Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a CLD that develops primarily in neonates who are born at 24–26 weeks gestation weighing <1,000 g and who receive prolonged oxygen therapy and/or positive pressure ventilation.[144] The increase in survival among very premature newborns has increased the number of infants with this disorder, challenging the health care system. In the literature the terms *BPD* and *CLD* are often used interchangeably, as they will be in this chapter.

Definitions: Old and New

In 1967, Northway, Rosan, and Porter described BPD as a type of CLD that developed in premature infants with severe RDS who were treated with positive pressure mechanical ventilation and oxygen.[145] These infants had severe respiratory failure at birth; required aggressive ventilatory support; and, as a result, developed severe lung injuries and remained dependent on oxygen for long periods of time. Originally, Northway's group postulated that oxygen toxicity caused BPD, but research has revealed that multiple complex mechanisms cause the disease. Northway and colleagues' description of BPD is now referred to as classic, or "old," BPD. This descriptor recognizes that in the postsurfactant, post–antenatal steroid era, the picture of BPD has changed and a "new" BPD has emerged. BPD is now known to occur in term and preterm neonates with a variety of neonatal conditions, including apnea, meconium aspiration, pneumonia, and congenital heart disease as well as primary lung disease. Today, infants with BPD may have only mild lung disease at birth and receive only brief periods of mechanical ventilation and oxygen therapy.

Northway and colleagues' original description of BPD outlined the radiologic, pathologic, and clinical criteria associated with four stages of the disease (Table 10-6).[145] Bancalari and associates, in 1979, further defined an infant with BPD as one who requires positive pressure ventilation for at least three days during the first week of life, has clinical signs of respiratory distress, requires supplemental oxygen to maintain an oxygen tension (PaO_2) of 50 torr for >28 days, and shows radiographic evidence of BPD.[146] Since its original description, the presentation and progression of BPD have changed, but the initial characteristics and definitions remain salient to an understanding of this disorder.

As smaller and sicker infants survive because of new technologies (including surfactant replacement therapy, high-frequency ventilation, and prenatal and postnatal steroids), new BPD has emerged. The severe form of BPD originally described was seen primarily in premature infants who were ventilated mechanically using high pressures and had prolonged exposure to high levels of inspired oxygen. New BPD is a milder form of CLD seen

TABLE 10-6
Stages of Bronchopulmonary Dysplasia (Classic)

Stage	Time	Pathologic Findings	Radiologic Findings	Clinical Features
I (mild)	2–3 days	Patchy loss of cilia; bronchial epithelium intact; profuse hyaline membranes	Air bronchograms; diffuse reticulogranularity (identical to RDS)	Identical to RDS
II (moderate)	4–10 days	Loss of cilia; fewer hyaline membranes; necrosis of alveolar epithelium; regeneration of bronchial epithelium; ulceration in bronchioles	Opacification; coarse, irregularly shaped densities containing small vacuolar radiolucencies	Increased O_2 requirements and increasing ventilatory support when recovery is expected; rales, retractions
III (severe)	10–20 days	Advanced alveolar epithelial regeneration; extensive alveolar collapse; bronchiolar metaplasia and interstitial fibrosis; bronchial muscle hypertrophy	Small radiolucent cysts in generalized pattern	Prolonged O_2 dependency; $PaCO_2$ retention; retractions; early barrel chest; severe acute episodes of bronchospasm
IV (advanced-chronic)	1 month	Obliterative bronchiolitis; active epithelial proliferation; peribronchial and some interstitial fibrosis; severe bronchiolar metaplasia	Dense fibrotic strands; generalized cystic areas; large or small heart; hyperinflated lungs; hyperlucency at bases	Increased chest anteroposterior diameter; cor pulmonale; frequent respiratory infection; prolonged O_2 dependency; failure to thrive

From Korones SB. 2011. In *Assisted Ventilation of the Neonate,* 5th ed., Goldsmith JP, and Karotkin EH, eds. Philadelphia: Saunders, 390. Reprinted by permission.

in smaller infants who do not necessarily have severe lung disease at birth.[147]

The newer descriptions of BPD reflect our understanding of the disorder as one of altered lung development with decreased numbers of alveoli and abnormal blood vessel development rather than lung damage.[144,148] However, a clear definition of BPD remains elusive. Some clinicians define BPD as a requirement for supplemental oxygen at day 28 of life; however, this definition may inaccurately label infants who have an acute illness at the end of the first month of life as having BPD or miss infants who subsequently develop the need for supplemental oxygen.[147] Others have proposed the need for oxygen at 36 weeks postmenstrual age as a better criterion for defining BPD.[149] In 2001, the National Institutes of Health (NIH) convened a consensus panel to address these inconsistencies. That panel agreed on the definition of BPD shown in Table 10-7. The NIH definition requires a minimum of 28 days of supplemental oxygen and defines the severity of the disease by the amount of oxygen required.[150] It is important to note that under this definition, infants being treated with supplemental oxygen for nonpulmonary problems—for example, for congenital anomalies such as diaphragmatic hernia—are not considered to have BPD unless they also have parenchymal lung disease. To further refine this definition, some clinicians have suggested that infants receiving supplemental oxygen at 28 days or 36 weeks corrected age, undergo an oxygen needs test. This test involves challenging the infant by gradually reducing the inspired oxygen to room air. Those infants with an oxygen saturation of <90 percent after 30 minutes on room air would be deemed to have BPD.[151]

