Bronchopulmonary Dysplasia

Introduction

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease (CLD) that is seen in preterm infants who had respiratory distress syndrome (RDS) at birth and continue to require supplemental oxygen and/or ventilator support beyond 36 weeks corrected gestational age (CGA). In addition to premature birth, risk factors include the need for supplemental oxygen and ventilator support. Factors such as intrauterine growth restriction, infection (acquired either in utero or postnatally), patent ductus arteriosus (PDA), and genetic predisposition may contribute to the pathogenesis of this disorder. For nurses who work in the NICU as well as those who are involved in the delivery, resuscitation, and stabilization of preterm infants, understanding the disease process, treatment, and outcomes will allow patient care to be based on a strong scientific foundation.

Definition

The definition of BPD has evolved over the years as viability thresholds for preterm infants have decreased; thus, it often is described as "old BPD" versus "new BPD." This is a reflection on the distinct embryologic differences in pulmonary development at different gestational ages. It also is influenced by changes in treatment strategies and by technological and pharmacological options that exist today.

Etiology of BPD/CLD

Pulmonary disease of the newborn is multifactorial. Infants develop respiratory distress and possibly BPD/CLD in part because there is an interruption in the development of the lungs and inability to manufacture surfactant necessary to prevent alveolar collapse. Other factors that contribute to the pathogenesis of BPD include inflammation, genetic predisposition, clinical management techniques of respiratory failure, and response to infection or oxygen toxicity. These factors may increase the likelihood of chronic lung changes and support the need for continued support.

Old BPD

This form of CLD was first described in the 1960s by Northway, who observed radiographic changes in late preterm infants who had been exposed to aggressive mechanical ventilation and high concentrations of oxygen (Northway, 1990). This damage occurred in the late saccular stage of lung development with X-ray findings consistent with extensive inflammation and fibrotic and cystic changes in the lung parenchyma and airways. The diagnosis of BPD was assigned to the infant if he or she was oxygen dependent at 28 days of age.

As the practice of neonatology evolved and new technological and treatment modalities were developed, the gestational age at which infants were surviving became lower and lower. Exogenous surfactants improved lung compliance and reduced oxygen requirements. Ventilators designed for use in this patient population became increasingly more sophisticated. These innovations and others allowed for gentler methods of ventilation and, in some cases, reduced damage to airways and resultant fibrosis. However, as survival improved in extremely preterm infants, there was an inverse relationship seen in the severity of BPD with gestational age. Today, approximately two-thirds of infants who develop BPD are extremely low birth weight (< 1,000 g) and less than 28 weeks gestation at the time of their birth.

New BPD or CLD

As knowledge of factors that contribute to the development of BPD grew, neonatal centers worked to refine their management of respiratory diseases in preterm infants. Many centers have seen a reduction of the clinical presentation in the older preterm infant, but they have now noticed a different form of CLD that may not be associated solely with the absence of surfactant, high oxygen exposure, or lung damage related to ventilation. Although providers thought that reduction of volutrauma and surfactant replacement would significantly decrease BPD, chronic changes in respiratory function in full-term or near full-term infants experiencing antenatal infection,

pulmonary hypoplasia, and meconium aspiration have instead been noted. This new BPD results in impaired organogenesis of the lung (what historically was called pulmonary insufficiency), impaired distal lung growth, decreased microvascular development, and impaired pulmonary function in the first years of the infant's life. Rather than being able to assign the diagnosis of BPD solely based on the presence of oxygen at a specific gestational or chronologic age or on X-ray findings, the newer form of BPD is related more to the pulmonary outcomes of infants that are severely affected by respiratory disease. This is why some centers use the term *CLD* to describe this new form of respiratory disease.

A consensus conference in 2000 at the National Institutes of Health (NIH) suggested that the diagnosis of BPD/CLD be defined by a more clinical severity–based definition related to the level of respiratory support needed nearer to term gestation. The new definition uses oxygen dependency at 36 weeks postconceptual age (PCA), total duration of oxygen supplementation (> 28 days), positive pressure requirements, and gestational age of infant (< 32 weeks) to delineate the three degrees of severity: mild, moderate, and severe. Infants stratified by these diagnostic criteria rarely progress to severe BPD/CLD. Of those with the severest BPD, approximately 75% will be discharged on home oxygen therapy or require a tracheostomy for long-term ventilation.

Definitions

Mild BPD/CLD is assigned if there is a need for supplemental oxygen for more than 28 days but not by 36 weeks PCA.

Moderate BPD is defined as a need for supplemental oxygen for more than 28 days but the fraction of inspired oxygen (FiO_2) was less than 30% at 36 weeks PCA.

Severe BPD is defined as an oxygen requirement for more than 28 days and more than 30% FiO_2 and/or positive pressure ventilation (CPAP or ventilation) at 36 weeks PCA.

Genetics

As our knowledge of genetic expression and the ability to identify specific markers in the DNA of individuals have expanded, so too has the understanding of which of these markers may predispose or increase the likelihood of an individual developing different diseases, including BPD. For example, twin studies have shown that lacking the portion of the arm that expresses surfactant protein B (SP-B) may increase the risk of BPD. In addition, other gene pathways that regulate things such as DNA repair, mitochondrial energy metabolism, and control cell growth may be altered in the developing premature infant, resulting in their response to factors such as infection, exposure to oxygen, and growth. The continued study of the genome may lead to future opportunities to intervene earlier in the disease process by altering ventilation strategies or by tailoring therapies for those infants at highest risk.

