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# Bronchopulmonary Dysplasia

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## Educational Gap

The 2010 NICHD Neonatal Research Network report used new severity-based and physiologic definitions of bronchopulmonary dysplasia (BPD) to estimate that as many as 68% of very-low-birthweight infants can be diagnosed with BPD. As the definition of the condition changes, recommendations for management continue to evolve.

## Objectives

After reading this article, readers should be able to:

1. Define BPD.
2. Describe the epidemiology and pathogenesis of the "new BPD" as opposed to the old BPD.
3. Discuss the multisystem organ outcomes associated with BPD.
4. Outline a plan of care for infants who have BPD.

## Introduction

Many advances in neonatology in the last several decades have allowed for the resuscitation, support, and survival of more preterm infants. The mortality associated with respiratory disease in this population of micropremies has been altered significantly by the use of antenatal corticosteroids, postnatal surfactant, improved respiratory support technology, and enhanced nutritional strategies, but the risk of developing long-term respiratory morbidity remains very high. Although the clinical presentation now differs from its original description, BPD continues to be one of the most common complications of premature infants. This disease presents several challenges to clinicians, and its effects can be seen not only in the lungs of these infants but also in many other organ systems.

## Background and Definition

Before the 1960s and the advent of mechanical ventilation, premature infants who developed respiratory distress syndrome (RDS) either died in the first week after birth or survived without respiratory morbidity. The introduction of mechanical ventilation to neonatal intensive care improved survival of infants who otherwise would have died from RDS but also resulted in a new form of lung injury.

In 1967, Northway et al (1) described the development of a new chronic lung disease in a group of premature infants who had RDS and had received prolonged ventilation with high concentrations of oxygen and high peak inspiratory pressures. The mean age of these infants was 34 weeks' gestation with a mean weight of 2.4 kg. These infants all required oxygen at 28 days after birth and had progressive changes on chest radiograph that were graded in severity.

## Abbreviations

<b>BPD:</b>	bronchopulmonary dysplasia
<b>CPAP:</b>	continuous positive airway pressure
<b>ELBW:</b>	extremely low birthweight
<b>FIO<sub>2</sub>:</b>	fraction of inspired oxygen concentration
<b>INSURE:</b>	intubation surfactant extubation
<b>NCPAP:</b>	nasal continuous positive airway pressure
<b>NICHD:</b>	National Institute of Child Health and Human Development
<b>PAH:</b>	pulmonary arterial hypertension
<b>PDA:</b>	patent ductus arteriosus
<b>PMA:</b>	postmenstrual age
<b>RDS:</b>	respiratory distress syndrome
<b>VLBW:</b>	very low birthweight

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Pathologic examination of lung tissue in these infants revealed necrotizing bronchiolitis, vascular changes consistent with pulmonary hypertension, infiltration with inflammatory cells, and alternating areas of alveolar over-inflation and atelectasis with pulmonary fibrosis (Fig 1). This disease was termed BPD to emphasize that both the airway and parenchyma of the lung tissues were affected. These abnormalities were attributed to ventilator-induced injury as well as to oxygen therapy.

Since that time, there have been several advances in the care of preterm infants. These advances (prenatal corticosteroids, surfactant therapy, gentle ventilation techniques, postnatal corticosteroids, and improved nutritional support, etc) have altered the course of lung disease in this population. As a result, our understanding and definition of BPD also have changed over time. In 1979, Bancalari and colleague (2) offered the first alteration to Northway's original definition: supplemental oxygen requirement at 28 days, chronic changes on chest radiograph, and tachypnea with crackles or retractions. A grading system was omitted.

With advances in medical care, more preterm infants needing oxygen at 28 days did not require its use in later weeks and before discharge. For that reason, the definition was altered again in 1988: a criterion for BPD was then defined as oxygen supplementation at 36 weeks' post-menstrual age (PMA). (2) This definition proved more useful than one in which the infant had an oxygen need at 28 days after birth; several studies revealed that requiring supplemental oxygen at 36 weeks' PMA more accurately predicted abnormal pulmonary outcome at 2 years of age.

