The New BPD

Alan H. Jobe, MD, PhD*

Author Disclosure
Dr. Jobe did not disclose any financial relationships relevant to this article.

Objectives
After completing this article, readers should be able to:

1. Explain the anatomy of the new bronchopulmonary dysplasia (BPD).
2. List the factors that contribute to BPD.
3. Explain the effect of corticosteroids on alveolarization.
4. Explain the contribution of mechanical ventilation and supplemental oxygen to BPD.

Introduction

BPD was described by Northway and associates in 1967 as a syndrome of severe lung injury in preterm infants receiving mechanical ventilation and high levels of supplemental oxygen. (1) The mean birthweight of the infants who survived mechanical ventilation with BPD was 2.3 kg, and the mean gestational age was 34 weeks. Subsequently, Bonikos and colleagues demonstrated that oxygen exposure alone could cause many of the anatomic changes of BPD in newborn mice. (2) The initial description of BPD occurred in the era when mechanical ventilation was just beginning to be used for preterm infants and few infants whose birthweights were less than 1 kg survived. This “classical” BPD was characterized by prominent airway injury, epithelial metaplasia, smooth muscle hypertrophy, and parenchymal fibrosis alternating with emphysema. The experimental work during that era demonstrated that the causes of BPD were primarily mechanical ventilation and oxygen exposure of the preterm lung. (3)

Fortunately, neonatal care practices and outcomes have changed over the last 25 years, with the use of continuous positive airway pressure, antenatal corticosteroids, surfactant, improved ventilation equipment and strategies, and improvements in nutrition and other care practices. Now many infants whose birthweights are less than 1 kg and gestational ages are less than 28 weeks survive. The infants described by Northway have almost no long-term lung-related morbidity in 2006. However, the incidence of BPD in survivors of preterm birth has not decreased because of the survival of large numbers of extremely low birthweight (ELBW) infants whose gestational ages are less than 28 weeks and birthweights are less than 1 kg. The epidemiology of BPD has changed. With the improvements in care, factors other than mechanical ventilation and oxygen exposure contribute to the occurrence of BPD in ELBW infants, including postnatal sepsis, patent ductus arteriosus, and antenatal chorioamnionitis. (4) Some ELBW infants now develop BPD without initially having severe respiratory distress syndrome (RDS) or initially requiring much supplemental oxygen or mechanical ventilation. (5)

In 1999, I reviewed the clinical associations with BPD and relevant experimental studies and used the term “new BPD” to describe the arrest in lung development that is prominent in this new form of the disease in ELBW infants. (6) The term now is being used frequently to describe a progressive lung injury syndrome in ELBW infants characterized clinically by hazy lungs, minimal cystic emphysema or hyperinflation that is apparent on chest radiographs, a persistent oxygen requirement that slowly resolves, less airway reactivity, and less pulmonary hypertension (blue spells) than in the past. Infants who have died of the new BPD have minimal fibrosis or airway injury but a striking decrease in normal alveolar septation and microvascular development. (7) These anatomic findings demonstrate that the new BPD is less of an injury syndrome and more of a syndrome resulting from processes that interfere with lung development. This review highlights the multiple factors that can alter lung development to yield the new BPD.

*Professor of Pediatrics, Division of Pulmonary Biology, Cincinnati Children’s Hospital, University of Cincinnati School of Medicine, Cincinnati, Ohio.
Diagnosis of BPD

The diagnosis of BPD is confounded by a series of definitions that have been used over the years and by changes in the patients at risk. (8) The diagnosis of BPD as characteristic changes on the chest radiograph and oxygen need at 28 days after birth initially used for large infants does not apply well to ELBW infants because few have normal chest radiograph findings and most are receiving some oxygen at this time point. The diagnosis of BPD as oxygen need at 36 weeks postmenstrual age (PMA) has been used in most recent reports. A National Institutes of Health Workshop in 2000 recommended a graded diagnosis for BPD to describe better the clinical status of affected infants (Table). (8) Because clinicians do not have evidence-based criteria for the use of supplemental oxygen, oxygen use and target saturations vary widely in clinical practice. Walsh and colleagues (9) developed an oxygen needs test to make the diagnosis of BPD more consistent across clinical services. The physiologic test for oxygen need also is described in the Table. When evaluated across 17 clinical units in the National Institute of Child Health and Human Development Neonatal Research Network, the diagnosis of BPD decreased from 35% to 25% of the infants whose birthweights were less than 1,250 g surviving to 36 weeks’ gestation. (9)