Inflammation

Inflammation is a major factor in the development of BPD. The initiation of inflammation appears to cause impairment of the growth of alveoli and of the microvasculature. The ability of the infant to block inflammation by their own anti-inflammatory mediators is limited and may be easily overwhelmed. There is growing evidence that the persistent imbalance on the side of pro-inflammatory mediators and inadequate anti-inflammatory mediators is important in the pathogenesis of BPD.

Maternal chorioamnionitis is the single most important cause of preterm delivery, with severe chorioamnionitis seen frequently in infants who are born at less than 30 weeks gestation. Infants born in the presence of chorioamnionitis have a higher rate of BPD/CLD. The infant may present with mild to moderate RDS at the time of birth, rapidly improve with exogenous surfactant and ventilation, and wean to low ventilator support or continuous positive airway pressure (CPAP). Chest X-ray findings at that time may have been consistent with mild RDS. Sometime after the first week of life, the infant will exhibit symptoms of worsening respiratory distress and increased oxygen requirements without associated infection. Chest X rays may show progressive development of

atelectasis, scarring, and hyperinflation—all consistent with BPD.

The development of this atypical CLD is thought to be a systemic response by the infant following exposure to intrauterine infection. The fetus responds to this environment by increasing its inflammatory biomarkers, such as chemokine, pro- and anti-inflammatory cytokines, proteases and their inactivated inhibitors, and growth factors. Infants who were exposed to intrauterine infection and had histologic confirmation of chorioamnionitis were found with elevated interleukin 6 present in the cord blood and went on to develop BPD. The presence of these inflammatory biomarkers creates a complex interaction that alters subsequent lung maturation.

Disruption of Vasculogenesis

Inflammation in utero results in a cascade of events following delivery; one of these, decreased vascular endothelial growth factor (VEGF), has a major impact on the development of new pulmonary vessels, pulmonary capillary beds, and ultimately, alveoli. In the presence of inflammation, VEGF regulation is altered. Pathways that lead to VEGF production are inhibited, which leads to reduced production of growth factors. These are required for new healthy lung tissue to grow. Infants born at the threshold of viability are at highest risk because they have very few vessels and alveoli developed at birth. In addition, exposure to the higher levels of oxygen in extrauterine life also will contribute to the abnormal development of pulmonary circulation. Infants with severe BPD often will have comorbidities such as cor pulmonale or pulmonary hypertension caused in part by the interruption of pulmonary vascular growth.

Oxygen Toxicity

In the developing fetus, weeks 23–30 are a period of active development of the pulmonary system. Fetuses move from simple bronchial "tubes" to saccules, which are the precursors to alveoli. This growth occurs in utero in what would be considered hypoxic by extrauterine factors. Preterm birth interrupts this development and events such as chorioamnionitis or hyperoxia can result in changes to the growth and further branching of the lung, specifically alveolar development. Although it was thought that high levels of oxygen (>40%) were toxic to the neonatal lung, there is strong evidence indicating that even room air (21%) may result in lung injury.

Ventilator-Induced Injury

Initiation of positive pressure ventilation during resuscitation often triggers a cascade of damage and changes to the airways and alveoli of the preterm infant. Volutrauma, the overdistension of the airway, causes stretching of the air sac on inspiration. At the end of the expiratory phase of the respiratory cycle, partial or total collapse potentially can alter the stretch responsive mediators in the preterm infant's lung. Overventilation may induce an inflammatory response of the lungs, with large numbers of neutrophils being released. This can lead to scarring and alteration in existing lung tissue. The use of CPAP immediately after delivery and continued use in the NICU versus intubation after delivery was thought to reduce some of the mechanical injuries by mechanical ventilation. However, in a large randomized controlled study that evaluated CPAP versus mechanical ventilation, there was no difference found in BPD at 36 weeks (Geary, 2008).

Treatment

Despite increasing knowledge about factors that contribute directly to BPD/CLD, there is still uncertainty as to which treatment modalities are most successful in reducing the incidence of and treating the infant with BPD. Awareness of the importance of ventilation and nutritional and pharmacologic management will allow the team to apply best practices to improve both short- and long-term outcomes.

Ventilation/Oxygen

Reduction of volume and distending airway pressure will help reduce volutrauma and minimize alterations in the architecture of the developing airway. The use of positive pressure, even CPAP, has an impact on the ability of the neonate to continue to grow new saccules and alveoli, even after birth. Maintaining functional residual capacity and avoiding repeated bouts of atelectasis is an increasingly common strategy. Oxygen, though essential to avoid tissue damage and allow for anabolic growth, also can be damaging in concentrations that are higher

than necessary. Studies have evaluated what is considered a "safe range" for oxygen saturations and have recommended the range of 90%–95%. However, it is more important to avoid frequent swings in oxygen saturations from hypoxic to hyperoxic states, because this affects overall growth and neurodevelopmental outcomes.

