# Bronchopulmonary Dysplasia

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**Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory disease that results from complications related to the lung injury during the treatment of respiratory distress syndrome, or develops in older infants when abnormal lung growth occurs. The definition and classification of BPD have changed since the original diagnosis was established many years ago. The incidence of BPD continues to grow as lower-birth-weight infants continue to survive. The primary focus of all treatment associated with premature infants is on prevention of BPD. Surfactant replacement, invasive and noninvasive ventilation techniques, management of the patent ductus arteriosus, cautious management of**

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**oxygen therapy, caffeine, inhaled nitric oxide, and changes in delivery room practices have been studied to assess their effects on the development of the disease. Other strategies used to reduce the long-term effects of this chronic lung disease include bronchodilators, inhaled and systemic steroids, nutrition management, and selected ventilator strategies. The prevention of BPD is targeted at minimizing effects of this pulmonary disease and preventing the long-term sequelae associated with its treatment.** *Key words: bronchopulmonary dysplasia, BPD, surfactant replacement*. [Respir Care 2009;54(9):1252–1262. © 2009 Daedalus Enterprises]

## Introduction

Bronchopulmonary dysplasia (BPD) is the most familiar chronic respiratory disease that results from complications related to the lung injury during the treatment of respiratory distress syndrome (RDS) in low-birth-weight premature infants, or when abnormal lung development occurs in older infants.[1] Infants < 30 weeks gestation are particularly at risk for these detrimental long-term outcomes that encompass high morbidity and mortality rates in populations of neonatal intensive care unit graduates.[1-3] BPD is diagnosed in about 20% of 60,000 infants who are born at < 30 weeks gestation and weigh < 1,500 g.[4] Infants develop BPD in about 1.5% of all newborn births. The incidence of BPD appears to be growing in conjunction with the increased survival of very-low-birth-weight infants who are treated for and recover from RDS.[5,6] BPD rates are slightly higher in very-low-birth-weight infants and decrease incrementally with increased gestational weight, with > 50% of infants less than 750 g, 15% of infants greater than 1,000 g, and about 7% of infants greater than 1,250 g.[7,8]

The primary goal of BPD prevention is to avoid or minimize the extent of a disease that may result in lifetime consequences, including persistent lung abnormalities. The current treatments for BPD appear to have reduced its severity, as goals for interventions have been focused on preventive care strategies and advanced techniques that treat and control the disease.[9] Surfactant-replacement therapy, treatment of the patent ductus arteriosus, noninvasive ventilation (NIV), advanced invasive ventilator management, prenatal steroid use, improved nutrition, avoiding the effects of prolonged oxygen exposure, and treating infection and inflammation associated with its treatment currently compose the treatment standards for BPD, which have contributed to this overall improvement.[10]

## Definition of BPD

The definition of BPD has many facets, and would be better understood if it encompassed the entire scope of clinical signs and symptoms, noted standards for response to therapeutic treatment, established a degree of severity, and predicted long-term pulmonary outcomes. However, several factors found to have led to BPD in diverse populations of patients have made this difficult to accomplish. The National Institutes of Health, a world-renowned medical research agency, and the Vermont Oxford Network, a collaboration of experts focused on the quality and safety of care for infants, have made attempts to establish guidelines that reflect the current standards of practice for interventions such as administering supplemental oxygen to neonates. The importance of these guidelines, which required clinicians to manage patients with targeted oxygen saturation ranges, was noted to have a direct effect on a decreased incidence of BPD.[7] An emphasis on identifying inherent and biochemical markers related to BPD, the overall degree of respiratory impairment, and long-term outcomes led to the current classification and definition of BPD.

In 2001 the National Institute of Child Health and Human Development defined and classified BPD by gestational age and supplemental oxygen requirement. Infants < 32 weeks postmenstrual age presenting with clinical manifestations of the disease, requiring supplemental oxygen at 28 days of life, and who were weaned to room air by 36 weeks or at discharge were considered to have mild BPD. Infants requiring < 30% continuous oxygen at 36 weeks postmenstrual age or at discharge were considered to have moderate disease. Infants remaining on ≥ 30% oxygen and on continuous positive airway pressure (CPAP) were considered to have a severe form of the disease. For infants > 32 weeks gestation, the identical oxygen requirement was implemented at day of life 56.[9]