In one study, the need for supplemental oxygen at 36 weeks' PMA in very low birthweight (VLBW) infants

(birthweight <1,500 g) had a better positive predictive value than the 28 postnatal day definition for abnormal outcome (63% vs 38%). Outcome was normal in 90% of infants who did not require oxygen at 36 weeks' PMA. (3)

Over time, this definition (oxygen requirement at 36 weeks' PMA) has become less useful and predictive because of increased survival of extremely low birthweight (ELBW) infants (birthweight <1,000 g or gestational age <30 weeks) and the widening spectrum of disease severity with improved treatment of RDS. The failure to include gestational age at birth or disease severity has led to concerns that this definition is inadequate, especially when comparing the efficacy of different therapeutic interventions or long-term outcome of ELBW infants who develop BPD.

The definition of BPD/chronic lung disease of infancy in preterm infants was reviewed at a June 2000 National Institute of Child Health and Human Development (NICHD)/National Heart, Lung, and Blood Institute workshop. As a result of this meeting, a consensus, *severity-based* definition of BPD was proposed. (2) The consensus addressed two groups of infants born at <32 weeks' estimated gestational age. For infants requiring supplemental oxygen at 28 days, there was an assessment done at 36 weeks' PMA. Those infants breathing room air at 36 weeks' PMA were defined as having mild BPD. Those infants needing <30% fraction of inspired oxygen concentration ( $F_{iO_2}$ ) supplementation were defined as having moderate BPD. Those infants requiring >30%  $F_{iO_2}$  or positive pressure ventilation were defined as having severe BPD.

Although not specified in the consensus BPD definition, it was recommended that a physiologic test confirming the need for supplemental oxygen be performed. The primary objective of this project was to determine the predictive validity of the proposed severity-based diagnostic criteria for BPD on pulmonary, neurodevelopmental, and growth outcomes at 18 to 22 months corrected age.

## Epidemiology

Preterm delivery affects 12.5% of pregnancies in the United States, and preterm infants are at high risk for long-term medical impairments, including BPD and chronic lung disease of infancy. (4) Risk of BPD is inversely related to both birthweight and gestational age at birth. The incidence of BPD has not changed substantially since Northway first described it in 1967, but the characteristics of the infants who have BPD have changed dramatically.

Classically, BPD occurred in preterm infants who had been treated with high ventilation pressures and oxygen

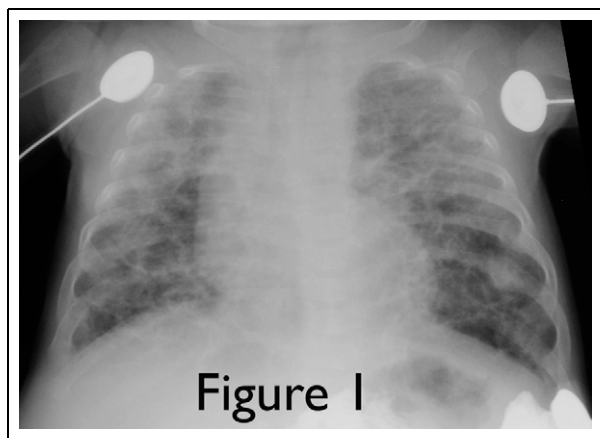


Figure 1. Chest radiograph of an infant with old bronchopulmonary dysplasia. The infant is intubated and the lungs appear cystic and scarred with areas of hyperinflation and atelectasis.

concentrations for severe RDS. The mean birthweight of these infants was ~1,900 g, and the mean gestational age was 32 weeks. (5) With the advent of antenatal corticosteroids, continuous positive airway pressure (CPAP), surfactant, and improvements in ventilation techniques, the epidemiology of BPD has changed. BPD is now infrequent among infants weighing >1,200 g or born at >30 weeks' gestation. (2)

With advances in neonatal care, more and more infants whose birthweights are <1 kg and who are born at <28 weeks' gestation are surviving and being diagnosed with BPD. These infants frequently have been treated with antenatal corticosteroids and postnatal surfactant and often have mild RDS and require much less respiratory support after birth than patients who have classic BPD. These new infants have not been exposed to the aggressive ventilation pressures and high oxygen concentrations as were the infants who have classic BPD; thus, other factors must be contributing to lung disease also.