Incidence

The incidence of BPD is difficult to report because it depends both on the definition of BPD used and also on the accuracy of gestational age determination in the study population. A review by Bhandari and Panitch found the incidence of BPD, defined as oxygen need at 36 weeks postmenstrual age, to be about 30 percent among infants with birth weights <1,000 g.[152] This is similar to the rate of 35 percent found by Walsh and colleagues in a study of 1,598 inborn infants weighing <1,250 g who remained hospitalized at 36 weeks postmenstrual age.[151] Sahni and colleagues identified rates of BPD, defined as oxygen need at 28 and 36 weeks, to be 21.1 and 7.4 percent, respectively.[153] Ehrenkranz and colleagues applied the NIH definition of BPD in a retrospective review of 4,866 infants (birth weight ≤1,000 g, gestational age <32 weeks, alive at 36 weeks postmenstrual age) born between 1995 and 1999 and found that 77 percent of the infants met the criteria for BPD, with 30 percent having moderate disease and 16 percent severe BPD. Of those who met the NIH criteria and were seen in follow-up at 18–22 months corrected age, 35 percent had required rehospitalization for respiratory illnesses and 40 percent had received medications for a pulmonary condition.[154]

TABLE 10-7
Definition of Diagnostic Criteria for BPD

Gestational age	<32 weeks	≥32 weeks
Time point of assessment	36 week PCA or discharge to home, whichever comes first	>28 days, but <56 days postnatal age or discharge to home, whichever comes first
	Treatment with oxygen >21% for at least 28 days ***plus***	
Mild BPD	Breathing room air at 36 weeks PCA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need* for <30% oxygen at 36 weeks PCA or discharge, whichever comes first	Need* for <30% oxygen at 56 days postnatal age or discharge, whichever comes first
Severe BPD	Need* for <30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 weeks PCA or discharge, whichever comes first	Need* for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge, whichever comes first

Key: NCPAP = nasal continuous positive airway pressure; PCA = postconceptional age; PPV = positive-pressure ventilation.

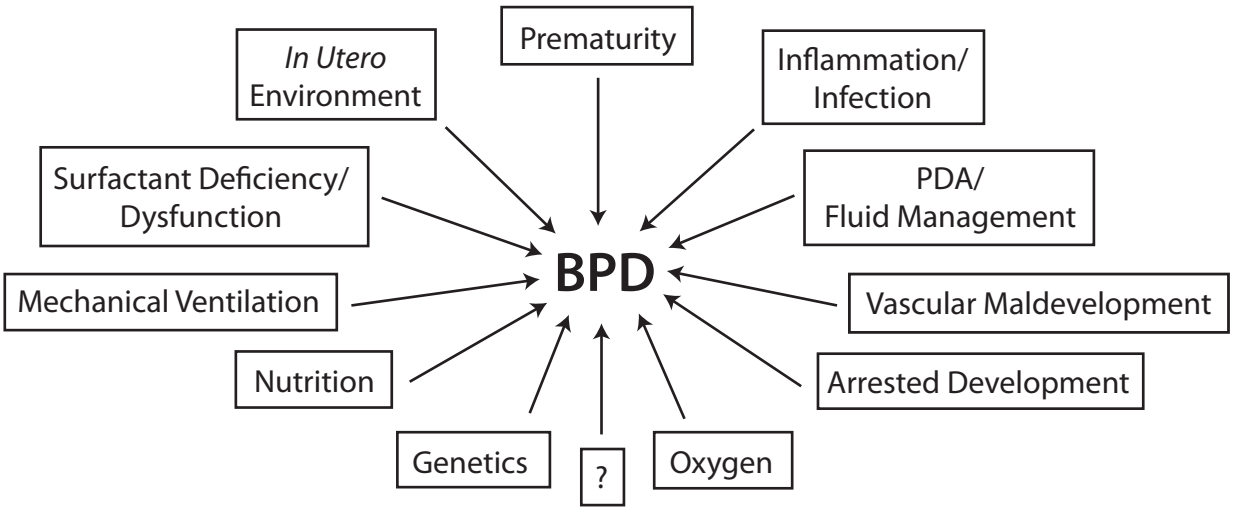
*A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range. BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most commonly RDS. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) are considered common to the broad description of BPD and have not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen >21 percent and/or positive pressure for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen >21 percent means that the infant received oxygen >21 percent for more than 12 hours on that day. Treatment with oxygen >21 percent and/or positive pressure at 36 weeks PMA, or at 56 days postnatal age or discharge, should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and following 36 weeks PMA, 56 days postnatal age, or discharge.

From: Jobe AH, and Bancalari E. 2001. Bronchopulmonary dysplasia. *American Journal of Respiratory Critical Care Medicine* 163(7): 1726. Reprinted by permission.

Pathogenesis

Bronchopulmonary dysplasia has been attributed to oxygen toxicity, barotrauma, volutrauma, lung immaturity, inflammation, and infection (Figure 10-10). The causes are multifactorial and likely include acute lung injury, arrested lung development, as well as abnormal repair processes that occur in the lung. Normal lung growth and development are disrupted by a premature birth. The immature lung, already deficient in surfactant, is then exposed to adverse stimuli.