## Classification of BPD

The pathology of "classic" or "old-style" BPD was described in populations of larger premature infants prior to utilization of surfactant-replacement therapy. Classic BPD was characterized by lung inflammation, airway injury secondary to interstitial and alveolar fluid overload, lung parenchyma fibrosis due to hyperinflation and the development of small airways disease, smooth-muscle hypertrophy, and oxidative stress.[2,9] Clinical practice strategies employing aggressive mechanical ventilation and high levels of oxygen in addition to exposures to steroids for antenatal infections were largely responsible for the devel-

opment of classic BPD. As advanced therapies evolved and a more conservative approach was taken for treating the primary respiratory component of the disease, the classic form of BPD began to change. However, the single focus on prevention and treatment of RDS could not eliminate classic BPD without achieving a reduction in premature births.[2,9]

With increasing survival in lower-birth-weight and gestational-age neonates, a "new BPD" was identified and presented itself in the earlier stages of an infant's gestational development, before alveolarization had been completed. New BPD is found in very-low-birth-weight infants and is created due to exposure to antenatal infection.[9] These patients typically have less inflammation and fibrosis, and may require only a moderate degree of supplemental oxygen or ventilator support. Risk factors produced inflammatory responses in the very-low-birth-weight neonates, which created further risk for injury.[2] "New BPD" is characterized by slightly different histological changes, including alveolar arrest or reduction in distal alveolar growth, less airway injury, more uniformity in lung inflation, and a reduced incidence of fibroproliferation.[8,9] More advanced therapies today produced strategies that prevent the need for invasive mechanical ventilation altogether or minimize settings to gently ventilate the lungs, stress aggressive management of patent ductus arteriosus and postnatal infections, and streamline fluid management and nutrition.[9] BPD has been classified on a scale of 1 to 3, indicating the degree of severity based on supplemental therapies required (Table 1).[11,12] Despite an increased availability of options for treatment, the prevention of BPD has not been successfully accomplished, and a lack of evidence of pathogenesis-focused strategies in current best practices has resulted in persistent development of the disease.

Table 1. Bronchopulmonary Dysplasia Classification

| BPD Grade | Description |
|---|---|
| 1 | Supplemental oxygen for ≥ 28 d and on room air at 36 wk post-menstrual age, or at discharge (for infants < 32 wk post-menstrual age at birth); or at 56 d, or at discharge (for infants ≥ 32 wk post-menstrual age at birth), whichever comes first |
| 2 | Supplemental oxygen for ≥ 28 d and receiving supplemental effective oxygen < 30% at 36 wk post-menstrual age/discharge (< 32 wk post-menstrual age) or at 56 d/discharge (≥ 32 wk post-menstrual age) |
| 3 | Supplemental oxygen for ≥ 28 d and receiving supplemental effective oxygen ≥ 30% oxygen or on nasal continuous positive airway pressure or mechanical ventilation at 36 wk post-menstrual age/discharge (< 32 wk post-menstrual age) or at 56 d/discharge (≥ 32 wk post-menstrual age) |
| 1P | Supplemental oxygen for ≥ 28 d with documentation that oxygen saturation is ≥ 90% on room air at 36 wk post-menstrual age/discharge (< 32 wk) or at 56 d/discharge (≥ 32 wk post-menstrual age) |
| 2P | Supplemental oxygen for ≥ 28 d with a documented need for supplemental effective oxygen < 30%, based on failure to maintain oxygen saturation of ≥ 90% in a formal timed weaning trial at 36 wk post-menstrual age/discharge (< 32 wk post-menstrual age) or at 56 d/discharge (≥ 32 wk post-menstrual age) |
| 3P | Supplemental oxygen for ≥ 28 d and on CPAP or mechanical ventilation or supplemental effective oxygen ≥ 30% based on failure to maintain oxygen saturation ≥ 90% in a formal timed weaning trial at 36 wk post-menstrual age/discharge (< 32 wk) or at 56 d/discharge (≥ 32 wk post-menstrual age) |

(Adapted from References 11 and 12.)

## Physiologic BPD

The clinical definition of BPD determines the extent of the disease based on the level of oxygen administration. However, variation across neonatal centers' criteria, oxygen administration practices, and saturation targets produced a wide range of outcomes. As a result, an attempt was made to create a more standardized interpretation and understanding of BPD, through a physiologic definition. Walsh et al employed a physiologic test and response to room air for infants 36 weeks ± 1 week.[4] The test consisted of challenging patients by conducting a 30-min room-air trial if the patient was on < 30% oxygen or was > 96% saturated on > 30%.[4] Sicker infants requiring > 30% oxygen with oxygen saturation in the 90–96% range were labeled with the diagnosis of BPD without the challenge test. The physiologic definition lessened the variances in outcomes of BPD among 16 participating centers and further standardized the method of diagnosis based on a physiologic variable.