Nutrition

Infants born prematurely miss an important window of intrauterine growth. Care providers are limited in their ability to deliver calories and nutrients, yet these infants have very high energy requirements to meet basic metabolic functions, even without their need to grow. Delay in establishing positive nitrogen balance with early introduction of protein and lipids is known to decrease alveolar number and delay extrauterine growth. Establishment of enteral feeds as early as possible with maternal breast milk provides the infant with growth factors found in maternal milk such as inositol, which has a role in cell membrane maintenance and maturation of pulmonary surfactant. Infants with BPD/CLD may need up to 130 kCal/kg/day to achieve positive growth. Some of these infants are fluid sensitive, and meeting high caloric needs with a restricted fluid intake can be a clinical challenge.

Medication Management

Although there is no "magic bullet" for BPD, the use of certain medications during the course of the disease may help to reduce severity and manage symptoms associated with long-term ventilation. Controversy remains surrounding the use of these medications. Antenatal steroids have been found to reduce mortality, RDS, and intraventricular hemorrhage (IVH) in preterm infants. Although antenatal steroids reduce risk factors for the development of BPD, they do not reduce the incidence of BPD. Antenatal steroids may reduce the severity of BPD, but there is conflicting evidence in this area.

Surfactant

The introduction of surfactant into the NICU has significantly changed outcomes of neonatal patients. Previously, infants as mature as 36 weeks gestation had prolonged and difficult RDS courses, with many ending with the cystic BPD described in early neonatal literature. The widespread use of surfactant has, in part, reduced the threshold of survival so that NICUs are routinely resuscitating and later discharging preterm infants born at 24 weeks gestation. The debate of early versus late surfactant delivery after birth recognizes that surfactant should be given early in the clinical presentation of respiratory symptoms to reduce complications associated with RDS (e.g., pneumothorax, pulmonary interstitial emphysema, chronic lung disease, or death). Early use of surfactant also has been shown to reduce the risk for BPD or death at 28 days, even though surfactant use has not reduced the overall incidence of BPD.

Caffeine

Although caffeine is commonly used in infants to treat apnea of prematurity, it also has an impact on ventilation and has been shown to prevent BPD. Infants who received caffeine in the first week of life were shown to have a reduction in duration of positive pressure ventilation by 1 week when compared with the placebo group (Picone, Bedetta, & Paolillo, 2012). Caffeine may possess the ability to prevent respiratory failure in infants following extubation and may be related to adenosine receptors in the brain that affect capillary permeability, inflammation, and lung remodeling.

Vitamin A

Vitamin A is essential for immunity, growth, and the integrity of the epithelial cells that line the respiratory tract. Most preterm infants have low levels of vitamin A because of decreased intrauterine growth, which then increases the risk for BPD/CLD. In a large, multicenter, randomized, controlled study that compared giving 5000 IU of vitamin A intramuscularly three times a week for the first month of life versus placebo, results showed a significant decrease in either death or CLD in the treatment group (Beveja & Christou, 2006). Analysis of both groups at 18–24 months showed no change in mortality or neurodevelopmental outcomes, but the number of infants who required oxygen at 1 month or 36 weeks PCA was statistically significant. Vitamin A has been subjected to recurrent drug shortages over the past several years. The current status of this drug can be found on the U.S. Food and Drug Administration (FDA) website in the Current Drug Shortages Index.

Corticosteroids

The extremely preterm infant often has a reduced cortisol response that may increase the response to inflammation seen in the lungs. This can affect the preterm infant's lung that has been exposed to inflammation from maternal chorioamnionitis as well as mechanical ventilation and exposure to oxygen.

Systemic corticosteroids have strong anti-inflammatory properties. Systemic steroid use in infants with RDS allows for rapid weaning from both mechanical ventilation and high levels of oxygen. During the 1980s, steroid use was thought to have a major impact on the reduction of BPD and the improvement of neonatal outcomes. Dosing strategies were widely divergent in terms of initiation and duration of treatment and dosage. However, in the 1990s, as these infants were followed in high-risk clinics, there was a concerning increase in poor neurodevelopmental outcomes, reduced head circumference, and some potentially worse outcomes once the child reached school age with poor cognitive and motor skills.

In 2002, the American Academy of Pediatrics (AAP) released a policy statement regarding the use of postnatal corticosteroids for prevention or treatment of CLD in preterm infants. It called for limiting steroid use to exceptional clinical circumstances and counseling families about the risk of adverse neurodevelopmental outcomes.

In 2010, following an update of a systematic review of studies, the AAP released a revised policy statement on the use of postnatal corticosteroids to prevent or treat BPD. The academy continues to stress concerns about long-term neurodevelopmental outcomes in infants exposed early to steroids. However, following the review of the literature, the AAP now recommends judicious use of dexamethasone at a later time (after day 7) if the infant is unable to be weaned from the ventilator. The rationale is that, at this point, the risk of cerebral palsy from exposure to dexamethasone compared with the higher rate of mortality if not treated is equal.

The small studies that have been reported since then do not show an increase in adverse neurodevelopmental outcomes when steroids are used after the first 7 days of life. There also was no difference in the response to high- versus low-dose dexamethasone, resulting in the conclusion that low doses and shorter duration of treatment can achieve the same effect as high dose or prolonged therapy.

In 2017, a large Cochrane review concluded that inhaled corticosteroids given to infants age 7 days or older who were at high risk for developing BPD/CLD did not reduce death or BPD rates and did not decrease ventilator days or oxygen requirement (Shah, Ohlsson, Halliday, & Dunn, 2017). The authors did not recommend inhaled corticosteroid use at that time.