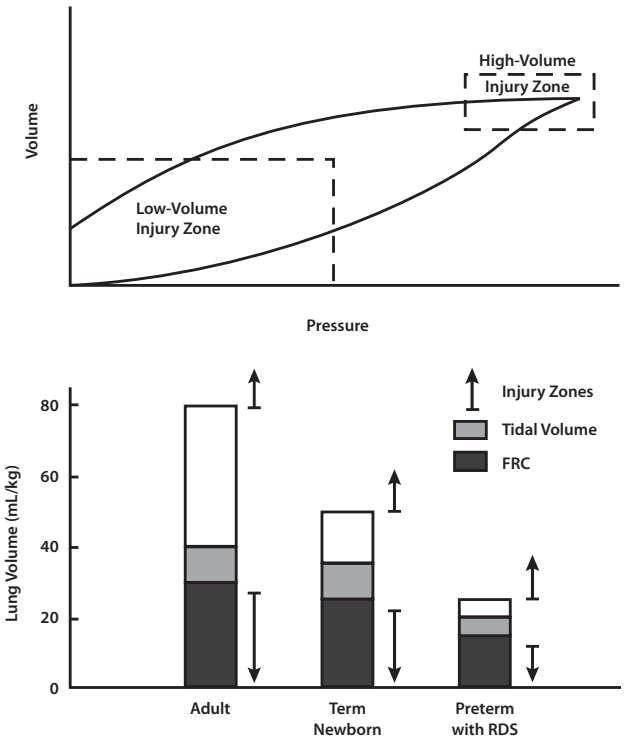
FIGURE 10-10
Factors contributing to the development of BPD.



From: Chess PR, et al. 2006. Pathogenesis of bronchopulmonary dysplasia. *Seminars in Perinatology* 30(4): 172. Reprinted by permission.

FIGURE 10-11
Injury zones in the lung.

The upper graph shows a pressure-volume curve and indicates the low- and high-volume injury zones. Lung volumes for a normal adult, a term newborn, and a preterm infant with RDS are given in mL/kg in the lower graph. The low- and high-volume injury zones are indicated by arrows. The preterm lung is susceptible to injury with ventilation because of the small volume per kilogram between the two injury zones.



From: Jobe AH, and Ikegami M. 1998. Mechanisms initiating lung injury in the preterm. *Early Human Development* 53(1): 86. Reprinted by permission.

Oxygen

Oxygen has been implicated in the development of BPD since the disorder was first described in the 1960s.[145] Although the development of BPD in infants exposed to minimal or no supplemental oxygen supports the notion that oxygen is not essential for the development of BPD,[146,155] it continues to be implicated as a major factor.[156]

Two types of oxygen toxicity have been described in BPD. The first type results in damage from the toxic effects of oxygen on the lung tissue. The second type is indirect damage that results from maladaptive physiologic responses to hyperoxia. Ventilated infants are particularly at risk of injury as a result of the formation of toxic metabolites of oxygen, which damage the airway, the lining of the capillaries, and the alveolar epithelium.[157] These by-products come in two forms: free radicals and reactive oxygen species (ROS). Free radicals include the superoxide radical ($O_2^-\cdot$)and the hydroxyl free radical (OH^-). Both reactive oxygen species have unpaired electrons in their outer orbital shells, a molecular conformation that makes it possible for both, but particularly the hydroxyl free radical, to damage DNA, proteins, and lipids. Essentially, free radicals destabilize organic molecules by either donating electrons to or accepting electrons from these species. In contrast, ROS include non-free radicals such as hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$); ROS are nonradical by-products of oxygen metabolism that are injurious on their own and that may also be transformed into free radicals.

Free radicals and ROS are normal, physiologic by-products of a variety of cellular processes, including energy production, immune cell function, and drug metabolism. Under homeostatic conditions, the production of free radicals and ROS is balanced by endogenous antioxidants, which either act as scavengers or stimulate antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Further antioxidant defenses are conferred by trace elements such as selenium and amino acids, including taurine.[158] Additionally, there is good evidence to suggest that exogenous molecules, such as antioxidant factors in breast milk (including lactoferrin and thioredoxin) and vitamins C and E, serve to reduce the toxicity of oxygen for the newborn infant.[159–161]

When hyperoxia, reperfusion, or inflammation cause increased free radical production that overwhelms the body's antioxidant defense mechanisms, these free radicals can damage cell membranes and unravel nucleic acids, a process referred to as oxidative stress.[162] Newborn infants in general, and premature infants in particular, are known to be at high risk for oxidative stress because of deficiencies in antioxidants.[162,163] Other causes of oxidative stress in this population include lung immaturity, which necessitates exposure to oxygen therapy; increased susceptibility to infections and inflammation; and the presence of free iron in the premature infant's system, which serves as a catalyst for ROS reactions.[164] There is mounting evidence that hyperoxia is a key injury stimulus in premature infants and that it is linked to the pathogenesis of a variety of disorders, including BPD and ROP.[157,165] Supporting this theory is the fact that, in animal models, prolonged exposure to oxygen is associated with markers of inflammation and the appearance of pro-inflammatory

cytokines such as interleukin (IL)-1α.[166,167] Lung abnormalities such as decreased septation and decreased lung surface area have been found to persist even after recovery from hyperoxic exposure.[167] Furthermore, SOD and CAT decrease lung injuries associated with oxygen toxicity.[168] The appearance of the antioxidant SOD coincides with the onset of surfactant synthesis by Type II pneumocytes.[169]

Reactive oxygen species' injuries to epithelial and endothelial cells result in pulmonary edema and activation of inflammatory cells.[157] As pulmonary edema progresses, proteins leak into the alveoli, inhibiting the surface tension properties of surfactant, thereby exacerbating the surfactant deficiency of prematurity.[162] The resulting cycle of worsening atelectasis, decreased lung compliance, and increased $\dot{V}_A/\dot{Q}_C$ mismatch leads to the need for higher oxygen and ventilator settings, which increases oxidative stress.