While the clinical and physiologic definitions of BPD differ, so do the outcomes. The BPD rates among centers employing the physiologic definition were lower than those using the clinical definition.[4] However, the incidence and development of BPD remains around 20–25% on average, and continues to be dependent on a number of factors. Extreme prematurity in very-low-birth-weight infants and implementation of general patient care strategies such as ventilator management, oxygen administration, and their associated response have played a role in the prevalence of BPD.

## Pathophysiology of Developing BPD

Premature infants are exposed to a variety of treatment modalities, including positive-pressure ventilation, supple-

mental oxygen, and pharmacologic therapy, and are predisposed to the toxic effects of oxygen because they are devoid of antioxidants or have lower than normal levels of vitamins E and D at birth.[10] BPD was originally associated with oxygen toxicity, and the mechanism for its development seemed to be directly related to its use. However, other factors, such as prolonged hypocarbia developing secondary to invasive positive-pressure ventilation and ventilator associated lung-injury, became increasingly important considerations and eventually were identified as risk factors for developing BPD.[13] The emphasis on reducing lung volumes starting within the first minutes of life was derived from this theory and continues to be a primary focus in clinical practice today. Prenatal infection has also been shown to play an important role as a risk factor for BPD. Acute or chronic infection can lead to a reduction in alveolar development. Inadequate management of a patent ductus arteriosus may result in reduced heart function, accumulation of additional lung fluid, and infection, and additionally serve as contributing risk factors. Inflammation plays a key role in BPD development and results from exposure to a number of factors that may contribute to the release of pro-inflammatory cytokines that are found in samples of lung fluid as early as the first moments of life (Fig. 1). Other mediators exemplified by the presence of neutrophils may inhibit surfactant production or contribute to the development of lung fibrosis. Leukotrienes, which cause edema, bronchoconstriction, or mucus production, have also been found to be in large quantities in the lungs of infants who were developing BPD.

Ventilator-induced lung injury (VILI) is a common complication of mechanical ventilation in premature infants and may predispose the infant to abnormal lung growth and development, BPD, and other organ damage. The mechanisms surrounding VILI commonly seen are not homogenous and may result in surfactant inactivation or malfunction. VILI consists of many components, including alveolar septal damage, inflammation, fibrosis, and pulmonary edema.[14] Attar and Donn state that preventing VILI is dependent on: limiting high airway pressures that induce barotrauma and tidal volume ($V_T$) that cause *volutrauma*; preventing alveolar collapse and re-expansion injury that results in *atelectrauma*; and an associated inflammation referred to as *biotrauma*.[14] Clinical management including a protective lung strategy is necessary for the reduction in pulmonary edema and alveolar recovery.

Preserving lung health is the primary focus of BPD management. Because the infant's end-expiratory volume or subglottic volume is affected by BPD, it is important to maintain this critical volume to promote fetal lung growth. In RDS a reduction of this volume is identified via visualization of the chest wall and diaphragmatic excursion. Loss of end-expiratory volume is evident in an infant with

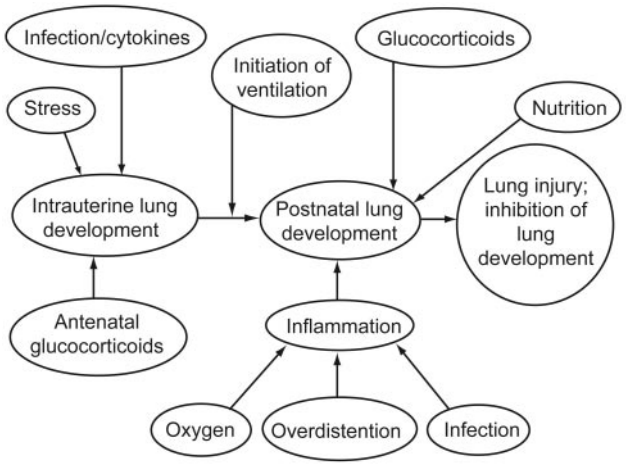


Fig. 1. There are many factors involved in the pathogenesis of bronchopulmonary dysplasia. From prenatal to postnatal, every step of the way is crucial to protecting the infant from harm caused by the influences surrounding the management of prematurity or those predisposed to lung disease. (From Reference 13a, with permission.)

respiratory distress. Failure to maintain recruitment of end-expiratory volume in symptomatic infants not treated with NIV may result in increased pulmonary vascular resistance, reduced surfactant production, and increased work of breathing, which may further complicate desired outcomes of the lung through decreased compliance and increased airway resistance. As a result, additional ventilatory support or adjunctive therapies may be investigated, and may in turn contribute to the development of BPD.