The evolving definition of BPD confounds the literature that identifies BPD as an outcome measure. The NICHD Neonatal Research Network released a report in 2010 combining data from infants from the Neonatal Research Network VLBW registry with birthweights of 401 to 1,500 g and gestational ages of 22-0/7 to 28-6/7 weeks born at 20 centers in the United States from 2003 to 2007. Using the new severity-based definition, 68% of these infants were diagnosed with BPD: 27% mild, 23% moderate, and 18% severe. Using the traditional (supplemental oxygen at >36 weeks' PMA) definition, 42% of these infants were diagnosed with BPD; and using the physiologic definition, 40% of these infants were diagnosed with BPD. (6) These percentages are similar to those reported by Ehrenkranz et al (5) in 2005 in a study designed to validate the NICHD definition of BPD. The authors of this study looked at infants from 14 centers who were delivered before 32 weeks' gestation. With the traditional (oxygen requirement at 36 weeks) definition, 44% were diagnosed with BPD. Employing the severity-based definition, 76% had BPD: 30% mild, 30% moderate, and 16% severe. Standardization of this definition becomes critical as we research prevention and intervention.

## Pathology

As discussed, the old BPD was a condition diagnosed in preterm infants who had hyaline membrane disease treated with high ventilator pressures and high oxygen concentrations before the introduction of antenatal corticosteroid and postnatal surfactant therapy. This disease was hallmarked by airway inflammation, fibrosis,

and smooth muscle hypertrophy. The new BPD is a form of chronic lung disease that occurs despite the better neonatal care: CPAP, improved ventilators, antenatal corticosteroids, and surfactant.

In normal human lung development, alveolarization begins at ~36 weeks' gestation. In the new BPD, lung development arrests before alveolarization, and the lungs have larger but much fewer alveoli than normal lungs (Fig 2). (7) The pulmonary microvasculature is likely to be dysmorphic in the new BPD, but there is controversy over whether it is increased or decreased. (8) Lung biopsy typically is not performed in patients who have BPD, so the histopathologic information available is from infants who have died and is therefore biased toward severe changes and may not be completely representative of the lung anatomy of those living with less severe BPD.

## Pathogenesis

Infants born prematurely have underdeveloped lungs and also have faced stressors that contributed to their prematurity. Many of these same insults may play a role in the development of BPD by directly halting lung development or by triggering an inflammatory response.

Chorioamnionitis, which is inflammation of the fetal membranes, usually caused by an ascending infection, has long been investigated as a possible cause of BPD. Multiple studies have revealed an increased risk of BPD in the presence of maternal chorioamnionitis, whereas others have revealed no difference or decreased risk. In 2009, in a large 13-year hospital cohort study aimed at studying the relationship between BPD and chorioamnionitis, umbilical vasculitis, and neonatal sepsis, Lahra et al (9) found histologic chorioamnionitis to be protective

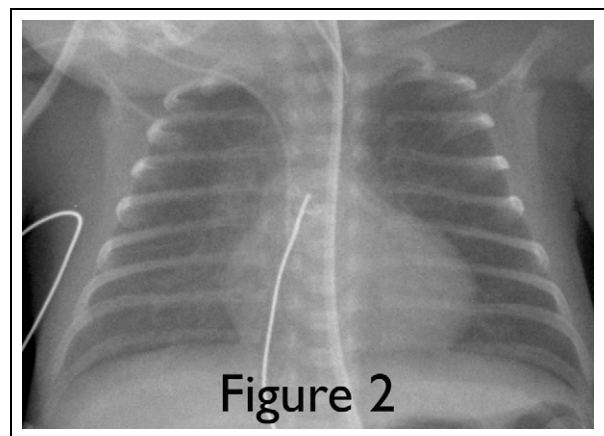


Figure 2. Chest radiograph of an infant with new bronchopulmonary dysplasia. The lungs have diffuse haziness. Note the surgical clip from patent ductus arteriosus ligation.

against BPD. In this same study, umbilical vasculitis conferred more protection against BPD than chorioamnionitis alone, leading Wright and Kirplani (4) to postulate whether the fetal response to chorioamnionitis may play a role in BPD development in a recent review article. This article provides an overview of the potential role of transcription factor nuclear factor  $\kappa$ B and inflammation in the pathogenesis of BPD.