In response to the direct damage to cells caused by oxygen free radicals, a second phase of damage occurs. This phase is characterized by the proliferation of alveolar Type II cells and, ultimately, tissue fibrosis.[157] A number of markers of peroxidation (oxidative damage) have been found in the tracheal fluid and urine of neonates who later develop BPD. These changes are often seen only a few hours or a day after birth, supporting the theory that prenatal inflammation is also important in the development of BPD.[170]

Lung Trauma

Positive pressure ventilation is known to be important in the pathogenesis of BPD because of the contribution of pressure (barotrauma) and volume (volutrauma) to initiation of the inflammatory cascade. Dreyfuss and Saumon report that mechanical ventilation in animals using volumes greater than lung capacity injures the alveoli, resulting in leukocyte migration into the lungs, increased tissue permeability, and leakage of fluid into the interstitial tissue and alveoli.[171] Equally damaging is ventilation using volumes below FRC, which results in cyclic collapse of the alveoli (atelectotrauma).[172] The lung injury zones are illustrated in Figure 10-11. Without adequate tools to measure FRC, it can be very difficult to avoid injury when mechanically ventilating a premature infant.

In some cases, it is likely that injury to the lungs begins during the initial resuscitation of the neonate as clinicians try to establish ventilation quickly. This finding was illustrated by Bjorklund and colleagues who found that as few as six breaths at high tidal volumes prior to surfactant administration resulted in significant lung injury in preterm lambs.[173]

Several studies have also demonstrated an inverse relationship between the development of BPD and PCO_2 levels.[174,175] In fact, Garland and colleagues reported that low PCO_2 before surfactant administration was a stronger predictor of BPD than was the severity of lung disease. This finding supports the theory that hyperventilation plays a significant role in lung injury and subsequent development of BPD.[172]

Inflammation and Infection

Inflammation is now recognized as playing a significant role in the development of BPD. Chorioamnionitis and the presence of elevated cytokine levels *in utero* initiate a pulmonary inflammatory response that is thought to alter wound healing, alveolarization, and vascular development in immature lungs.[176–178]

The pulmonary vasculature contains numerous neutrophils that can trigger an inflammatory response, resulting in the release of enzymes that ultimately disrupt the extracellular matrix of the lung.[179] This response can also be initiated after birth as a result of alveolar injury secondary to oxidative stress or mechanical injury.[176] Young and colleagues found a significant increase in BPD in infants weighing between 700 and 1,000 g with positive initial endotracheal cultures compared with those with cultures that did not grow bacteria.[180] The same association was not found for infants less than 700 g. Similarly, Watterberg and colleagues demonstrated that neonates born following chorioamnionitis experienced mild initial respiratory distress but needed more ventilatory support in the second week of life.[181]

Several infectious agents have been implicated in the development of BPD, among them Chlamydia and adenovirus.[182] *Ureaplasma urealyticum* has been identified as being associated with the development of BPD,[183] but it is unclear whether treating Ureaplasma with antibiotics reduces the incidence of BPD.[184] Studies have demonstrated that this organism may cause a chronic subclinical pneumonia, increasing ventilation and oxygen requirements. It has been suggested that infection may act as an additional stimulus in the inflammatory response, with recruitment of neutrophils and activation of the arachidonic acid cascade ultimately leading to BPD.

TABLE 10-8
Potentially Better Practices for Reducing CLD in LBW Infants

Practice	Level of Evidence*
Provide vitamin A supplementation	Level 1
Decrease fluid administration	Level 3
Administer postextubation CPAP	Level 1
Institute permissive hypercarbia	Level 2
Decrease supraphysiologic corticosteroid exposure in premature infants	Level 1
Provide prophylactic surfactant for infants with birth weights <1,000 g or delivery room CPAP for infants with birth weights >1,000 g	Level 1
Reduce ventilator days	Level 1–5
Use high-frequency ventilation or low tidal volume ventilation	Level 1–2
Provide gentle ventilation in the delivery room	Level 2–3

* Muir Gray Classification System 70:

Level 1—Strong evidence from at least one systematic review of multiple well-designed randomized controlled trials

Level 2—Strong evidence from at least one properly randomized controlled trial of appropriate size

Level 3—Evidence from well-designed trials without randomization including single group, prepost, cohort, time series, or matched case controls

Level 4—Evidence from well-designed nonexperimental studies preferably from more than one center or research group

Level 5—Opinion of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees

Adapted from: Sharek PF, et al. 2003. Evaluation and development of potentially better practices to prevent chronic lung disease and reduce lung injury in neonates. *Pediatrics* 111(4): e428. Reprinted by permission.

Nutrition

Compromised nutritional status may also exacerbate the development of BPD in the premature infant.[185] Adequate caloric and protein intake is required for cell growth and division. Copper, zinc, iron, manganese, and selenium are required cofactors for antioxidant enzymes and may be necessary for repair of elastin and collagen. Vitamin E may provide antioxidant protection, but research findings are inconclusive. Vitamin A deficiency may also play a significant role in the pathogenesis of BPD because this vitamin is essential for differentiation, integrity, and repair of respiratory epithelial cells.[185,186] Vitamin A supplementation in neonates has been shown to reduce the production of pro-inflammatory cytokines.[187] Malnutrition in the premature infant can impair macrophages and neutrophil and lymphocyte function, which protect the lung against infection.[188]

Other Risk Factors

Other factors that have been correlated with the pathogenesis of BPD include a genetic predisposition, excessive fluid intake, lipid infusion, and gas temperature and humidification in the ventilator circuit.[189] Research suggests that infants are more likely to develop BPD if there is a family history of airway reactivity (including asthma).[190,191] Fluid overload can cause pulmonary edema. Several studies have shown that a persistently patent ductus arteriosus increases the risk of developing BPD.[95,192]