While NIV techniques can support maintenance of the end-expiratory volume, invasive mechanical ventilation minimizes normal control of the patient's $V_T$ breathing laryngeal responses, which in turn adversely affects the end-expiratory volume. Injury results from the physical presence of an artificial airway, the air leaking around the uncuffed airway, and the associated pressure applied to the trachea and the lungs.[15] Minimal exposure to positive-pressure ventilation has also been shown to alter the normal developmental process of alveolar growth. Volutrauma and lower-airway disease may result from ventilation of the lungs with varying time constants.[10] Lung compliance is reduced from inflammation and edema of the airways, obstruction of the small airways, and parenchymal fibrosis or atelectasis.[7]

## Interventions and Strategies for BPD Prevention

### Antenatal and Systemic Corticosteroids

Antenatal corticosteroid administration has been successfully administered to mothers who are at risk of de-

livering a premature infant. The inflammatory component of BPD was targeted with the implementation of antenatal corticosteroids for selected patients with prenatal risk factors.[16] While this practice has successfully reduced the incidence of premature death, intraventricular hemorrhage, and RDS, the incidence of developing BPD has not been impacted.

### Prenatal Antibiotics and Infection Prevention

Infants born to mothers with chorioamnionitis would seem to be at greater risk for developing BPD. Although BPD is multifactorial, the presence of chorioamnionitis as a contributor to the inflammatory process of infection is a single risk factor that may or may not contribute to its development.[17] Long-term exposure to maternal infection has been shown to result in inflammation, and often requires prenatal antibiotic treatment of the infection to prevent further neonatal compromise. Normal development and alveolar growth may be directly affected by inflammation and infection, and may eventually result in the development of BPD.[18] Recent findings indicate that BPD results from the presence of pro-inflammatory cytokines and macrophages related to infections that alter normal mechanisms of alveolar development.[19]

### Management Practices in the Delivery Room

Resuscitation in the delivery room has seen a plethora of change in the past decade. The use of many modalities, including CPAP, T-piece resuscitation, blended oxygen, ventilatory techniques, and surfactant replacement, have forever impacted the management of premature newborns in the first minutes of life. Recent focus on early intervention CPAP, because of its potential for a reduction in length of stay, has become a focused strategy of many.[20]

Blended oxygen is recommended over 100% to prevent oxidative stress and reduce the incidence of long-term sequelae caused by its administration. There is no specific starting fraction of inspired oxygen ($F_{IO_2}$) recommended, because of a lack of research to support its risks or benefits on the development of BPD. However, the International Liaison Committee on Resuscitation recommends using 100% with the initiation of resuscitation, then reducing to a blended source to minimize the potential long-term adverse effects from oxygen administration.[21] Potential damage from oxygen delivery during resuscitation continues to be an area of concern for those who are most at risk for oxidant injury: the premature infant. The level of $F_{IO_2}$ used in resuscitation of these patients is carefully selected.[21]

To minimize the potential for acute lung injury in the critical moments of life, the Neonatal Resuscitation Program guidelines suggest using a lower target inflation pressure range, between 20 cm $H_2O$ and 25 cm $H_2O$. When administered correctly but without the desired effect, caregivers may go as high as 40 cm $H_2O$.[22] T-piece resuscitation was added as an alternative for achieving consistent pressures and effective ventilation. Studies identifying a superior method of positive-pressure delivery and desired outcomes on the development of BPD have not been demonstrated at this time. Special ventilatory techniques, such as sustained lung inflations or implementing prolonged inspiratory times and pressure holds to maintain mean airway pressure, recruit functional residual capacity, and reduce lung injury, have been investigated.[23] Harling et al measured inflammatory markers in lung fluid in patients receiving sustained inflation and revealed that this technique did not decrease the incidence of lung injury in the delivery room.[24] Long-term effects with Neonatal Resuscitation Program guidelines implementation, and outcomes associated with them, continue to be an area of research concentration.

Surfactant administration at or immediately following management in the delivery room has been shown to generate positive effects on the reversal of atelectasis in RDS. However, the risks and benefits must be weighed before committing to intubate the patient, even for a short period of time. Surfactant administration in the delivery room (early) is a practice that has not shown to have greater benefit than delivering it in the intensive care unit (late).[25] The future of and changes in surfactant administration is an area currently under investigation, with hopes of providing a noninvasive method for delivery.

