. 1999;181(4):773–9.
11. Groneck P, Götze-Speer B, Speer CP, Oppermann M, Eiffert H. Association of pulmonary inflammation and increased microvascular permeability during the development of bronchopulmonary dysplasia: a sequential analysis of inflammatory mediators in respiratory fluids of high-risk preterm neonates. Pediatrics. 1994;93(5):712–8.
12. Speer C. Pulmonary inflammation and bronchopulmonary dysplasia. J Perinatol. 2006;26(S1):S57.
13. Grigg JM, Barber A, Silverman M. Increased levels of bronchoalveolar lavage fluid interleukin-6 in preterm ventilated infants after prolonged rupture of membranes. Am Rev Respir Dis. 1992;145(4 Pt 1):782–6.
14. Todd DA, Earl M, Lloyd J, Greenberg M, John E. Cytological changes in endotracheal aspirates associated with chronic lung disease. Early Hum Dev. 1998;51(1):13–22.
15. Mirro R, Armstead W, Leffler C. Increased airway leukotriene levels in infants with severe bronchopulmonary dysplasia. Am J Dis Child. 1990;144(2):160–1.
16. Jónsson B, Tullus K, Brauner A, Lu Y, Noack G. Early increase of TNFα and IL-6 in tracheobronchial aspirate fluid indicator of subsequent chronic lung disease in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1997;77(3):F198–201.
17. Clement A, Chadelat K, Sardet A, Grimfeld A, Tournier G. Alveolar macrophage status in bronchopulmonary dysplasia. Pediatr Res. 1988;23(5):470.
18. Jobe AH, Ikegami M. Antenatal infection/inflammation and postnatal lung maturation and injury. Respir Res. 2001;2(1):27.
19. Philip AG. Oxygen plus pressure plus time: the etiology of bronchopulmonary dysplasia. Pediatrics. 1975;55(1):44–50.
20. Hodgman JE, Mikity VG, Tatter D, Cleland RS. Chronic respiratory distress in the premature infant: Wilson-Mikity syndrome. Pediatrics. 1969;44(2):179–95.
21. Perrone S, Bracciali C, Di Virgilio N, Buonocore G. Oxygen use in neonatal care: a two-edged sword. Front Pediatr. 2017;4:143.
22. Resch B, Gutmann C, Reiterer F, Luxner J, Urlesberger B. Neonatal Ureaplasma urealyticum colonization increases pulmonary and cerebral morbidity despite treatment with macrolide antibiotics. Infection. 2016;44(3):323–7.
23. Lowe J, Watkins WJ, Edwards MO, Spiller OB, Jacqz-Aigrain E, Kotecha SJ, Kotecha S. Association between pulmonary ureaplasma colonization and bronchopulmonary dysplasia in preterm

infants: updated systematic review and meta-analysis. Pediatr Infect Dis J. 2014;33(7):697–702.
24. Viscardi RM, Kallapur SG. Role of Ureaplasma respiratory tract colonization in bronchopulmonary dysplasia pathogenesis: current concepts and update. Clin Perinatol. 2015;42(4):719–38.
25. Moss TJ, Nitsos I, Knox CL, Polglase GR, Kallapur SG, Ikegami M, Jobe AH, Newnham JP. Ureaplasma colonization of amniotic fluid and efficacy of antenatal corticosteroids for preterm lung maturation in sheep. Am J Obstet Gynecol. 2009;200(1):96.e1–6.
26. Jobe AH. Antenatal associations with lung maturation and infection. J Perinatol. 2005;25(S2):S31.
27. Kramer BW, Kallapur S, Newnham J, Jobe AH. Prenatal inflammation and lung development. In: Seminars in fetal and neonatal medicine: 2009. Elsevier; 2009. p. 2–7.
28. Kallapur SG, Kramer BW, Knox CL, Berry CA, Collins JJ, Kemp MW, Nitsos I, Polglase GR, Robinson J, Hillman NH. Chronic fetal exposure to Ureaplasma parvum suppresses innate immune responses in sheep. J Immunol. 2011;187(5):2688–95.
29. Nair V, Loganathan P, Soraisham AS. Azithromycin and other macrolides for prevention of bronchopulmonary dysplasia: a systematic review and meta-analysis. Neonatology. 2014;106(4):337–47.
30. Kallapur SG, Kramer BW, Jobe AH. Ureaplasma and BPD. In: Seminars in perinatology: 2013. Elsevier; 2013. p. 94–101.
31. Tramper J, Zhang H, Foglia EE, Dysart KC, Padula MA, Sullivan KV, Jensen EA. The association between positive tracheal aspirate cultures and adverse pulmonary outcomes in preterm infants with severe Bronchopulmonary dysplasia. Am J Perinatol. 2017;34(01):96–104.