Bronchodilators

Increased airway reactivity and decreased lung compliance are hallmarks of BPD/CLD. The use of beta-agonists such as albuterol to improve these clinical complications was a method to improve airway compliance and reduce incidence of bronchospasm. However, in a randomized, controlled study to evaluate use in the infant with BPD, there was no difference in mortality, incidence of BPD, duration of ventilation, or oxygen requirement when the treatment and control groups were compared. Although there may be a short-term response to bronchodilators, it does not appear that chronic use of this medication group improves outcomes.

Diuretics

Neonates with BPD/CLD have high caloric requirements, often resulting in high daily fluid intake. Alveolar edema, capillary leak from inflammation or lung injury, and volume overload because of left to right shunting across the PDA can result in pulmonary edema. This excess fluid can alter lung compliance and function.

The most common diuretic used is furosemide (Lasix), a loop diuretic. Furosemide works to increase interstitial fluid reabsorption and increase urine output. There is a transient improvement in both oxygen requirement and lung compliance, which is seen clinically but not always reflected by blood gases. A Cochrane meta-analysis reviewed the use of furosemide to treat infants with BPD/CLD and showed no benefit to duration of oxygen

requirement, ventilator support, CLD/BPD, or death. There are several risks involved with the use of furosemide. It may delay the closing of the ductus arteriosus, because furosemide stimulates renal production of prostaglandin. Ototoxicity, electrolyte disturbances, nephrocalcinosis (kidney stones), or bone demineralization also are potential complications of this therapy.

Another class of diuretics, thiazides, has less of an effect on diuresis but also less of an impact on the infant's electrolyte homeostasis. Thiazides have a short-term effect on pulmonary function but do nothing to improve or alter the outcomes or severity of BPD. Use of thiazides is thought to reduce the use of furosemide, thereby reducing the side effects.

Oxygen

Oxygen remains the most commonly used drug in the NICU. Tissue oxygenation is essential for life. Chronic hypoxia can contribute to the development of pulmonary hypertension, necrotizing enterocolitis, IVH, and adverse neurodevelopmental outcomes. In infants with BPD/CLD, episodes of acute hypoxia also may increase airway resistance. Oxygen toxicity has been associated with alterations in pulmonary development. Excessive oxygen levels may increase production of free oxygen radicals and cytokines that increase inflammation, which then inhibits the development of alveoli and the microvascular growth. These alterations affect critical organ blood vessel development in the lung and eyes, leading to increased rates of BPD and severe retinopathy of prematurity (ROP).

There is not a clear range of oxygen saturations that avoids both short- and long-term complications. Studies have examined preterm infants beyond the first 28 days of life. The STOP-ROP and Benefits of Oxygen Saturation Targeting (BOOST) trials evaluated using target saturation ranges in two groups—low (saturations 89%–94%) and high (saturations 95%–98%)—and the impact on growth, development, and changes in prethreshold ROP. In the BOOST study, there was no significant difference in the outcome measures (growth or development) between the two groups. In the high saturation group, a longer duration of oxygen therapy, greater need for home oxygen, and increased rate of BPD/CLD was found. In the STOP-ROP study, there was no change in the progression of the ROP between the groups; however, the researchers also reported that the group with lower saturations had fewer incidences of pneumonia or BPD exacerbations. There is concern that targeted saturations (less than 90%) may be associated with increased risk of death based on the recent BOOST II trial. Several multicenter, randomized, controlled studies are underway to determine the most appropriate target saturations for preterm infants.

Once the diagnosis of BPD/CLD has been made and the infant is on oxygen (nasal cannula or positive pressure device), it is important to maintain saturations in the 90%–95% range. This promotes growth and avoids using more energy to breathe because of lower oxygen saturations. It also reduces the risk of developing pulmonary hypertension and vasoconstriction. Some infants with BPD will require oxygen for up to 2 years of life, either by cannula or by ventilator with a tracheostomy in the most severe of cases.

Nitric Oxide

The use of inhaled nitric oxide (iNO) is part of the NICU toolbox to manage full-term infants with persistent pulmonary hypertension of the newborn (PPHN). iNO decreases pulmonary vascular resistance, improves ventilation/perfusion mismatch, and provides bronchodilation. In addition, iNO has been found to have an anti-inflammatory effect and may assist in remodeling of the pulmonary vasculature following chronic hypoxic failure. Several randomized trials evaluating the use of iNO in low-birthweight infants have produced inconsistent results, with a limited number of patients experiencing a reduction in the incidence of BPD. In 2010, the NIH issued a consensus statement on the use of iNO in preterm infants. The recommendation was that iNO should not be used routinely in the care of infants younger than 34 weeks to prevent BPD or alter neurodevelopmental outcomes. However, they did not rule out the use of this treatment in extreme cases as a lifesaving measure. Studies are underway to evaluate timing, dose, and duration of iNO use and potential respiratory and long-term outcomes in the preterm infant. Currently, it does not

have widespread acceptance as a useful therapy for preventing BPD.

Other Possible Therapies

Attempts to target specific issues that surround BPD, such as inflammation and tissue growth, have led to small studies examining other interventions that may lead to a reduction of the incidence or the severity. One such intervention is the administration of stem cells to the neonate with the goal of targeting damaged lung tissue and providing healthy cells to generate new growth. Systemic treatment with erythromycin is given to reduce ureaplasma colonization, which may play a role in developing BPD/CLD, although the role ureaplasma plays in developing CLD remains controversial. Heliox, a mixture of helium and oxygen, has been found to aid ventilation in infants with BPD/CLD and to decrease work of breathing, improve gas exchange, and decrease respiratory support requirements. These findings have been noted anecdotally and require more rigorous study before efficacy can be determined.