Delivery room practices continue to change in an effort to reduce the incidence of BPD that results from resuscitation. Advances in neonatal care may promote increased survival and a decreased incidence of lung disease if optimal strategies are determined, implemented, studied, and proven with substantial evidence. The neonatal community is committed to helping reduce the risk factors of BPD by continuing to assess the reliability and outcomes related to these techniques

### Surfactant-Replacement Therapy

Surfactant replacement has become a standard of care for more than a decade. Early and late surfactant replacement has been implemented in clinical practice and has played a role in the development or prevention of BPD. Goals of surfactant replacement include treating RDS while reducing the incidence of VILI, which has led to a focus on BPD prevention. Surfactant administration has been shown to be effective in neonates without prolonged need for mechanical ventilation, while the timing of surfactant administration may reduce the development of BPD if given early in the course of treatment.[9] Benefits such as a

reduction in mortality in infants < 30 weeks gestation have been realized. Surfactant replacement has increased the survival of very-low-birth-weight infants and in turn increased the duration of mechanical ventilation, but has not changed the incidence and complications of "new BPD," especially in very-low-birth-weight infants.[9,26] Although surfactant replacement has changed the management of premature infants with RDS, it does not treat BPD but instead has been used as a primary prevention strategy.

### Oxygen Therapy

Historically, supplemental oxygen was administered to neonates to stimulate them to breathe.[27] BPD and other respiratory disorders warranted supplemental oxygen administration, but appropriate target levels of oxygen were not readily established with the early treatment of premature infants. As a result, the positive and negative effects of oxygen therapy in clinical practice were identified. In 2005 the National Institute of Child Health and Human Development devised a workshop with the intention to recognize evidence-based practices. As a result, hyperoxia was recognized as a cause for an increase in proliferation of type II alveolar cells and resulted in important alterations in surfactant development and production.[9] Because higher oxygen saturation ranges provided little to no benefit to premature infants < 30 weeks gestation and in turn created oxidative stress, lower target ranges of 85–93% were implemented.[28] BPD, retinopathy of prematurity, impaired brain development, and infection may be caused by oxygen toxicity.[28]

Hypoxia can have a direct effect on brain growth and development. Maintaining patients in targeted oxygen saturation ranges has been shown to be difficult and thus has resulted in long-term adverse effects of oxygen therapy. Severe hypoxemia in early and late gestation infants further increases the degree of lung disease and mortality.[6] In established BPD a slightly higher oxygen saturation of 88–94% is recommended to prevent right-sided heart failure accompanying BPD. It has been difficult to establish a single oxygen saturation variable that can be effectively used to provide optimal management of BPD without major adverse effects. However, saturation around 90% seems to provide the best stability of both heart and lung function in older infants.[29] However, in patients with severe BPD and cor pulmonale, higher target oxygen saturation is recommended.[6]

### Noninvasive Ventilation Practices

CPAP and nasal intermittent NIV are strategies utilized in the early management of acute respiratory disease such as RDS and apnea of prematurity. CPAP has been used since the 1970s as a modality to prevent alveolar collapse by maintaining mean airway pressure through various types of nasal interfaces, and reducing the need for invasive mechanical ventilation.[10] Nasal CPAP has been associated with the reduction of effects on VILI and BPD development; however, no single type of CPAP has been identified as superior to another.[10] Conflicting opinions about the timing of application with early-intervention CPAP has been disputed by the experts. While Ho et al[30] indicate that early-intervention CPAP has not been shown to affect the incidence of BPD or mortality, Aly et al argued that CPAP implemented early in the patient's course has been shown to reduce the incidence of BPD without increasing morbidity, as long as the clinicians managing it were experienced with the specifics of its care.[31] Nasal CPAP continues to be the most widely used noninvasive modality.

NIV with a set frequency, peak pressure, and positive end-expiratory pressure has been used as an escalation technique to avoid invasive mechanical ventilation when CPAP alone is not sufficient. NIV is delivered through nasal prongs or mask interface, in the form of nasal intermittent mandatory ventilation through a ventilator, nasal synchronized intermittent mandatory ventilation (SIMV), or non-synchronized from a bi-level CPAP system. The success of NIV is variable, depending on the device, the understanding and training of the caregiver applying it, and the settings and parameters applied. Synchronized NIV has been associated with greater $V_T$ delivery, reduced work of breathing, and a reduction in the need for intubation and BPD, especially in infants < 30 weeks gestation.[1,3] Although potential complications of all noninvasive modes include gastric distention or rupture, damage to the nares or occiput by the interface, or apnea, the benefits of NIV are positive and in most cases outweigh the risks. All noninvasive modalities continue to provide an important degree of clinical benefit for infants during many phases of their respiratory illness. Clinical studies are focused on the prevention of BPD, especially in low-birth-weight infants who are at the greatest risk.