Pathology

The pathologic features of BPD first described by Northway and colleagues are divided into four stages (see Table 10-6). This classic, or "old," BPD described by Northway and colleagues begins with an exudative and early repair stage. That stage is followed, in severe cases, by a chronic fibroproliferative phase marked by widespread fibrosis with atelectasis and emphysema, as well as capillary vascular damage resulting in reduced alveolar development.[145]

In the original descriptions of BPD, characteristics of mild disease included patchy loss of cilia accompanied by mucosal breakdown of the airway lining followed by edema of the bronchi, blood vessels, and alveolar septa. Infants with moderate BPD experienced extensive loss of cilia in the bronchial lining cells and had evidence of inflammatory cells. Areas of atelectasis and metaplasia of cells lining the conductive airways also occurred. Infants with severe BPD developed necrosis of the airway lining resulting in excessive amounts of debris containing necrotic epithelial cells, mucus, and inflammatory cells. Areas of atelectasis and hyperinflation caused a $\dot{V}_A/\dot{Q}_C$ mismatch.[193,194]

Upper airway damage in infants with traditional BPD included tracheal, subglottic, and bronchial stenosis; polyps; granulomas; and tracheo- and bronchomalacia. Airway hyperactivity was commonly found in infants with BPD and often persisted into childhood.

Lungs affected by BPD in the postsurfactant era are less likely to have significant fibrosis, airway or smooth muscle hypertrophy, or epithelial metaplasia.[195] Under the definition of BPD, lungs show uniform inflation with fewer but larger alveoli. Other findings include a disruption of the collagen network around the saccules and dysplastic Type II cells in the saccules.[196]

The proposed mechanism for these findings is a disruption in alveolarization occurring as a result of damage to the developing capillaries and the alveolar

crest cells.[150] Before 36 weeks gestation, the functional respiratory units in the lung consist primarily of saccules. During the late saccular stage (after 20 weeks gestation), septal crest cells infiltrate these saccules, dividing each saccule into multiple alveoli. This septation process is accompanied by proliferation of alveolar capillaries that nourish the developing alveoli. Much of this development takes place in the relative hypoxemia found in the normal human fetus. Animal research suggests that inflammatory damage to the crest cells and the alveolar vasculature arrests septation, resulting in the findings of fewer, larger alveoli.[197]

Some researchers have proposed a three-stage model for the new definition of BPD, which might be useful in designing research studies.[198] The perinatal and early postnatal stage (Stage 1) represents opportunities to prevent BPD and is characterized by injury caused by inflammation. Evolving BPD (Stage 2) occurs at 7–14 days of age; interventions at this stage are aimed at diminishing the severity of the disease. In established BPD (Stage 3), which occurs at 21–35 days of age, characteristics include over-reactive airways, pulmonary edema, and oxygen dependency.

Prevention

Prevention of BPD begins with the elimination of preterm birth. If this is not possible, attempts should be made to accelerate lung maturity through administration of antenatal corticosteroids. The benefit of antenatal steroids in lessening the severity of RDS and, subsequently, BPD has been clearly shown.[199]

Numerous preventive strategies have been proposed, but few have been shown to significantly reduce the incidence of BPD in LBW infants. Using a research-to-practice translation process, representatives from nine member hospitals in the Neonatal Intensive Care Quality Collaborative developed a list of nine evidence-based potentially better practices (PBPs) aimed at reducing the incidence and severity of CLD in LBW infants.[200] Table 10-8 lists these practices. The levels of evidence supporting these PBPs varied. A report on the challenges and successes in implementing these PBPs was published.[201] The evidence supporting selected PBPs is presented in the following sections.

Avoid Ventilation

It was hoped that the introduction of surfactant therapy in the 1990s would reduce CLD. Although survival rates for LBW infants did increase following the introduction of this therapy, rates of BPD remained the same or increased.[202]

Assisted ventilation has come under intense scrutiny. Efforts have been made to reduce the impact of mechanical ventilation by avoiding intubation altogether, reducing the number of days on mechanical ventilation, and reducing the barotrauma and volutrauma linked to conventional mechanical ventilation. To this end, a variety of devices has been developed to support the LBW infant with respiratory disease. These include nasal CPAP (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV), high-frequency ventilation (HFV), and synchronized mechanical ventilation (SIMV). None of these modes of ventilation have been shown to prevent BPD, but some results are promising.[202]

In a groundbreaking paper published in 1987, Avery and colleagues compared survival rates and rates of BPD in eight U.S. NICUs.[203] They found that, despite similar survival rates for LBW infants among the facilities, the incidence of BPD was significantly lower at Columbia Presbyterian Medical Center in New York. The most striking difference between Columbia and the other centers was the early use of nasal prong CPAP with less dependence on intubation and mechanical ventilation at Columbia. Similarly, Sahni and colleagues reported that in infants weighing <1,250 g managed primarily with bubble CPAP, the incidence of BPD was 7.4 percent.[153] In a study done in New Zealand, Meyer and colleagues examined the preferential use of bubble CPAP and noted an incidence of CLD of 19 percent compared with an average of 45 percent in 28 other centers. These investigators also noted a trend toward a decrease in late-onset sepsis.[204] Studies are now examining the early use of surfactant followed by rapid extubation to CPAP, an approach dubbed INSURE.[205] The use of the INSURE protocol at one institution in Sweden resulted in a 50 percent reduction in the number of infants requiring mechanical ventilation.[205]

A 2007 Cochrane review compared early surfactant replacement therapy followed by extubation to nasal CPAP with the use of rescue surfactant replacement and mechanical ventilation. The authors found that prophylactic surfactant and extubation to CPAP is associated with a reduction in the need for mechanical ventilation, fewer air leaks, and a lower incidence of BPD.[206]