32. Husain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. Hum Pathol. 1998;29(7):710–7.
33. Coalson JJ. Pathology of new bronchopulmonary dysplasia. In: Seminars in neonatology: 2003. Elsevier; 2003. p. 73–81.
34. Coalson JJ. Pathology of bronchopulmonary dysplasia. In: Seminars in perinatology: 2006. Elsevier; 2006. p. 179–84.
35. Coalson JJ, Winter V, deLemos RA. Decreased alveolarization in baboon survivors with bronchopulmonary dysplasia. Am J Respir Crit Care Med. 1995;152(2):640–6.
36. Fiaturi N, Russo JW, Nielsen HC, Castellot JJ. CCN5 in alveolar epithelial proliferation and differentiation during neonatal lung oxygen injury. J Cell Commun Signal. 2018;12(1):217–29.
37. D'Alessandro A, Nozik-Grayck E, Stenmark KR. Identification of infants at risk for chronic lung disease at birth. Potential for a personalized approach to disease prevention. In: American Thoracic Society; 2017.
38. Jobe AH, Steinhorn R. Can we define bronchopulmonary dysplasia? J Pediatr. 2017;188:19–23.
39. Svenningsen N, Björklund L, Lindroth M. Changing trend in perinatal management and outcome of extremely low birthweight (ELBW) infants. Acta Paediatr. 1997;86(S422):89–91.
40. Davis PG, Morley CJ, Owen LS. Non-invasive respiratory support of preterm neonates with respiratory distress: continuous positive airway pressure and nasal intermittent positive pressure ventilation. In: Seminars in fetal and neonatal medicine: 2009. Elsevier; 2009. p. 14–20.
41. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, Ferrelli K, O'Conor J, Soll RF, Group VONDS. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128(5):e1069–76.
42. Carlo W. Gentle ventilation: the new evidence from the SUPPORT, COIN, VON, CURPAP, Colombian Network, and Neocosur Network trials. Early Hum Dev. 2012;88:S81–3.
43. Kennedy KA, Cotten CM, Watterberg KL, Carlo WA. Prevention and management of bronchopulmonary dysplasia: lessons learned from the neonatal research network. In: Seminars in perinatology: 2016: Elsevier; 2016. p. 348–55.
44. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362(21):1970–9.
45. Hascoet J-M, Espagne S, Hamon I. CPAP and the preterm infant: lessons from the COIN trial and other studies. Early Hum Dev. 2008;84(12):791–3.
46. Pfister RH, Soll RF. Initial respiratory support of preterm infants: the role of CPAP, the INSURE method, and noninvasive ventilation. Clin Perinatol. 2012;39(3):459–81.
47. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2012;11(11):CD001456.
48. Soll RF, Pfister RH. Evidence-based delivery room care of the very low birth weight infant. Neonatology. 2011;99(4):349–54.
49. Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Neonatology. 2013;104(2):124.
50. Polin RA, Carlo WA. Surfactant replacement therapy for preterm and term neonates with respiratory distress. Pediatrics. 2014;133(1):156–63.
51. Thome UH, Carlo WA. Permissive hypercapnia. In: Seminars in neonatology: 2002. Elsevier; 2002. p. 409–19.
52. Thome UH, Genzel-Boroviczeny O, Bohnhorst B, Schmid M, Fuchs H, Rohde O, Avenarius S, Topf H-G, Zimmermann A, Faas D. Permissive hypercapnia in extremely low birthweight infants (PHELBI): a randomised controlled multicentre trial. Lancet Respir Med. 2015;3(7):534–43.
53. Keszler M, Sant'Anna G. Mechanical ventilation and bronchopulmonary dysplasia. Clin Perinatol. 2015;42(4):781–96.
54. Peng W, Zhu H, Shi H, Liu E. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2014;99(2):F158–65.
55. Keszler M, Donn SM, Bucciarelli RL, Alverson DC, Hart M, Lunyong V, Modanlou HD, Noguchi A, Pearlman SA, Puri A. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr. 1991;119(1):85–93.
56. Shetty S, Greenough A. Neonatal ventilation strategies and long-term respiratory outcomes. Early Hum Dev. 2014;90(11):735–9.
57. Cools F, Askie LM, Offringa M, Asselin JM, Calvert SA, Courtney SE, Dani C, Durand DJ, Gerstmann DR, Henderson-Smart DJ. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. Lancet. 2010;375(9731):2082–91.
58. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Long-term effects of Caffeine therapy for Apnea of prematurity. N Engl J Med. 2007;357(19):1893–902.
59. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Caffeine therapy for Apnea of prematurity. N Engl J Med. 2006;354:2112–21.
60. Doyle LW, Schmidt B, Anderson PJ, Davis PG, Moddemann D, Grunau RE, O'brien K, Sankaran K, Herlenius E, Roberts R. Reduction in developmental coordination disorder with neonatal caffeine therapy. J Pediatr. 2014;165(2):356–359.e2.
61. Schmidt B, Davis PG, Roberts RS. Timing of caffeine therapy in very low birth weight infants. J Pediatr. 2014;164(5):957–8.
62. Dobson NR, Patel RM, Smith PB, Kuehn DR, Clark J, Vyas-Read S, Herring A, Laughon MM, Carlton D, Hunt CE. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. J Pediatr. 2014;164(5):992–998.e3.

63. Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, Stoll BJ, Lemons JA, Stevenson DK, Bauer CR. Vitamin a supplementation for extremely-low-birth-weight infants. N Engl J Med. 1999;340(25):1962–8.
64. Ambalavanan N, Kennedy K, Tyson J, Carlo WA. Survey of vitamin a supplementation for extremely-low-birth-weight infants: is clinical practice consistent with the evidence? J Pediatr. 2004;145(3):304–7.
65. Ambalavanan N, Tyson JE, Kennedy KA, Hansen NI, Vohr BR, Wright LL, Carlo WA. Vitamin A supplementation for extremely low birth weight infants: outcome at 18 to 22 months. Pediatrics. 2005;115(3):e249–54.
66. Darlow BA, Graham P, Rojas-Reyes MX. Vitamin A supplementation to prevent mortality and short-and long-term morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2016;2016(8):CD000501.
67. Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau P-H, Carnielli V, Van den Anker JN, Meisner C, Engel C, Schwab M. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med. 2015;373(16):1497–506.
68. Nakamura T, Yonemoto N, Nakayama M, Hirano S, Aotani H, Kusuda S, Fujimura M, Tamura M. Early inhaled steroid use in extremely low birthweight infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2016;101(6):F552–6.
69. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;3(3):CD004454.
70. Eichenwald EC, Stark AR. Are postnatal steroids ever justified to treat severe bronchopulmonary dysplasia? Arch Dis Child Fetal Neonatal Ed. 2007;92(5):F334–7.
71. Doyle LW, Ehrenkranz RA, Halliday HL. Dexamethasone treatment in the first week of life for preventing bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology. 2010;98(3):217–24.
72. Doyle LW, Ehrenkranz RA, Halliday HL. Dexamethasone treatment after the first week of life for bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology. 2010;98(4):289–96.
73. O'shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. Pediatrics. 1999;104(1):15–21.
74. Halliday HL. Update on postnatal steroids. Neonatology. 2017;111(4):415–22.
75. Shinwell ES, Lerner-Geva L, Lusky A, Reichman B. Less postnatal steroids, more bronchopulmonary dysplasia: a population-based study in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed. 2007;92(1):F30–3.
76. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, Stoll BJ, Buchter S, Laptook AR, Ehrenkranz RA. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med. 2011;183(12):1715–22.
77. Baud O, Trousson C, Biran V, Leroy E, Mohamed D, Alberti C. Association between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. JAMA. 2017;317(13):1329–37.
78. Ofman G, Perez M, Farrow KN. Early low-dose hydrocortisone: is the neurodevelopment affected? J Perinatol. 2018;38(6):636.
79. Parikh NA, Kennedy KA, Lasky RE, Tyson JE. Neurodevelopmental outcomes of extremely preterm infants randomized to stress dose hydrocortisone. PLoS One. 2015;10(9):e0137051.
80. Onland W, Offringa M, Cools F, De Jaegere AP, Rademaker K, Blom H, Cavatorta E, Debeer A, Dijk PH, van Heijst AF. Systemic hydrocortisone to prevent bronchopulmonary dysplasia in preterm infants (the SToP-BPD study); a multicenter randomized placebo controlled trial. BMC Pediatr. 2011;11(1):102.
81. Cheong JL, Doyle LW. An update on pulmonary and neurodevelopmental outcomes of bronchopulmonary dysplasia. In: Seminars in perinatology: 2018. Elsevier; 2018.
82. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, Thomas S, Stocks J. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. Am J Respir Crit Care Med. 2010;182(2):237–45.
83. Hennessy EM, Bracewell M, Wood N, Wolke D, Costeloe K, Gibson A, Marlow N, Group ES. Respiratory health in pre-school and school age children following extremely preterm birth. Arch Dis Child. 2008;93(12):1037–43.