### Invasive Mechanical Ventilation Management

Invasive mechanical ventilation is one of the major contributors to the development of BPD in infants. There is currently no ideal strategy for mechanical ventilation that is optimal for minimizing the risks of pulmonary sequelae. There are also inconsistencies in determining what $V_T$ constitutes appropriate gas exchange without alveolar impairment. However, synchronized and patient-triggered modes of tidal ventilation with consistent $V_T$ delivery is preferred to prevent auto-triggering and increased work of breathing, especially in infants < 1,000 g.[32] The most common modes

employed in early management of RDS include pressure controlled continuous mandatory ventilation (CMV), pressure controlled intermittent mandatory ventilation (IMV) (with mandatory breathing "synchronized" to patient inspiratory effort, commonly referred to as SIMV). Adaptive pressure controlled (ie, volume-targeted pressure control) with CMV or IMV is becoming more popular. Pressure support of spontaneous breaths is often used with IMV. CMV is employed in the early management of RDS to decrease patient respiratory muscle work, especially during the period of surfactant replacement, while guaranteeing a set peak inspiratory pressure or $V_T$. Adaptive pressure control provides consistent $V_T$ delivery, but no proven benefits for gas exchange.[27] Volume-targeted ventilation has reduced the incidence of episodes of hypocapnia and invasive ventilation days.[33] Singh et al showed a marginal decrease in the incidence of BPD using volume-controlled ventilation.[34] Mandatory minute ventilation provides backup support of $V_T$ and/or a minimal respiratory rate in the event the patient cannot meet the minute-volume target. However, the inconsistencies in breathing patterns and volumes in neonates have been a barrier for its long-term implementation.[35]

High-frequency oscillatory ventilation (HFOV) was introduced many years ago as an alternative strategy for mechanical ventilation. The initial goal of HFOV was focused on reducing the incidence of alveolar stretch and consequent VILI.[33] Many studies conducted over the past decade demonstrate variable outcomes. The practice of utilizing HFOV in neonatal intensive care units for the prevention of BPD remains unpredictable. Proactive strategies and HFOV, noted in a meta-analysis in low-birth-weight infants, revealed a minimal reduction in the development of BPD and no significant changes in neurologic outcomes.[33] Rescue strategies utilized in respiratory failure have not proven to affect or reduce the incidence of BPD in premature infants.[9]

Neither tidal nor high-frequency ventilation strategies have been regarded as optimal for the prevention of BPD. In a number of studies comparing high-frequency and tidal ventilation there were not significant differences in the development of BPD, but complications such as air leak syndromes have been evident in high-frequency modes.[6] Avoidance of invasive mechanical ventilation is pivotal in BPD prevention. However, when invasive ventilation is used, the focus on minimizing complications must be the objective.

Permissive hypercapnia is a method of minimizing the complications caused by many facets of invasive ventilation. Permissive hypercapnia has led to a reduction in the number of invasive ventilator days in premature infants.[36] To minimize the amount of damage caused by invasive ventilation, strategies including short inspiratory times, modest $V_T$, and low pressures can provide enough ventilation to meet elevated target $CO_2$ ranges.[9] Normalized $CO_2$ values ($< 40$ mm Hg) were associated with a higher incidence of the development of BPD.[37] Higher $CO_2$ targets of 45–55 mm Hg are now recommended and acceptable in order to reduce the days of ventilation. However $P_{CO_2} > 55–65$ mm Hg ranges were indicative of neurologic impairment, incidence of BPD and death in the first 7 days of life.[9]

Minimizing the exposure to oxygen remains a priority in the newborn at risk for BPD. Permissive hypoxemia strategies prevent the exposure to high oxygen levels that lead to serious long-term effects on mortality and other complications involving impaired vision and lung disease.[38]

Infants exposed to high levels of oxygen showed an increase in oxygen dependence, retinopathy of prematurity, and longer requirements for invasive ventilation.[6] Lowering target saturations in selected situations, as with low-birth-weight infants, may be beneficial and prevent the development of severe lung disease.

### Treatment of Patent Ductus Arteriosus and Its Relationship With BPD

Premature infants are at risk for developing a patent ductus arteriosus early in their course of treatment. There are varying opinions on the optimal treatment for this complication of prematurity. Those who developed a patent ductus arteriosus or were at risk for right-heart failure were more likely to develop BPD. Fluid balance is interrupted by the presence of a patent ductus arteriosus, but can be controlled by applying positive expiratory pressure, invasively or noninvasively. Closure of the patent ductus arteriosus is often accomplished by pharmacologic intervention with indomethacin or ibuprofen, or through clinical management by fluid restriction and oxygen. Patients who fail pharmacologic or clinical management of the patent ductus arteriosus require surgical closure to prevent the development of BPD. However, Kabra et al demonstrated that infants receiving surgical closure in the early neonatal period had an increased risk of developing neurological impairment following the surgery, which later resulted in BPD.[23]