In randomized controlled studies using NIPPV, a trend to lower rates of BPD among infants treated with NIPPV was noted, although the numbers did not reach

statistical significance.[207,208] A more recent study published by Kugelman and colleagues found that in the 84 infants 28–33 weeks gestational age in their study, those randomized to NIPPV for the initial treatment of RDS were significantly less likely to require ventilation than were those in the CPAP group (25 percent vs 49 percent). Those infants also had significantly lower rates of BPD (5 percent vs 33 percent, $p<.05$, for infants <1,500 g).[209]

Permissive Hypercapnia

Permissive hypercapnia ($PaCO_2$ 45–55 mmHg) is another strategy that has been suggested to ensure a more gentle approach to ventilation aimed at reducing volutrauma and barotrauma. In addition to reduced barotrauma, animal data have demonstrated that lambs exposed to supplemental CO_2 to levels of 100 mmHg had fewer markers of pulmonary inflammation than did control lambs with normal levels of CO_2.[210] Clinical trials of permissive hypercapnia in human infants have been limited and have failed to demonstrate a consistent reduction in CLD.[211,212] The Cochrane review of this topic also failed to find a significant benefit to permissive hypercapnia.[213]

Fluid Restriction

Excessive lung water has been shown to be a risk factor for the development of BPD.[214] Lung injury and inflammation result in capillary leak, leading to pulmonary edema. Restricting fluid intake to the minimum necessary to provide adequate calories for growth has been recommended for infants at risk of developing BPD.[155,215] A meta-analysis examining fluid intake showed that restricted intake in preterm infants was associated with a lower risk of mortality and a trend toward a lower incidence of BPD.[109] Excessive sodium administration has also been shown to contribute to fluid retention and should be avoided.[216]

Antioxidant Therapy

Vitamin A is one of the only preventive strategies that has been clearly shown to reduce the incidence of BPD.[202] A randomized controlled trial of vitamin A supplementation in VLBW infants found that infants in the treatment group had significantly lower rates of oxygen dependency at 36 weeks than did control infants.[217] A Cochrane review of vitamin A in the prevention of BPD concurred with these findings.[218] Despite these conclusions, a survey of 207 Level III NICUs found that only 20 percent of training units and 13 percent of nontraining units routinely give vitamin A supplements to VLBW infants.[219]

Antioxidant agents other than vitamin A have been explored in the quest to reduce the incidence of BPD. These agents include intratracheal superoxide dismutase[220] and *N*-acetylcysteine.[221] Neither agent demonstrated a significant difference in BPD rates between study and control populations.

Signs and Symptoms

Early clinical signs of BPD may begin within the first week of life, when recovery from the initial disease (for example, RDS) is anticipated. Most LBW infants who develop "new" BPD have a relatively mild course of respiratory distress, but apnea or poor respiratory drive may delay extubation from mechanical ventilation.[95] These infants are weaned quickly to low ventilator settings and low concentrations of inspired oxygen. Following a honeymoon period with minimal or no supplemental oxygen, these infants progressively deteriorate, requiring increased ventilatory support. This deterioration may coincide with the onset of a symptomatic PDA or the diagnosis of a bacterial or viral infection.[155] Clinically, the infant may have retractions, diminished breath sounds, and fine crackles.

During the early phases of mild to moderate CLD, the changes on x-ray and in pulmonary function are usually mild. Persistent diffuse haziness may be the only change evident on x-ray.[155] As BPD progresses, a fine lacy pattern may develop in the parenchyma, and some hyperinflation with occasional large cysts may be seen on x-ray.[222]

A number of scoring systems have been developed to assist clinicians in predicting which infants with RDS will develop BPD.[223,224] The purpose of these scoring systems is, in part, to determine which infants to enroll in clinical trials investigating BPD treatments.[223] In these clinical trials, criteria found to be predictive of BPD development included the following two: a logistic regression analysis combining birth weight, five-minute Apgar scores, and PIP at 12 hours of age;[223] with FiO_2 >.30 and ventilation index <0.51 (10,000/peak pressure × rate × PCO_2) at 14 days.[224]

Treatment

The etiology and pathophysiology of BPD are multifactorial; the treatment is multifaceted. Management of the infant with BPD requires a multidisciplinary team in which all members are aware of the infant's response to various treatments. The

goal is to promote growth and maintain homeostasis in all systems, while keeping the infant free from infection and gradually weaning the ventilator and oxygen. Prevention and early recognition of the many complications associated with BPD are essential.

Oxygen Therapy

The clinician, knowing that oxygen therapy is necessary but also causes further damage to the infant with BPD, must strive for a fine balance. As the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) study demonstrated, infants maintained at a higher oxygen saturation range had more severe BPD than did those in a lower range.[225] Although optimal oxygen levels for LBW infants are unknown, targeting an oxygen saturation of 88–92 should help to decrease the severity of BPD.[225] At the same time, adequate oxygen levels should be maintained to avoid pulmonary hypertension and promote tissue growth. Oxygen should be reduced gradually based on the infant's tolerance.

Using pulse oximetry and physical findings, the nurse should continuously assess the infant with BPD to determine oxygen requirements. During activities that may stress the infant—bathing; feeding; painful procedures, including laboratory work; and endotracheal tube suctioning—additional oxygen may be required. Following these activities, the infant should be given time to stabilize before the oxygen is reduced to baseline levels.

Parents should be taught to maintain adequate oxygen saturations at all times: while the infant is awake, feeding, and asleep. They also need to be taught to observe for respiratory distress, cyanosis, irritability, and early signs of respiratory infections.