Treatment of Severe BPD

Many infants who have severe BPD remain ventilator dependent despite maximal medical management; they can remain in the NICU for as long as 1 year. These infants have unique challenges and additional management strategies may need to be employed.

Ventilation

As with the infant who has RDS in the first days and weeks of life, the goal for older, more chronically affected infants remains the same: minimize oxygen requirements and mechanical ventilation support. However, in infants with severe BPD/CLD, these goals are more difficult to achieve. Infants with severe BPD/CLD need to maintain oxygen saturation levels in a range allowing for adequate oxygenation, yet avoiding extreme swings. Chronic hypoxia has been shown to diminish neurodevelopmental outcomes and can cause vascular remodeling in the pulmonary and cardiac vessels. This results in pulmonary hypertension (PH) or cor pulmonale. Infants with severe BPD may have reduced lung compliance and increased airway reactivity, much like that of a child with asthma. In some but not all cases, use of bronchodilators for acute symptom management may improve bronchospasm. In addition, long-term endotracheal intubation or tracheotomy may result in tracheobronchomalacia, which presents as airway obstruction unresponsive to bronchodilators. These infants may require a higher amount of positive end expiratory pressure to reduce collapsing of the central airway on exhalation. To minimize these episodes, sedation, and in some cases, temporary pharmacologic paralysis may be required.

Weaning infants with severe BPD must include attempting to "normalize" blood gases that have previously been allowed to reflect a higher degree of carbon dioxide retention and compensatory metabolic alkalosis. The carbon dioxide set point of some chronic infants has been allowed to go as high as the mid 60s in an effort to wean the infant off of the ventilator. There is usually an accompanying metabolic alkalosis as the infant attempts to normalize his or her acid base balance. If the infant's electrolytes are within normal limits, additional medications to reduce the alkalosis—such as Diamox, a carbonic anhydrase inhibitor, or arginine hydrochloride—may need to be added.

If multiple attempts to extubate the infant with severe BPD have not been successful, performing a tracheotomy should be considered. Placement of a tracheostomy (trach) in an older NICU patient may have some direct benefits. First, it may allow for easier ventilator weaning due to less dead space and decreased airway resistance. The trach allows for better clearance of secretions and is usually more comfortable for the infant, thus reducing the need for sedation. The risk associated with placement of a trach needs to be considered. Most infants who progress to requiring tracheostomies will require long-term ventilator support that may extend into the home setting. Trachs offers a more stable airway and may allow the older infant more freedom of movement. This permits more normal play and feeding options and promotes better neurodevelopmental outcomes.

Pulmonary Hypertension

Some infants with severe BPD will go on to develop PH, resulting in increased morbidity and mortality. The

mechanism of action is not known, but it has been suggested that this is a result of changes in the pulmonary vasculature related to hypoxia and exposure to inflammation and ventilator-induced injury. Alterations of growth factors and vascular tone may lead to thickening of the ventricles and septum and abnormal growth of capillaries throughout the cardiac structure. Infants also may have elevated pulmonary vascular resistance, precipitated by the presence of chronic hypoxia, hypercapnea, and acidosis.

Diagnosis of pulmonary hypertension can be difficult. Echocardiograms, which evaluate the velocity of regurgitation through the tricuspid valve, with pulmonary pressures being compared to systemic pressures, are more commonly used. The echocardiogram also can be helpful to assess the heart's response to initiation of a particular therapy.

Treatment of PH in the infant with BPD/CLD is determined by the severity. Often, in milder forms of PH, avoidance of hypoxia and optimizing overall growth is all that is required. In more severe forms of PH, additional support may include ventilation and medications such as iNO, sildenafil, and bosentan. There is a higher incidence of mortality in infants with this severity of BPD/CLD.

Although it has proven effective in acute PPHN, in this subgroup of NICU patients, iNO is not an ideal therapy due to its expense and unwieldy long-term use. Sildenafil has been used in long-term treatment of PH. Animal studies have been conducted to determine the efficacy of sildenafil's use earlier in the life of preterm infants to decrease the incidence or severity of BPD. There is little known about the long-term effects of sildenafil's use in this patient population. There is concern about the safety of this drug, and the FDA has issued an advisory about the use of sildenafil in children between the ages of 1 and 17 with PH. Bosentan also is being evaluated for use in treating BPD/CLD infants with PH. Bosentan, an antagonist of ET-1, which is a neurohormone released from the vascular endothelium and a potent vasoconstrictor, has been shown to reduce endothelial smooth muscle constriction, hypertrophy, and hyperplasia in adult populations. It has a direct antifibrotic effect that makes it appealing for treating BPD. Much like sildenafil, bosentan is used with extreme caution in the NICU population because there is no data on patients younger than 9 months in currently published studies.

Complications and Long-Term Outcomes

Long-term morbidities in infants with BPD/CLD have included ROP, cerebral palsy, cognitive and behavioral difficulties, speech and feeding disorders, and long-term pulmonary disease. They often require physical, speech, and occupational therapy—to address issues such as feeding aversion, developmental milestone delays, speech delays, and dental problems related to long-term intubation with oral endotracheal tubes—as well as diligent monitoring of growth. These infants may require frequent rehospitalization during the first 2 years of life due to their lung disease.