### Caffeine Administration

Caffeine has been used for the specific purpose of inhibiting the action of adenosine, which controls the sleep and wake cycle of an infant. Caffeine stimulates the respiratory center of a premature infant and prevents severe cases of apnea that might otherwise result in intubation and invasive mechanical ventilation.[39] Minute ventilation, primarily by the $V_T$ component, increased as a result of caffeine administration. In premature infants, caffeine has

been shown to prevent BPD by reducing the need for additional respiratory support that may result in long-term sequelae. In a multicenter trial ($n = 35$), infants < 1,250 g who received caffeine had lower BPD rates (35% compared to 44%) than infants who did not receive it. In addition, invasive ventilator days, need for CPAP, and supplemental oxygen were reduced by caffeine administration.[5] There is evidence supporting the benefits of routine caffeine use in infants < 1,250 g without long-term effects on gastrointestinal, neurodevelopmental, or other complications.

### Inhaled Nitric Oxide Therapy

Inhaled nitric oxide has been studied to determine its role in the prevention of BPD. The role of inhaled nitric oxide as a selective vasodilator decreases inflammation and improves ventilation and perfusion mismatch while returning normal lung growth patterns via enhanced distribution of perfusion.[7] The use of inhaled nitric oxide continues to have a myriad of conflicting outcomes. In 2006 Kinsella et al found that premature infants in respiratory failure on invasive mechanical ventilation and nitric oxide did not decrease the incidence of BPD.[7] Ballard reported that lower-birth-weight infants receiving low-dose inhaled nitric oxide had no significant reduction in BPD, but positive neuroprotective effects were demonstrated.[40] The focus on inhaled nitric oxide administration had previously been on treatment outcomes. As it was brought to the lower-birth-weight infants, treatment started early in their management course reduced neurologic injury and BPD.[41]

### Management of BPD

The survival of the BPD patient requires diligence and attention to details of medical management. The specific requirements of long-term care change over the course of the disease. Clinical scenarios change as the infant develops and encounters specific needs for care. Strategies for the acute management of RDS exist and are well established. The focus, however, changes with each stage of development.

By the completion of the first month of life the infant requiring long-term oxygen therapy with either noninvasive or invasive ventilation may require more stringent management of oxygenation, with a lower targeted saturation level: 89–94%.[3] A higher $P_{aCO_2}$ level is generally acceptable (< 70 mm Hg, with a target of 55 mm Hg). As the severe-BPD patient develops non-homogenous lung disease and invasive ventilation is required, a volume-targeted strategy with slightly higher $V_T$ (than used in the management of RDS) is preferred, to maintain a consistent $V_T$ and mean airway pressure.[3] Positive end-expiratory pressure may need to be increased in the event that atelectasis and higher $F_{IO_2}$ is required. Longer inspiratory time is also utilized to enhance ventilation uniformity within the lung units. The primary goal of treatment for existing BPD is to maintain adequacy of gas exchange while reducing the complications of ventilation strategies.

### Bronchodilators and Inhaled Corticosteroids

Use of $\beta$ agonists in premature infants is hotly debated, due to the questionable ability of the airway to respond. The increase in airway resistance present in RDS may be caused by bronchial smooth-muscle constriction and contribute to the severity of BPD. These medications have been used in the long-term care of BPD patients to address the response to airway hyperactivity that causes flow limitation and obstruction through narrowing of the bronchi. This adjunctive therapy used to obtain short-term response has not been shown to reduce mortality, the number of invasive ventilator days, or oxygen requirement in these infants.[5,42,43] Inhaled steroids such as beclomethasone have been initiated late in the management of RDS or early BPD, with hopes of reducing chronic, persistent airway inflammation in ventilated patients.[36] Ventilated infants receiving inhaled steroids over a prolonged period of time (1–4 wk) have been shown to be successfully extubated using this regimen. When comparing intravenous to inhaled steroids for the management of BPD, systemic steroids reduced inflammation faster than their inhaled counterparts; however, after 2 weeks of treatment, inhaled steroids proved to be as beneficial as systemic steroids without the unwanted adverse effects.[44]

### Systemic Corticosteroid Administration

Systemic steroid administration for infants with RDS was formerly implemented as an early management strategy to prevent BPD by reducing invasive ventilator days.[45] However, adrenal suppression was feared as an unwanted adverse effect from this strategy. While the anti-inflammatory effects of systemic steroids were deemed beneficial in helping the patient wean from mechanical ventilation and reduce the incidence of BPD, retinopathy of prematurity, and patent ductus arteriosus, concerns about neurodevelopmental health, including an increased incidence of cerebral palsy, and uncharacteristic neurologic examinations were associated with early administration of steroids. Practices later changed to short-term, low-dose dexamethasone courses that produced no untoward adverse effects of adrenal suppression. Later the focus changed to low-dose steroid administration with hydrocortisone, to treat de-

creases in cortisol levels resulting from stress and controlled by the adrenocorticotropic hormone. Hydrocortisone administration increased the level of survival and reduced the incidence of BPD.[39] However, untoward complications, including intestinal perforation, remain as treatment risks when combined with other medications, such as indomethacin or ibuprofen, used to treat the patent ductus arteriosus.[38]