A potential role of *Ureaplasma* colonization in the infant lung in the pathogenesis of BPD has been considered for several years. *U urealyticum* and *U parvum* are isolated commonly from the chorioamnion in histologic chorioamnionitis and can colonize the skin, eyes, mucous membranes, and respiratory tract of infants. Schelonka et al (10) published a meta-analysis of 23 studies in 2005, which revealed a significant association between *Ureaplasma* spp colonization and BPD at 36 weeks' corrected gestational age ( $P < .001$ ); however, the largest reported effect was seen in the smallest studies, and the authors cautioned that this finding may be due to reporting bias.

Bacterial sepsis has been shown consistently to be associated with higher rates of BPD. In one cohort study, BPD rates went from 35% to 62% after early onset sepsis, a result that was validated subsequently in a population study. (4) Neonatal sepsis is a strong indicator of chronic lung disease, and, notably, coagulase-negative staphylococcal infection has been shown to be as strongly associated with BPD as infection with other gram-positive and gram-negative pathogens. (9)

In addition to infection, the presence of a hemodynamically significant patent ductus arteriosus (PDA) has been shown to be associated with increased risk of BPD. Lung endothelial damage from left-to-right shunting through a PDA as well as an increased need for mechanical ventilation due to pulmonary edema and lung dysfunction may play a role in increasing BPD risk. However, indomethacin prophylaxis does not decrease rates of BPD despite decreasing the incidence of PDA, and PDA ligation increases BPD risk rather than decreasing it, so the relationship between PDA and BPD does not appear to be a direct cause-and-effect one. (11) High volumes of fluid intake in the first few days after birth may predispose to both conditions, leading to an apparent association. Lower serum cortisol levels in VLBW infants correlate with both PDA and BPD risk, indicating that early adrenal insufficiency may explain the association between PDA and BPD. (12)

Mechanical ventilation places an infant at risk for barotrauma and volutrauma if the body is ventilated at high tidal volumes. This association was seen with the old BPD, but it may still play a role in the new BPD as well. Although airway overdistension is seen most often in

infants requiring prolonged mechanical ventilation, even a small number of large volume breaths can create injury, especially in surfactant-deficient lungs that do not inflate uniformly. Injury is most likely to happen during initial resuscitation efforts, due to the fine balance of establishing functional residual capacity while attempting to use ventilatory volumes below the total lung capacity.

Oxygen toxicity also can put infants at risk for developing BPD. Hyperoxia can arrest lung development, create reactive oxygen species, and trigger the inflammatory cascade. (7)(13) In a recent clinical study, preterm infants born at 24 to 28 weeks' gestation were randomly assigned to initial neonatal resuscitation with 30% or 90% oxygen, and the incidence of BPD was reduced in half in the 30% oxygen group, 15.4% vs 31.7%. Additionally, this study revealed that biomarkers of oxidative stress were increased in the 90% oxygen group and correlated with later development of BPD. (13)

### Multisystem Organ Outcomes

BPD is a chronic illness that persists after hospital discharge, and infants afflicted with BPD have up to 50% higher rates of rehospitalization in the first year after birth. (8) Lung disease can persist into adulthood, including such pathology as airway obstruction, reactive airways, and emphysema. (8) Aside from chronic lung disease, BPD has other sequelae that affect growth, cardiovascular health, and neurodevelopment.

Increased respiratory effort in infants who have BPD increases their metabolic demands and, therefore, increases the number of calories needed per day. Adequate nutrition is important in these infants also to help improve their overall health, to help repair any damaged lung tissue, and to decrease the risk of recurrent respiratory tract infections. Infants who have chronic lung disease also may need inositol, free fatty acids, vitamin E, and vitamin A, although only vitamin A has shown benefit when administered as a supplement to these infants. (14) Close attention to nutrition and growth of these patients during hospitalization as well as in outpatient follow-up is important to ensure appropriate progress.