84. Greenough A. Long-term pulmonary outcome in the preterm infant. Neonatology. 2008;93(4):324–7.
85. May C, Kennedy C, Milner AD, Rafferty GF, Peacock JL, Greenough A. Lung function abnormalities in infants developing bronchopulmonary dysplasia. Arch Dis Child. 2011;96(11):1014–9.
86. Greenough A, Alexander J, Burgess S, Chetcuti P, Cox S, Lenney W, Turnbull F, Shaw N, Woods A, Boorman J. Home oxygen status and rehospitalisation and primary care requirements of infants with chronic lung disease. Arch Dis Child. 2002;86(1):40–3.
87. Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S, Chetcuti P, Shaw N, Woods A, Boorman J. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Arch Dis Child. 2001;85(6):463–8.
88. Gibson A-M, Doyle LW. Respiratory outcomes for the tiniest or most immature infants. In: Seminars in fetal and neonatal medicine: 2014. Elsevier; 2014. p. 105–11.
89. Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates AL. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Dev Med Child Neurol. 2000;42(1):53–60.
90. Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. In: Seminars in perinatology: 2006. Elsevier; 2006. p. 227–32.
91. Hintz SR, Kendrick DE, Stoll BJ, Vohr BR, Fanaroff AA, Donovan EF, Poole WK, Blakely ML, Wright L, Higgins R. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics. 2005;115(3):696–703.
92. Van Marter LJ, Kuban KC, Allred E, Bose C, Dammann O, O'shea M, Laughon M, Ehrenkranz RA, Schreiber MD, Karna P. Does bronchopulmonary dysplasia contribute to the occurrence of cerebral palsy among infants born before 28 weeks of gestation? Arch Dis Child Fetal Neonatal Ed. 2011;96(1):F20–9.
93. Natarajan G, Pappas A, Shankaran S, Kendrick DE, Das A, Higgins RD, Laptook AR, Bell EF, Stoll BJ, Newman N. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. Early Hum Dev. 2012;88(7):509–15.
94. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, Baley J, Singer LT. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003;112(5):e359.
95. Vohr BR, Bell EF, Oh W. Infants with bronchopulmonary dysplasia: growth pattern and neurologic and developmental outcome. Am J Dis Child. 1982;136(5):443–7.
96. Moyer-Mileur LJ, Nielson DW, Pfeffer KD, Witte MK, Chapman DL. Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia. Pediatrics. 1996;98(4):779–83.

97. Martin RJ, Abu-Shaweesh JM. Control of breathing and neonatal apnea. Neonatology. 2005;87(4):288–95.
98. Polin RA, Fox WW, Abman SH. Fetal and neonatal physiology E-book. Elsevier Health Sciences; 2011.
99. Rhein LM, Dobson NR, Darnall RA, Corwin MJ, Heeren TC, Poets CF, McEntire BL, Hunt CE, Caffeine Pilot Study G. Effects of caffeine on intermittent hypoxia in infants born prematurely: a randomized clinical trial. JAMA Pediatr. 2014;168(3):250–7.
100. Eichenwald EC, Aina A, Stark AR. Apnea frequently persists beyond term gestation in infants delivered at 24 to 28 weeks. Pediatrics. 1997;100(3):354–60.
101. Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, Martin RJ, Redline S. Prevalence and risk factors for sleep-disordered breathing in 8-to 11-year-old children: association with race and prematurity. J Pediatr. 2003;142(4):383–9.
102. Paavonen EJ, Strang-Karlsson S, Räikkönen K, Heinonen K, Pesonen A-K, Hovi P, Andersson S, Järvenpää A-L, Eriksson JG, Kajantie E. Very low birth weight increases risk for sleep-disordered breathing in young adulthood: the Helsinki Study of Very Low Birth Weight Adults. Pediatrics. 2007;120(4):778–84.
103. Emancipator JL, Storfer-Isser A, Taylor HG, Rosen CL, Kirchner H, Johnson NL, Zambito AM, Redline S. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. Arch Pediatr Adolesc Med. 2006;160(2):203–10.
104. Marcus CL, Meltzer LJ, Roberts RS, Traylor J, Dix J, D'ilario J, Asztalos E, Opie G, Doyle LW, Biggs SN. Long-term effects of caffeine therapy for apnea of prematurity on sleep at school age. Am J Respir Crit Care Med. 2014;190(7):791–9.
105. Tapia IE, Shults J, Doyle LW, Nixon GM, Cielo CM, Traylor J, Marcus CL. Group CfAoPSS: perinatal risk factors associated with the obstructive sleep apnea syndrome in school-aged children born preterm. Sleep. 2016;39(4):737–42.
106. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723–9.
107. Jensen EA, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence-based approach. Am J Respir Crit Care Med. 2019;200(6):751–9.