Mechanical Ventilation

Like oxygen, mechanical ventilation is a known risk factor for infants with BPD. It is important to use the most modest settings possible to maintain appropriate levels of gas exchange. It is also important to set reasonable targets for PCO_2 and PO_2 and to work toward the shortest possible duration of mechanical ventilation. Few prospective randomized trials have been conducted to determine the combination of ventilator settings that either limits the severity or prevents the development of BPD; however, some general principles can be applied. To minimize both barotrauma and atelectotrauma, the lowest peak airway pressure that provides an adequate tidal volume should be used.[226] A PEEP adequate to avoid airway collapse is also important. Higher PEEP levels (6–8 cmH_2O) may be needed in infants with floppy airways secondary to prolonged ventilation.

Synchronized intermittent mandatory ventilation and pressure support ventilation (assist-control) are designed to improve interaction and reduce antagonism between infant-generated and mechanically generated breaths (see Chapter 9). The ability of SIMV to limit lung overdistention reduces the need for the neonate to fight the ventilator breaths. Intuitively, synchronized ventilation should be of benefit in reducing the incidence and severity of BPD; however, a large multicenter study failed to show any difference in the incidence of BPD.[227] A Cochrane review of synchronized ventilation did find a reduction of air leaks and a shorter duration of ventilation but did not find a reduction in the incidence of CLD with synchronized ventilators.[17] A Cochrane review of volume-targeted versus pressure limited ventilation did demonstrate a reduction in BPD, duration of ventilation, and airleaks for those infants receiving volume ventilation.[228] Studies that are more recent have demonstrated a positive effect of volume-targeted ventilation on lung inflammation in premature infants.[229,230] Longer-term follow-up is needed to assess for a reduction in BPD rates.

High-frequency ventilation (see Chapter 12) has been evaluated to determine its impact on BPD, again with mixed results. Thome and colleagues found that in infants 24–30 weeks, use of HFV with high lung volumes did not confer any benefit in preventing BPD compared with conventional ventilation.[231] A meta-analysis of two trials using high-frequency oscillatory ventilation (HFOV) concluded that the use of HFOV may reduce CLD rates somewhat, but the findings were inconsistent.[232] The Cochrane review of high-frequency jet ventilation (HFJV) found that the use of HFJV moderately reduces CLD rates but may increase the risk of IVH.[233]

Medications

Long-term management of infants with BPD often includes treatment with many drugs such as vitamins, diuretics, bronchodilators, and in some cases, steroids. The decision to use each drug should be individualized. The addition of each drug to the infant's management plan should be closely monitored to prevent the "polypharmacy" phenomenon associated with BPD care. For a detailed review of all medications used for the infant with BPD, see Chapter 11.

TABLE 10-9
Recommendations for Monitoring the Nutritional Status of Enterally Fed Hospitalized VLBW Infants

Intake/Output Monitoring	
Fluid intake (mL/kg/day)	Daily
Urine output (mL/kg/day)	Daily
Nutrient Intake	
Energy (kcal/kg/day)	Daily
Proteins (g/kg/day)	Daily if weight gain is poor
Anthropometric Monitoring	
Body weight (g)	Twice daily until stable, then daily
Length (cm)	Weekly
Head circumference	Weekly
Biochemical Monitoring	
Complete blood counts including platelet and reticulocyte count	Every 2 weeks
Serum electrolytes and blood urea nitrogen	Weekly if on diuretics or with fluid restriction; every 2 weeks when stable
Calcium, phosphorus, and alkaline phosphatase	Every 2 weeks
Total protein, albumin, prealbumin	Consider if weight gain is poor or blood urea nitrogen is low
Liver function tests	At 2 weeks, then every 2 weeks if there is evidence of cholestasis

Adapted from: Biniwale MA, and Ehrenkranz RA. 2006. The role of nutrition in the prevention and management of bronchopulmonary dysplasia. *Seminars in Perinatology* 30(4): 204. Reprinted by permission.

Nutrition

Despite improvements in parenteral and enteral nutrition, postnatal growth failure is still seen in LBW infants, especially those with BPD.[234] For infants with BPD, the incidence of growth failure in the immediate postdischarge period is estimated to be between 30 and 67 percent.[235] Studies have shown that children with BPD have increased resting energy levels and that growth failure in this population may contribute to adverse pulmonary and developmental outcomes.[236,237] More specifically, infants with BPD have a metabolic rate approximately 25 percent higher than infants without BPD, leading to a caloric requirement 20–40 percent higher than age-matched infants without BPD.[188]

The increased work of breathing resulting from decreased lung compliance, increased airway resistance, and tachypnea is one of the factors interfering with normal growth. Another concern is the delay in initiating and advancing enteral feedings in the presence of respiratory disease, feeding intolerance, and other complications.[188]

Parenteral Nutrition

Providing adequate nutrition to the VLBW neonate at risk for BPD is often quite challenging. The overriding goal is to provide adequate calorie and protein intake to support a rate of growth similar to that seen *in utero*. It is important to address the neonate's nutritional needs beginning on the first day of life. Initially, nutrition is provided in parenteral form, with enteral feedings started as soon as the infant is medically stable, ideally within the first few days of life. Recommended parenteral intake on the first day of life is 80–100 mL/kg/day of fluid, 2–3 g/kg of protein, 0.5–1 g/kg of fat emulsion, and 4–6 mg/kg/minute of glucose.[188] Proteins, fats, and carbohydrates are gradually increased to 4 g/kg, 3 g/kg, and 10–12 mg/kg/minute, respectively. Some clinicians have been reluctant to provide protein in the first few days of life because of concerns regarding side effects such as metabolic acidosis; however, a study by Thureen and others demonstrated that a protein intake as high as 3 g/kg on day 1 of life was well tolerated by VLBW infants.[238]

Enteral Feedings

Breast milk or formula is introduced as soon as possible after delivery in the form of trophic feedings. Commonly, however, infants with respiratory distress have periods of feeding intolerance or medical complications such as a PDA or sepsis, that delay their progression to full enteral feedings. Feedings are started at small volumes and increased slowly to decrease the risk of NEC. Human breast milk, although the preferred source of nutrition, does not provide adequate calories, protein, or minerals to meet the increased metabolic needs of premature neonates. Fortification with human milk fortifier, liquid formula concentrate, or protein powder may be used to address the deficits.