Infants who have BPD are at high risk for cardiovascular sequelae, including pulmonary arterial hypertension (PAH), cor pulmonale, and systemic hypertension. Studies reveal that 25% to 43% of patients who have BPD develop PAH as a complication, and in 14% to 38% of those who develop PAH, the condition is fatal. (15)(16) The true prevalence is difficult to know, given the lack of consensus for when and how to screen infants who have BPD for PAH. There is evidence to suggest that small for gestational age infants who have BPD are at an increased risk

for PAH. Severity of PAH also correlates with severity of BPD. (16)

Preterm infants have an increased risk of poor neurodevelopmental outcomes when compared with term infants, and BPD is an additional, independent risk factor. (17) Infants who have birthweights <1,500 g who have BPD have greater language delay as well as increased fine and gross motor impairment. (8) A prospective, longitudinal study following a cohort of children who have BPD revealed that the degree of neurodevelopmental impairment seen in patients who have BPD correlates with the severity of their lung disease, and that the impairment is still present at 3 and 8 years of age. (18)

## Prevention

### Antenatal

The potential for BPD begins while the infant is still in utero, and prevention measures begin at that point as well. BPD is a disease of the premature newborn, so obstetrical advancements decreasing the number of infants born prematurely would result in fewer patients who develop BPD. Antenatal corticosteroids administration is now the standard of care for women at 24 to 34 weeks' gestation with preterm labor to aid with fetal lung maturation, but their effect on the incidence of BPD is controversial. Some studies reveal benefit, whereas others reveal no benefit. (8) There is concern also from animal studies that corticosteroids themselves may lead to the arrest of alveolarization and microvascular development. (7)

### Postnatal

Given the multifactorial pathogenesis of BPD, a wide variety of pharmacologic and ventilatory measures play a role in BPD prevention as well.

**SYSTEMIC CORTICOSTEROIDS.** Postnatal corticosteroid therapy to help prevent BPD is an area of heated debate in neonatology. This therapy previously was the standard of care for these infants, with past evidence revealing that early corticosteroid administration (within the first 2 weeks after birth) to ventilated preterm infants decreased the risk of BPD and decreased time to extubation. Late (at >3 weeks after birth) corticosteroid administration did not decrease BPD risk but did facilitate earlier extubation. (19) Initially the adverse effects of concern with systemic corticosteroid use in preterm infants were the same as those for older children and adults: hyperglycemia, hypertension, gastrointestinal bleeding, hypertrophic cardiomyopathy, and infection. Long-term follow-up studies have now revealed a clear link between postnatal corticosteroid administration and poor neurodevelopmental

outcomes, including cerebral palsy. Currently, the use of postnatal corticosteroids in patients who have BPD or at risk for BPD is determined on a case-by-case basis and not recommended routinely. (20)

**AZITHROMYCIN.** Azithromycin and other macrolides have antibiotic as well as anti-inflammatory effects and are active against *Ureaplasma* infections, so these agents have been studied as potential therapies for BPD prevention in preterm infants. In a randomized controlled trial, no statistical significance was found giving VLBW infants a 6-week course of azithromycin compared with placebo. Of the subset of infants who were found to be colonized with *Ureaplasma*, however, azithromycin did decrease the incidence of BPD. (21)

**VITAMIN A.** Vitamin A (retinol) is involved in the regulation of lung development and injury repair, and low vitamin A levels in preterm infants have been associated with increased risk for developing BPD. (11)(12) Prophylactic vitamin A administration has been shown to decrease significantly the risk of BPD development in ELBW infants, yet no difference in neurodevelopmental impairment at 18- to 22-month follow-up has been seen between ELBW infants receiving vitamin A and controls. (22)(23)

**VITAMIN E AND SELENIUM.** Vitamin E has been investigated as a possible preventive agent for BPD, but study results have been mixed. Studies have failed to separate infants who have vitamin E deficiency from those without it when evaluating the role of vitamin E supplementation in preventing BPD. Selenium works synergistically with vitamin E to prevent peroxide formation, and supplementation of preterm infants who have selenium has not been shown to reduce risk of BPD development. (24)

**CAFFEINE.** During the international Caffeine for Apnea of Prematurity trial that compared caffeine to placebo given within the first 10 days after birth, a significant reduction in BPD at 36 weeks' PMA was seen in the caffeine group (36% vs 47%). (25) The mechanism by which caffeine decreases the risk of BPD is unknown.