The most commonly used diagnosis of BPD as oxygen need at 36 weeks PMA does not require antecedent exposures as part of the diagnosis (eg, RDS, mechanical ventilation), abnormalities on a chest radiograph, or any laboratory test. Therefore, the diagnosis is simply based on the need for oxygen in ELBW infants who have survived to 36 weeks’ gestation. This is a “soft” diagnosis relative to most diagnoses in medicine that generally include specific clinical associations and laboratory findings. Certainly part of the problem results from the progressive nature of and multiple associations with BPD in this unique group of infants. Perhaps it is helpful to think about the stages of BPD that are clinically relevant to developing and testing therapies for BPD (Fig. 1). Although the diagnosis of BPD presently is made at 36 weeks PMA, efforts to prevent BPD need to begin with antenatal exposures and to focus on the known associations with BPD in the minutes to days after preterm birth (Fig. 2). The factors associated with BPD in ELBW infants or in animal models that have a BPD phenotype are discussed in this article. However, an important caveat is that the clinical diagnosis of BPD does not have a direct link to the developmental abnormalities that cause the lung structural changes identified as the new BPD. Although we know that infants who die of the new BPD have a severe arrest in lung development, we know virtually nothing about

### Table. Bronchopulmonary Dysplasia (BPD) Workshop Definition of BPD for Infants at Gestational Ages of Less than 32 Weeks

<table>
<thead>
<tr>
<th>Treatment with oxygen &gt;21% for at least 28 days plus—</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Mild BPD</strong>: Breathing room air at 36 weeks postmenstrual age (PMA) or discharge</td>
</tr>
<tr>
<td>• <strong>Moderate BPD</strong>: Need for &lt;30% oxygen at 36 weeks PMA or discharge</td>
</tr>
<tr>
<td>• <strong>Severe BPD</strong>: Need for ≥30% oxygen and/or positive pressure (ventilation or continuous positive airway pressure) at 36 weeks PMA</td>
</tr>
</tbody>
</table>

### Physiologic Test for Diagnosis of BPD

| Infants at 35 to 37 weeks PMA receiving mechanical ventilation, continuous positive airway pressure, or >30% O₂ with saturation of <96% have BPD |
| Infants receiving <30% O₂ or ≥30% O₂ with saturation of >96% tested for O₂ need |
| — O₂ progressively decreased gradually to room air |
| — No BPD if saturation is >90% in room air for 30 min |

Adapted from Jobe and Bancalari (8) and Walsh, et al (9).

**Figure 1. Stages of bronchopulmonary dysplasia (BPD).** BPD may be initiated with an injury phase that may begin prior to preterm birth. The early injury generally occurs following preterm birth at 23 to 28 weeks’ gestation. The acute progression of BPD probably occurs after the initial injuries over the first several weeks after preterm birth. An infant is given a diagnosis of BPD at 36 weeks postmenstrual age. The chronic stages may last for months, and very little is known about the time frame required for partial or complete resolution of BPD.
the lungs of the majority of infants who survive with milder forms of BPD.