### Diuretic Therapy

Diuretic therapy was often initiated in the early stages of RDS and in early BPD when additional lung fluid accumulated as a result of renal insufficiency in prematurity in the pre-surfactant era.[5] Transient improvement of lung mechanics has been seen, but sustaining long-term benefits from diuretics has not been demonstrated using aerosolized or systemic forms.[46] Rapid-acting diuretics were shown to decrease the invasive ventilator days, oxygen requirement, mortality, and BPD.[5] Data have not supported a reduction in BPD using loop diuretics (furosemide) or the combination of thiazide (chlorothiazide) and potassium sparing (spironolactone) forms.[47] Diuretics are no longer recommended for routine management of the early or late phases of RDS. Diuretics are recommended for severe chronically ill patients for the management of accumulation of interstitial lung fluid, such as in cases of pulmonary edema.

### Nutrition Management

Nutrition and fluid management are important parts of maintaining and repairing injury caused by BPD. Caloric content must be increased to meet the high energy needs required to increase metabolic rate and oxygen consumption.[48] BPD energy requirements supersede standard infant caloric requirements by as much as 125%.[48] Fluid management must be pristine to prevent right-sided heart failure, a common complication of severe BPD. Fluid restriction may be accomplished by adding diuretics, but must be carefully monitored. Reducing lung fluid may improve lung function and decrease oxygen consumption and demand if cautiously implemented. Growth of BPD patients is dependent on adequate caloric intake and balance of protein, carbohydrates, fat, and key minerals such as calcium, phosphorous, and iron that are essential for growth and repair. Parenteral nutrition implemented during the early phase of BPD, in the form of lipids, is later followed by enteral nutrition consisting of high-calorie formulas composed of 10% protein, 50% fat, and 40% carbohydrate, on average. Carefully balancing the components is essential to prevent increased $CO_2$ production and ventilatory failure.

## Antioxidants and Other Adjunctive Therapies

### Vitamins A and E

Vitamin A (a retinol derivative) is essential for the integrity of the immune system, vision, growth, and the epithelial cells within the airway.[9,48] Lack of vitamin A found in premature infants reduces the number of cilia in the airways, which may result in the inability to mobilize secretions adequately. If administered at least 3 times per week for those at risk, vitamin A has been shown to decrease the incidence of BPD. Vitamin E is an antioxidant substance required for stabilizing the free radicals resulting from oxygen administration. It acts as a membrane stabilizer that prevents lipid membranes from oxidation. Unlike vitamin A, it does not play a role in the prevention of BPD, but has an effect on the development and progression of oxygen toxicity.[49] Maternal supplementation of vitamin E may reduce the incidence of pre-eclampsia and premature birth, but has not revealed a short-term or long-term benefit to the patient.

### Superoxide Dismutase

Superoxide dismutase is an antioxidant substance designed to eliminate free-radical damage caused by exposure to oxygen.[50] Tissue damage caused by oxygen has been tied to free radicals and superoxide anion. Superoxide dismutase has been shown to prevent cell injury in subjects presenting with oxidative stress. Its role may be beneficial in the prevention or treatment of oxidative stress and in BPD in premature infants. Superoxide dismutase's antioxidant enzymes provided additional benefit from a sustained decrease in inflammation and respiratory symptoms later in their post-neonatal intensive care unit course.

### Inositol

Inositol, a nutritional supplement found most commonly in breast milk, is essential for growth and development and the production of surfactant components.[43] Since the late 1990s, studies have been conducted to identify inositol's role in the prevention of BPD. Until recently, there was no statistically significant effect on the development of BPD. Inositol recently has been implicated in positive short-term neonatal BPD outcomes and additional reductions in retinopathy of prematurity.[51]

## Summary

BPD is a serious complication of the management of RDS, and the result of exposure to a combination of positive pressure from invasive mechanical ventilation, oxygen, and lack of antioxidants. Preventing BPD is a primary focus of those treating this challenging population of patients. The overall effects and cost of treatment, management, and long-term care of the neonate with BPD are astounding. Evidence-based practices are actively being sought, with ongoing research into the prevention and treatment of the disease being at the forefront of neonatal care.

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