Nursing Implications

The nurse at the bedside is the first line of defense for these vulnerable infants. It is through diligent assessment and monitoring that subtle changes are noted. Consistent and aggressive titration of oxygen delivery is very important. Prevention of oxygen toxicity is equally important for issues discussed earlier in this section. Assessment of comfort and pain with provisions of both nonpharmacologic as well as pharmacologic therapies will assist in maintaining a stable oxygen saturation range.

The hospital course of extremely preterm infants is defined by periods of ups and downs followed by long periods of feeling as though things will never change or get better. Many families are far away from their own social support network and experience isolation and loneliness due to the extended length of hospital stays. It is essential that the NICU staff refer parents to support venues in the hospital and nearby while their baby is hospitalized.

Maintaining breast milk supply over a long period of time is a difficult endeavor for the mother, but it is critical to the well-being of the infant. Ongoing support and management of this process is an integral part of the nurse's

role. Provision of skin-to-skin care is a major incentive for moms, who observe a noticeable increase in milk production after or during time with the baby. Later, as the infant is extubated and beginning to take oral feeds, close work with lactation specialists will help mom and baby transition successfully to breastfeeding if the baby is physiologically stable.

Parental inclusion in the daily care of their infant increases confidence in caring for their child as well as encourages engagement through the long days when things seem to be at a standstill. Inclusion of families as members of the multidisciplinary team conveys the message that they are very much a part of their baby's care. As the infant progresses to discharge, early teaching reduces the amount of overwhelming information provided at the last minute. Offering information and care activities early decreases anxiety and fear of not being able to care for their baby outside the hospital setting. Many parents will room-in with their child for a period of time as a transition to home. Follow-up by home healthcare providers offers reassurance and resources following discharge from the NICU.

Postdischarge follow-up may be challenging due to the number of subspecialty services involved. Coordinating visits as much as possible is recommended. Infants with BPD/CLD are at high risk for developing upper respiratory infections, such as respiratory synctial virus (RSV) in the first 2 years. It is important to provide education about limiting exposure to visitors and practicing good hand hygiene at home. Immunizations for care providers and siblings, including flu shots and a pertussis (whooping cough) vaccine booster shot, should be up to date. RSV immunoprophylaxis and appropriately timed immunizations should decrease the incidence of potentially lethal infections. Transfer of care to the community provider is accomplished through both verbal communication and by comprehensive discharge summaries. Providing the families with a copy of the discharge summary will help them convey vital information concerning their baby's hospital course should they need to seek emergency services for any reason.

References

Baveja, R., & Christou, H. (2006). Pharmacological strategies in the prevention and management of bronchopulmonary dysplasia. *Seminars in Perinatology, 30*, 209–221.

Geary, C. (2008). Decreased incidence of bronchopulmonary dysplasia after early management changes, including surfactant and nasal continuous positive airway pressure treatment at delivery, lowered oxygen saturation goals and early amino acid administration: A historical cohort study. *Pediatrics, 121*, 89–96. doi: 10.1542/peds.2007-0225

Northway, W. (1990). Bronchopulmonary dysplasia: Then and now. *Archives of Diseases in Childhood, 65*, 1076–1081.

Picone, S., Bedetta, M., & Paolillo, P. (2012). Caffeine citrate: When and for how long. A literature review. *Journal of Maternal-Fetal and Neonatal Medicine, 25*(5), 11–14.

Shah, V. S., Ohlsson, A., Halliday, H. L., & Dunn, M. (2017) Early administration of inhaled corticosteroids for preventing chronic lung disease in very low birth weight preterm neonates. *Cochrane Database of Systematic Reviews*, *1*, CD001969. doi: 10.1002/14651858.CD001969.pub4.

Bibliography

American Academy of Pediatrics Committee on Fetus and Newborn. (2010). Policy statement: Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. *Pediatrics*, *126*(4), 800–808. doi: 10.1542/peds.2010-154

Bancalari, E. (2000). Epidemiology and risk factors for the "new" bronchopulmonary dysplasia. *Neoreviews, 1*, 2. doi:10.1542/neo.1-1-e2

Baraldi, E., Carraro, S., & Filippone, M. (2009). Bronchopulmonary dysplasia: Definitions and long-term respiratory outcome. *Early Human Development, 85*(10 Suppl), S1–S3.

Baraldi, E., & Filippone, M. (2007). Chronic lung disease after premature birth. *The New England Journal of Medicine, 357*(19), 1946–1955.

Belcastro, M. (2004). Bronchopulmonary dysplasia: A new look at an old problem. *Newborn and Infant Nursing Reviews, 4*(2), 121–125.

Bhandari, A., & Bhandari, V. (2009). Pitfalls, problems and progress in bronchopulmonary dysplasia. *Pediatrics, 123*, 1562–1573.

BOOST II United Kingdom Collaborative Group. (2013). BOOST II oxygen saturation and outcomes in preterm infants. *The New England Journal of Medicine, 368*, 2094–2104.

Cerny, L., Torday, J. S., & Rehan, V. K. (2008). Prevention and treatment of bronchopulmonary dysplasia: Contemporary status and future outlook. *Lung, 186*, 75–89.