**Developmental Context for the New BPD**

The human lung has completed about 16 generations of dichotomous airway branching by about 16 to 18 weeks' gestation to yield approximately 65,000 saccules at the end of terminal bronchioles (Fig. 3). (10) Considerable mechanistic information is known about this airway branching, termed primary septation. Genes that are critical for primary septation include fibroblast growth factor (FGF), epidermal growth factor, and the transcription factor. Secondary septation is the process of alveolarization of the distal lung saccules. Alveolarization is the anatomic description of the protrusion of an elastin fiber and mesenchyme containing a double capillary network into the saccular lumen, resulting in subdivision of that saccule. (11) In humans, alveolarization normally begins at 32 to 36 weeks' gestation and continues for several years. Alveolarization is being studied intensively because of its relevance to BPD in infants and to emphysema in adults. Factors known to regulate alveolarization are FGF-18 and platelet-derived growth factor-A as well as pathways for collagen and elastin metabolism. However, BPD occurs most frequently between 23 weeks and 28 weeks' gestation in the human, about 1 month after airway branching has finished and as much as 3 months before alveolarization begins.

Burri (11) describes a process of three generations of saccular septations after 20 weeks' gestation to form 524,000 respiratory bronchioles. These distal saccules further divide into three generations of alveolar ducts. These six branching generations yield about $4 \times 10^6$ saccules that subsequently alveolarize after 32 to 36 weeks' gestation. This 64 times increase in saccular structures that occurs between about 20 weeks and about 32 to 36 weeks is a
complex phase of lung development between airway branching and alveolarization that does not have a name. The new BPD may result primarily from interference with the generation of respiratory bronchioles and alveolar ducts. Concurrently with the expansion of the gas surface areas of the fetal lung and alveolarization, there is a large expansion of the pulmonary microvasculature. The essential development of the pulmonary microstructure occurs during the onset, progression, and healing of BPD.

Pathology of BPD

The anatomic information available for infants who died of BPD is biased toward the most severe changes, with the anatomy demonstrating multiple changes that are consistent with altered lung development. The lungs have increased alveolar (saccular) diameters and fewer alveoli (saccules). (12) The collagen network around the saccules is disrupted, and elastin is not localized to fibers in sites for future secondary septation. (13) Acute severe inflammation is not apparent unless there has been a secondary infection. The saccules are lined with dysplastic type II cells that express increased amounts of mRNA for surfactant protein C. Several reports have described decreased platelet/endothelial cell adhesion molecule-1 (PECAM) staining as a marker for the endothelium of a decreased pulmonary microvasculature. (14) A recent report showed increased levels of PECAM protein and prominent staining of the pulmonary microvasculature in lungs of infants who died of BPD. (15) Certainly, infants who die of BPD have pulmonary hypertension and microvascular disease. These contrasting pathologic findings may represent true variability in the pathophysiology of BPD, perhaps related to the major inciting factors, or different stages in the progression of the lung abnormalities. The most striking abnormality in the lungs of infants who have BPD is the arrest of alveolarization, resulting in the appearance of emphysema (Fig. 4). However, there is very little anatomic information available for most infants who survive BPD. These lungs may have different findings.

Alveolarization: Lessons from Animal Models

Mice and other rodents are born at term with a saccular lung that begins to alveolarize at about 3 days of age. This postnatal timing of alveolarization, when combined with the transgenic technology available for mice, is ideal for investigating factors that can interfere with alveolarization. Mice made to overexpress proinflammatory cytokines such as tumor necrosis factor-alpha, transforming growth factor-alpha, interleukin (IL)-6, IL-1, and IL-13 during the period of alveolarization experience the development of “emphysema” because of a failure of alveolarization. (6) Alveolarization also can be inhibited by exposure of mice to hyperoxia, and hyperoxia causes inflammation. In preterm ventilated lambs and baboons, conventional or high-frequency ventilation disrupts alveolar septation (Fig. 5). (16) These animals also were exposed to increased oxygen levels, and oxygen alone can inhibit alveolarization. Supplemental oxygen and mechanical ventilation probably represent the combination of two hits to the fetal lung: one an oxidant injury and the other a stretch injury. Both injuries are transduced to activate inflammatory cascades. In ventilated baboons, the proinflammatory mediators IL-6 and IL-8 were chronically elevated in airway samples about 10-fold above values measured in term newborn baboons (Fig. 6). (17) Thus, the common theme for the inhibition of alveolarization is inflammation, suggesting that inflammation caused by any mechanism will interfere with alveolar septation.