Multivitamin supplementation, including vitamin D and iron, is indicated for infants receiving breast milk. Some support also exists for carnitine supplements as a mechanism for enhancing weight gain and catch-up growth.[239] Gastroesophageal reflux disease (GERD) often makes it difficult to provide adequate nutrition to infants with BPD. Reflux may alter lung function in these patients by causing aspiration of stomach contents and triggering bronchial reactivity. Neonates with suspected swallowing dysfunction should be evaluated by a feeding specialist. Conservative measures for managing reflux

include thickening the feedings, decreasing the volume of the feeding by increasing the number of feedings, and elevating the head of the bed at a 30-degree angle. Nipple feeding the infant with BPD can be problematic because of the negative oral stimulation from the endotracheal tube, gastric feeding tubes, and frequent oral suctioning.

Electrolyte and mineral imbalances often accompany BPD as a result of fluid restriction, diuretics, dexamethasone, and other medications. Monitoring of serum electrolyte levels is important to determine appropriate amounts of supplementation. Table 10-9 displays a suggested schedule for nutritional monitoring.

Nursing Care

Caring for the infant with BPD can be a frustrating experience for even the most experienced nurse. Although infants with the newer form of BPD are less likely to develop profound bronchospasms, or BPD "snits," they may still have episodes of increased airway resistance or hypoxia in response to stress, handling, or discomfort. They may not respond as readily to the usual soothing techniques such as rocking, patting, holding, or talking.[240] Learning to interpret the infant's behavior is essential in supporting the infant and family. Major considerations in caring for infants with BPD include limiting environmental demands when the infant loses control and identifying early signs of loss of control. In addition, staff members understanding when intervention is needed, and knowing strategies to reduce stress is invaluable. Each infant should have an individualized developmental plan constructed by the neonatal team.

Infants with BPD are at increased risk of neurodevelopmental delays beyond those associated with low birth weight alone. In a follow-up study done at eight years of age comparing term infants and VLBW infants with and without BPD, children from the BPD group demonstrated deficits in intelligence, reading, mathematics, and gross motor skills. Children in the BPD group were more likely to be enrolled in special education classes (54 percent) than were children in the VLBW-without-BPD group (37 percent) or term birth group (25 percent).[241] The risk for disabilities increases as birth weight decreases and more complications develop. Factors that appear to place infants with BPD at higher risk include moderate to severe IVH and low socioeconomic and parent education levels.[242]

Maximizing neurodevelopmental outcome in infants with BPD requires a multidisciplinary team approach. A team consisting of developmental specialists, physical therapists, speech therapists, neonatologists, and nurses should develop a plan of care to maximize neurologic growth and development. Goals include maximizing the environmental conditions in the NICU, reducing stress, and maintaining normal oxygen levels. Proper positioning in natural flexion using rolls and blankets is helpful. Minimizing stimulation and evaluating the infant's response to procedures using oxygen saturation monitoring as a guide are important. Evaluating and reporting the infant's responses to the various therapists help in developing an individualized plan of care.

Discharge planning should ensure that the family understands the plan of care, including handling, positioning, stimulation, and stress reactions. Teaching and supporting families who have an infant with BPD is a challenge for NICU nurses. The nurse is often coordinator of the various disciplines involved in the infant's care. Understanding their baby's treatment regimen and the importance of close medical follow-up may help with compliance and assist the parents in coping with the complexity of their infant's care. Parents need to be aware of the high risk of lower respiratory tract infections and rehospitalization despite optimal care and appropriate precautions. Preparing the infant and family for discharge is critical to a successful transition from the NICU environment to home. To assist NICUs in appropriate discharge planning, the American Academy of Pediatrics (AAP) has developed guidelines for the discharge of high-risk infants.[243] Before discharge, infants with BPD should be free from apnea, be taking all of their feedings by breast or bottle, and have oxygen requirements and medication regimens that are stable and manageable outside the hospital setting.[244] Care and attention must also be given to ensuring that the family is ready for discharge. Offering parents the opportunity to stay in the hospital overnight with their infant may help to ease the transition home.

Prognosis

Infants with BPD have an increased hospital readmission rate than their non-BPD counterparts, and respiratory abnormalities that persistent into adolescence.[245] The prognosis for infants with BPD is dependent on the severity of the disease and the infant's overall health status. A 1996 study reported that 50 percent of infants with severe BPD were readmitted to the hospital in the first year of life for lower respiratory tract infections.[246] This number has been reduced somewhat with the advent of respiratory syncytial virus

prophylaxis, the main cause of respiratory infections requiring hospitalization in prematurely born infants.

Long-term follow-up of infants with BPD suggests that these children experience progressive normalization of lung mechanics and, to some extent, lung volumes; however, abnormalities of the small airways persist.[152] Other follow-up studies have found that children who had BPD as infants have no difference in exercise capacity and no difference in FRC but do have a decrease in forced expiratory volumes and forced vital capacity.[247] It has also been reported that at five years of age, BPD survivors have a higher incidence of asthma than the general population.[248]