**PENTOXIPHYLLINE.** Pentoxifylline is a nonspecific phosphodiesterase inhibitor that has been shown to decrease pulmonary inflammation. In one study comparing the effectiveness of nebulized pentoxifylline to intravenous dexamethasone or placebo, nebulized pentoxifylline decreased the risk of BPD by 27% ( $P = .039$ ). There was no significant difference between the group treated with pentoxifylline and the group treated with dexamethasone. (26)

**CROMOLYN.** Cromolyn is a mast cell stabilizer frequently used to treat asthma. Randomized controlled trials have failed to reveal any protective effects of cromolyn sodium against BPD. (19)

**NITRIC OXIDE.** Animal models have shown benefit from inhaled nitric oxide on oxidative stress and lung development; however, studies in humans have had mixed results. (11) The National Institutes of Health Consensus Statement does not support the use of nitric oxide in the routine care of preterm neonates but does state that basic research and animal studies have provided important information about the benefits of inhaled nitric oxide on lung development and function in infants at high risk for BPD, despite the fact that clinical trials have been only partially able to demonstrate this effect. The National Institutes of Health statement goes on to recommend further research in this area. (27)

**ACETYLCYSTEINE.** Acetylcysteine is a mucolytic agent that has been investigated for its potential role in preventing BPD development when given to ventilated newborns. There is no evidence that the agent decreases the risk of BPD development. (20)

**SURFACTANT.** Surfactant therapy has revolutionized the care of preterm infants who have respiratory distress, but unfortunately this therapy has not led to a decrease in the incidence of BPD at 36 weeks. As discussed previously, surfactant has contributed to the transition from the old BPD to the new BPD by improving respiratory care in ELBW infants. Prophylactic surfactant treatment as part of the intubation surfactant extubation (INSURE) approach, in which infants are intubated for a brief period after birth for surfactant administration followed by immediate extubation to nasal respiratory support, is associated with a lower risk of BPD than later selective surfactant administration. (28)

**VENTILATORY STRATEGIES.** Ventilatory goals for preventing BPD have included permissive hypercapnia and gentle ventilation. Permissive hypercapnia is a strategy for managing ventilated preterm infants that allows for  $\text{PaCO}_2$  of 45 to 55 mm Hg and  $\text{pH} > 7.20$  in order to avoid high tidal volumes and pulmonary overinflation. (11) Clinical trials have not revealed a significant difference in BPD rates when permissive hypercapnia is employed, but the studies have revealed trends toward BPD reduction without adverse events. (29) Gentle ventilation refers to providing the smallest amount of respiratory support necessary to provide adequate oxygenation and ventilation while preventing significant barotrauma and volutrauma. Of note, adequate oxygenation is a difficult target, because

the optimal pulse oximetry saturation goals for preterm infants are currently under investigation and not well established. (30)

Authors of multiple studies have compared different ventilation modes in an attempt to determine the optimal respiratory care for preventing BPD. High frequency ventilation and conventional ventilation have been shown to have comparable rates of associated BPD. (11) A 2010 Cochrane review revealed lower rates of death or BPD among infants ventilated by using volume-targeted ventilation than those ventilated by using pressure-limited ventilation. (31)

There has been a recent trend in neonatology to move away from endotracheal intubation of ELBW infants to nasal CPAP (NCPAP). NCPAP has been used in the primary treatment of RDS to avoid intubation, as part of the INSURE approach, and as a step-down therapy after initial endotracheal ventilation once the infant is able to breathe spontaneously. Successful avoidance of endotracheal intubation in preterm infants by opting for nasal respiratory support has been gestational age dependent, with multiple studies revealing that ~50% of ELBW infants started on NCPAP will be ventilated subsequently. (11) The INSURE approach, as discussed above, is associated with lower rates of BPD than initial NCPAP followed by selective surfactant administration, mechanical ventilation, and extubation from lower respiratory support. (28)