Other factors that can interfere with lung development are corticosteroids and starvation. Newborn rabbits that are fed less calories have increased sensitivity to oxidant damage, and adult rodents that are starved develop an emphysematous lung, which returns to normal with refeeding. (18) There is no information in newborn humans about the effects of low caloric intake on lung development. However, nutritional status may be an
Both antenatal and postnatal corticosteroids inhibit alveolarization and pulmonary microvascular complexity in developing animals. (19) Fetal sheep and monkeys exposed to antenatal corticosteroids have a decrease in the mesenchyme and increased airspace volumes within 24 hours. Subsequently, the alveoli are larger and the lung has decreased numbers of alveoli. In sheep, the corticosteroid-induced changes that occur in the preterm lung have disappeared by term. Rodents that alveolarize after term birth have arrested alveolar septation when treated with corticosteroids. The corticosteroid effects on alveolarization are independent of inflammation. There is no information about how corticosteroid effects might interact with inflammation to influence alveolarization. Nevertheless, infants at risk of severe BPD are treated with corticosteroids, presumably to decrease inflammation. The risk-to-benefit ratio for a single antenatal course of betamethasone certainly favors corticosteroid therapy. (20) Infants likely to develop severe BPD also may benefit from postnatal corticosteroid treatments, but those treatments may adversely affect alveolarization. (21) Clinical benefit may depend on the importance of inflammation to the process that is being treated in the infant.

**Chorioamnionitis: A Pathway to BPD**

Most infants born prior to 30 weeks’ gestation have been exposed to inflammation because of an often subclinical ascending intrauterine infection caused by low-grade pathogens. The most frequent organisms associated with chorioamnionitis, which is defined as inflammation of the fetal membranes, inflammatory cells, or organisms in amniotic fluid, are *Ureaplasma* and *Mycoplasma* sp. (22) Infants exposed to chorioamnionitis or delivered after preterm prolonged rupture of membranes (a surrogate marker for chorioamnionitis) have a decreased incidence of RDS but also have an increased risk of BPD in some clinical series. In other series, the increased risk of BPD occurred in infants exposed to chorioamnionitis who then were ventilated or developed postnatal sepsis. (23) Consistent clinical cor-

**Figure 5.** Effect of conventional mechanical ventilation on alveolarization of preterm lamb lungs. Preterm lambs delivered at 126 days’ gestation (term is 150 d) were treated with surfactant and ventilated at rates of 20 or 60 breaths/min for 3 weeks. The ventilated lambs were similar to gestation-matched fetal lambs and had not alveolarized over 3 weeks in comparison to measurements for airspace area and radial alveolar count in term lambs. Redrawn from data of Albertine, et al. (16)
relates no doubt are confounded by the imprecision of the diagnosis of chorioamnionitis where, in most cases, there is no information on the duration, intensity, or the organisms responsible for the clinical or histopathologic diagnosis. Furthermore, the contrasting effects of clinical lung maturation with less RDS may tend to protect the infant from BPD, while the inflammation already present at birth may contribute to BPD.

The responses of fetal sheep to inflammatory mediators provide some insight about how the fetus copes with inflammation. Intra-amniotic injections of Escherichia coli endotoxin, the proinflammatory cytokine IL-1-alpha, or endotoxin from periodontal organisms cause chorioamnionitis (inflamed membranes, inflammatory cells, and increased IL-8 concentrations in amniotic fluid). (24) Within hours, the fetal lung becomes inflamed and the numbers of inflammatory cells increase in the airspaces over several days. The lung inflammation/injury response progresses with cytokine expression in the fetal lung, cell apoptosis and proliferation, and microvascular injury. (25)(26) Within 7 days, alveolar number decreases and alveolar size increases (Fig. 7). (27) This combination of microvascular injury and inhibition of alveolarization is a mild BPD phenotype caused by inflammation of the fetal lung. (29) Thus, inflammation in the absence of supplemental oxygen and ventilation can cause changes similar to BPD in the fetal lung. The clinical outcome of these fetal exposures is lung maturation characterized by larger lung gas volumes and large increases in surfactant lipids and proteins. (28) Fetal sheep lungs colonized by intra-amniotic injection of live Ureaplasma have minimal inflammation but striking lung maturation. (30) These results replicate the clinical experience that many ELBW infants do not have severe RDS, especially after chorioamnionitis or ruptured membranes.