Doyle, L. W., Davis, P. G., Morley, C. J., McPhee, A., Carlin, J. B., & DART Study Investigators. (2006). Low dose dexamethasone facilitates extubation among chronically ventilator dependent infants: A multicenter, international, randomized, controlled trial. *Pediatrics, 117*, 75–83.

Eichenwald, E., & Stark, A. (2009). Management of bronchopulmonary dysplasia. *Paediatrics and Child Health, 19*(12), 559–564.

Gomella, T. L., Cunningham, M. D., & Eyal, F. G. (2013). *Neonatology* (7th ed.). New York, NY: McGraw-Hill Education.

Gupta, S., Prasanth, K., Chen, C., & Yeh, T. (2012). Postnatal corticosteroids for prevention and treatment of chronic lung disease in the preterm newborn. *International Journal of Pediatrics, 2012*, 315642.

Jeeva Sankar, M., Agarwal, R., Deorari, A. K., & Paul, V. K. (2008). Chronic lung disease in newborns. *Indian Journal of Pediatrics, 75*, 369–376.

Johnson, T. J., Patel, A. L., Jegier, B. J., Engstrom, J. L., & Meier, P. P. (2013). Cost of morbidities in very low birth weight infants. *The Journal of Pediatrics, 162*(2), 243–249.

Merritt, T. A., Deming, D. D., & Boynton, B. R. (2009). The "new" bronchopulmonary dysplasia: Challenges and commentary. *Seminars in Fetal and Neonatal Medicine, 14*, 345–357.

Mosca, F., Colnaghi, M., & Fumagalli, M. (2011). BPD: Old and new problems. *Journal of Maternal-Fetal and Neonatal Medicine, 24*(Suppl 1), 80–82.

National Institute of Health. (2010). Consensus statement on nitric oxide for premature infants. *National Institutes of Health Consensus Statements, 27*(5), 1–34.

Papoff, P., Cerasaro, C., Caresta, E., Barbàra, C. S., Midulla, F., & Moretti, C. (2012). Current strategies for treating infants with severe bronchopulmonary dysplasia. *Journal of Maternal-Fetal and Neonatal Medicine, 25*(53), 15–20.

Paul, D. A., Zook, K., Mackley, A., & Locke, R. G. (2010). Reduced mortality and increased BPD with histological chorioamnionitis and leukocytosis in very-low-birth-weight infants. *Journal of Perinatology, 30*, 58–62.

Schulzke, S., & Pillow, J. (2010). The management of evolving bronchopulmonary dysplasia. *Paediatric Respiratory Reviews, 11*, 143–148.

Steinhorn, R. H., Kinsella, J. P., & Abman, S. H. (2013). Beyond pulmonary hypertension: Sildenafil for chronic lung disease of prematurity. *American Journal of Respiratory Cell and Molecular Biology, 48*(2), iii–v.

Thomas, W., & Speer, C. P. (2008). Nonventilatory strategies for prevention and treatment of bronchopulmonary dysplasia: What is the evidence? *Neonatology, 94*, 150–159.

Van Marter, L. (2009). Epidemiology of bronchopulmonary dysplasia. *Seminars in Fetal and Neonatal Medicine, 14*, 358–366.

Vaucher, Y. (2002). Bronchopulmonary dysplasia: An enduring challenge. *Pediatrics in Review 23*(10), 349–358.

Win, T., & Wiswell, T. (2008). Adjunctive therapies in chronic lung disease: Examining the evidence. *Seminars in Fetal and Neonatal Medicine, 13*, 44–52.

Bronchopulmonary Dysplasia: Information for Parents

What is bronchopulmonary dysplasia?

- *Bronchopulmonary dysplasia* (BPD), also called *chronic lung disease* (CLD), is a lung disease that can develop in babies who are born early and have breathing problems.
- *Broncho* means "airways or air tubes in the lungs." *Pulmonary* means "air sacs in the lungs."
- *Dysplasia* means "unusual changes in cells."
- *Chronic* means "long term."
- The lung tissue and airways of a premature baby are very soft and fragile. They are easily damaged and can become inflamed (swollen) and scarred.
- Once damaged, the growth of lung tissue and airways is abnormal and breathing becomes difficult.
- BPD is one of the most common lung diseases in children.

What causes BPD?

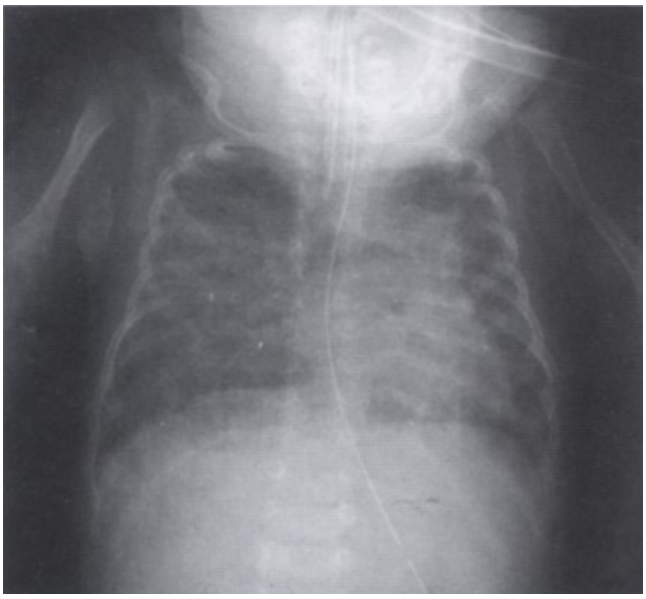
The exact cause of BPD is not known. The following are some things that make a baby more likely to develop BPD:

- BPD is most common in babies who have immature lungs. Babies born more than 10 weeks premature or weighing less than 2 pounds have the highest risk for developing BPD.
- Sometimes the very things that are needed to save the lives of preemie babies with respiratory distress syndrome (RDS) also can damage their lungs. Important treatments like oxygen and a breathing machine (ventilator) are very helpful. Sometimes a large amount of high pressure is needed to help breathing; however, high pressure also can be harmful to fragile lung tissue.
- Lung infections like pneumonia also can cause swelling in the airways and tissue of the lungs.

What are the signs of BPD?

BPD is usually suspected when a baby is between 1 and 2 months of age and has one or more of the following:

- A baby needs extra oxygen at 36 weeks corrected gestational age (about 1 month before the due date).
- A chest X ray shows lung damage.
- Ongoing breathing problems (breathes too fast or uses extra chest muscles to breathe) are present.



Chest X ray of baby with BPD/CLD. From "The Changing Face of Bronchopulmonary Dysplasia: Part 1," by K. Gracey, D. Talbot, R. Lankford, and P. Dodge., 2002, Advances in Neonatal Care, 2(6).

How do babies with BPD act?

Babies with BPD may have some or all of the following:

- fast, shallow, or noisy (grunting) breathing
- frequent coughing, wheezing, shortness of breath, and flaring of nostrils
- pulling of chest muscles inward between the rib spaces (retractions)
- sometimes look blue or dusky in color because of low blood oxygen levels
- need extra oxygen to grow and develop
- tire easily or breathe fast with feedings, which may slow growth and weight gain
- breathing may sound crackly or wet when listening with a stethoscope.

Is there a cure or treatment for BPD?

There is no quick cure for BPD, but there are many treatments that help babies breathe easier:

- Oxygen is used to make breathing easier and more comfortable. Some babies need to use oxygen at home. Oxygen may be needed for many weeks or months.
- Medications are sometimes used to help babies with BPD breathe easier. Surfactant and caffeine therapy in premature babies helps prevent BPD. Bronchodilators open the airways in the lungs. Corticosteroids help reduce inflammation in the lungs. Diuretics decrease fluid buildup in the lungs. Antibiotics treat bacterial lung infections, which are common in babies with BPD.
- High-calorie breast milk or formula gives your baby extra calories and nutrients to help growth and healing. Because some babies use so much energy just to breathe, they may need to be fed by a tube in the nose or stomach to make sure they take in enough calories to grow.
- Growth is the best treatment for BPD. With time, your baby will grow new, healthy lung tissue.
- In rare cases, some babies will have severe lung damage and need the help of a breathing machine (ventilator) for many months or more. If so, a tracheostomy is often used to help with breathing. A tracheostomy is a small hole in the neck that enables a special breathing tube to be put into the windpipe with a ventilator to support breathing.

Good News About BPD

- New devices (machines) make oxygen therapy and breathing machines more gentle on the baby's lungs.
- Medications help make breathing easier and decrease breathing problems.
- Most babies will outgrow BPD because they rapidly grow new lung tissue during the first 2 years of life.
- Babies with BPD can usually be cared for at home in close partnership with the baby's provider and pediatric pulmonologist. A *pediatric pulmonologist* is a doctor who specializes in the treatment of lung disease in children.

Going Home

Call your baby's provider right away if your baby has

- breathing problems that become worse or signs of respiratory infection:
  - fever
  - breathes faster than usual
  - works harder to breathe than usual
  - coughs, wheezes, or breathes more noisily than usual
  - pale, dusky, or blue lips or fingernails
  - more irritable or fussy than usual
  - tires more easily with breathing or feeding
  - spits up more than usual or doesn't want to eat.

If your baby stops breathing, start cardiopulmonary resuscitation (CPR) and call 911 or local emergency medical services right away.

Important Things to Remember

- Babies with CLD or other complications are at greater risk for ongoing lung problems. It will be important for you to know how your baby breathes "normally" and how his or her chest muscles look if he or she is having trouble breathing.
- Prevent lung infections. Always wash your hands before touching your baby or preparing your baby's food. Only allow people to visit your home when they are not sick. Keep young children away from your baby. Avoid crowds and day care centers.
- No smoking should happen around your baby. Limit exposure to pollution and other lung irritants.
- Encourage all people who care for your baby to get a flu shot before the start of cold and flu season and a pertussis (whooping cough) vaccine booster shot.
- Take your baby for all regular well-child check-ups and follow the recommended schedule for immunizations.
- Talk to your baby's provider about palivizumab (Synagis), a medication used to prevent respiratory syncytial virus infection in young children.
- Each follow-up appointment with the pediatric pulmonologist is important and is in addition to well-child check-ups with your baby's provider.
- If your baby needs to take special medications to help breathe easier, always follow the directions on the bottle or container that came from the pharmacy.
- You may be nervous at first, but with practice, you will become more comfortable caring for your baby with BPD. *Remember, it's always OK to ask for help!*