Nasal ventilation techniques have been adopted as well, with the terms nasal intermittent mandatory ventilation and nasal intermittent positive pressure ventilation often used interchangeably. (11) Nasal intermittent mandatory ventilation has been shown to decrease the rate of BPD when compared with NCPAP for treatment of RDS, although the authors caution that the number of infants who have birthweights  $< 1,500$  g in the study was small, and the results need to be validated in a powered study in the VLBW and ELBW populations. (32)

**NUTRITION.** Preterm infants at risk for BPD often are fluid-restricted, given that excessive fluid intake in the first 10 days after birth has been associated with an increased risk of developing BPD. (28)(33) Fortification of feedings often is necessary to make up for the calories otherwise lost by fluid restriction. Infants developing BPD may need up to 20% to 40% more kilocalories than their age-matched controls. Infants who have established BPD, continue to have increased caloric expenditure ~25% above their usual caloric needs, and 30% to 65% of these infants experience growth failure soon after initial hospital discharge. (24)

## Treatment of Established BPD

### Inhaled Steroids

Inhaled corticosteroids have long been used as a therapy for patients who have developing or established BPD, but the evidence supporting their use is mixed. A Cochrane systematic review of randomized controlled trials revealed that there is no evidence that early-inhaled corticosteroid therapy (at <2 weeks after birth) to ventilated preterm infants decreases the incidence of BPD. (34) Whether the same risk of long-term adverse neurodevelopmental outcomes exists for patients receiving inhaled corticosteroids for BPD compared with those receiving systemic corticosteroids remains unknown.

### Diuretics

Diuretics often are used in patients who have known BPD in an attempt to decrease pulmonary alveolar and interstitial edema and to improve lung function. A systematic review of clinical trials investigating the use of intravenous or enteral furosemide in infants who have evolving or established BPD revealed no effect or inconsistent effects in infants <3 weeks of age and only transient improvement in lung mechanics with a single dose of 1 mg/kg intravenous furosemide in infants >3 weeks of age. (35) Thus, routine use of systemic loop diuretics is not recommended in infants who have BPD.

Authors of multiple studies have reviewed the combination use of thiazides plus spironolactone in infants who have moderate BPD, and a Cochrane Review of the available literature revealed that chronic administration of distal diuretics to infants >3 weeks of age improves pulmonary mechanics. Thiazide plus spironolactone for 4 weeks improved lung compliance and decreased the incidence of death, but there is no evidence to show that this combination improves the long-term outcome in preterm infants who have BPD. (36) Aerosolized diuretics also have been investigated but have not demonstrated long-term benefit and are not recommended routinely. (19)

### Bronchodilators

Studies have revealed that inhaled bronchodilators, most commonly  $\beta$  adrenergic agonists, can aid with short-term improvement in lung function and may be helpful to infants who have BPD during acute exacerbations. (19) One multicenter randomized controlled trial investigating the role of inhaled bronchodilators in the prevention of BPD revealed no difference in occurrence of BPD, mortality, duration of ventilation support, and extent of oxygen therapy among ventilated preterm infants receiving 28 days of salbutamol plus placebo, salbutamol

plus beclomethasone, placebo plus placebo, or placebo plus beclomethasone. (37) Whether the lack of efficacy is due in part to difficulty assessing how much aerosolized medication is getting to the distal airways remains unknown, but for now, the therapeutic role of bronchodilators in patients who have BPD is for treating acute exacerbations and not chronic care.

## Summary

- Bronchopulmonary dysplasia (BPD) is a common condition in preterm infants born at <30 weeks, and its definition continues to evolve.
- From the condition's first characterization in the 1960s to its more recent severity-based and physiologic definitions, the epidemiology of BPD has shifted along with advancements in neonatal care, such as continuous positive airway pressure, surfactant therapy, and improved ventilators.
- The "old BPD," characterized by airway inflammation, fibrosis, and smooth muscle hypertrophy secondary to barotrauma and volutrauma, has all but disappeared, and the "new BPD," a disease of younger infants who have multifactorial chronic lung disease hallmarked by arrested lung development, is taking its place.
- Much is both known and unknown about the pathogenesis of the new BPD. A number of factors appear to contribute to the abnormal lung development seen in BPD, such as neonatal sepsis, patent ductus arteriosus, mechanical ventilation, and oxygen therapy. Fetal response to chorioamnionitis and *Ureaplasma* colonization also may play a role.
- Treatments that have been shown to be effective in reducing the incidence of BPD include vitamin A supplementation in extremely low birthweight infants and caffeine therapy for apnea of prematurity.
- Prophylactic surfactant with brief ventilation as part of the intubation surfactant extubation approach also has been found to reduce rates of BPD when compared with later selective surfactant administration with continued mechanical ventilation.
- Diuretics, inhaled bronchodilators, and inhaled corticosteroids frequently are used in patients who have BPD, but there is little to no evidence to support their routine, chronic use.
- Postnatal systemic corticosteroid therapy previously was the standard of care to prevent BPD, but the routine use of corticosteroids postnatally is now contraindicated because long-term outcome studies reveal that such use leads to global neurodevelopmental impairment.
- BPD is a chronic respiratory condition that can lead to cardiovascular disease and neurodevelopmental impairment. Close follow-up is essential with a primary care provider as well as a multidisciplinary team of providers to watch for the pulmonary,



cardiovascular, nutritional, and neurodevelopmental sequelae that can result from BPD.

- It is hoped that future work aimed at preventing preterm birth and research aimed at elucidating the optimal plan of care for infants at risk for and already diagnosed with the new BPD will lead to decreases in the incidence and sequelae of BPD.

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1. A boy born at 28 weeks' estimated gestational age (EGA) who requires 28% fraction of inspired oxygen concentration ( $\text{FiO}_2$ ) at 36 weeks of age is diagnosed with moderate bronchopulmonary dysplasia (BPD). His nursery course was relatively uncomplicated. Given that he received state-of-the-art treatment both before and after birth, in 2011 the pathologic basis of his lung disease would primarily involve
  - A. diffuse cystic changes.
  - B. fibrosis of bronchiolar walls.
  - C. ongoing inflammation.
  - D. reduced numbers of alveoli.
  - E. smooth muscle hypertrophy.
2. A boy born at 28 weeks' EGA is diagnosed subsequently with moderate BPD. Which of the following contributed most to the development of his BPD?
  - A. early onset bacterial sepsis.
  - B. indomethacin prophylaxis.
  - C. low tidal volume ventilation.
  - D. maternal chorioamnionitis.
  - E. prolonged exposure to 30%  $\text{FiO}_2$ .

3. Aside from averting premature birth, the most effective and safest way to prevent BPD in extremely low birthweight infants is the postnatal administration of
  - A. azithromycin.
  - B. cromolyn.
  - C. oral glucocorticosteroids.
  - D. selenium.
  - E. vitamin A.
  
4. A 5-month-old girl with moderate BPD still requires an  $\text{FiO}_2$  of 28%. Her long-term health is most likely to be promoted by
  - A. augmented caloric intake.
  - B. increased fluid intake.
  - C. inhaled bronchodilators.
  - D. inhaled glucocorticosteroids.
  - E. loop diuretics.
  
5. The life span of a patient with severe BPD is most likely to be determined by
  - A. alveolar development.
  - B. degenerative grey matter disease.
  - C. malnutrition.
  - D. obstructive airway disease.
  - E. pulmonary arterial hypertension.

### HealthyChildren.org Parent Resources From the AAP

The reader is likely to find material to share with parents that is relevant to this article by visiting this link:  
<http://www.healthychildren.org/English/ages-stages/baby/preemie/pages/when-baby-needs-oxygen-at-home.aspx>.

## Bronchopulmonary Dysplasia

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