Fetal sheep exposed continuously to intra-amniotic endotoxin for 28 days prior to preterm delivery have alveolar simplification but no progression of lung injury. Prolonged fetal exposure to endotoxin did not cause persistent lung abnormalities when the lambs were delivered close to term. (31) This surprising result demonstrates that the fetal lung can mount a rapid inflammatory response to inflammation/infection but that the inflammatory response need not be progressive or severe. The fetus copes with the inflammation with reversible effects on lung alveolarization and microvascular development, and induced lung maturation is the most clinically apparent outcome after preterm birth. However, antenatal exposure to inflammation has resulted in the recruitment

Figure 6. Interleukin (IL)-6 and IL-8 levels in airway samples from preterm ventilated baboons. The cytokines were increased at all time intervals relative to values for term newborn or adult baboons. Median values for multiple measurements were adapted from Coalson, et al. (17)
of monocytes to the airspaces that can mature to macrophages that have an increased inflammatory potential. (32) Fetal sheep exposed to intra-amniotic endotoxin 30 days before preterm delivery had increased numbers of inflammatory cells in their airspaces after mechanical ventilation, indicating that the antenatal exposure changed the postnatal inflammatory response to mechanical ventilation. (33) The clinical implication is that antenatal exposure to inflammation likely will not cause BPD, but antenatal inflammation may potentiate postnatal inflammatory events. Although no specific information is available for infants, most ELBW infants are exposed to antenatal corticosteroids and many will be exposed simultaneously to chorioamnionitis. Each exposure can cause BPD-type structural changes in the developing lung.

**Neonatal Resuscitation/Initiation of Air Breathing**

The previous discussion of chorioamnionitis described how antenatal exposure to inflammation or corticosteroids may promote the initiation of injury. The antenatal exposures may occur over days, weeks, or even months. The initiation of air breathing after preterm birth is a rapid transition that must occur quickly for the infant to survive, and most ELBW infants receive ventilatory support to facilitate the transition. The scheme of clinical variables that may contribute to BPD shown in Figure 2 has been modified in Figure 8 to emphasize the brief, but important, period of delivery room management. The fetal preterm lung is fluid-filled, often surfactant-deficient, and very easy to injure because lung structure is immature and the potential gas volume (total lung capacity) is small. For example, the total lung capacity for infants who have RDS is only 20 to 30 mL/kg in contrast to volumes of about 50 mL/kg for term infants and 80 mL/kg for adults. Lung injury occurs if the lung is ventilated from lung volumes below the ideal functional residual capacity (FRC) (a frequent occurrence with surfactant deficiency) or to volumes close to or above the total lung capacity (TLC). (34) The ELBW infant has great difficulty establishing a reasonable FRC because of surfactant deficiency, inadequate variables that may contribute to BPD shown in Figure 2.
respiratory drive, and a compliant chest wall. The clinician attempting to ventilate the infant cannot establish and maintain a reasonable FRC without consistent positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). Unfortunately, the FRC cannot be measured in clinical practice. Compliance of the preterm lung is highly variable because of the range of surfactant amounts and the TLC, which depend on surfactant amount and the amount of induced lung maturation. Thus, mechanical ventilation is very likely to injure the lung of the ELBW infant.

Injury is most likely to occur during neonatal resuscitation because of the physiologic difficulties of establishing an FRC while avoiding overdistention of the lung. The anxieties of clinicians to ventilate the infant quickly promote excessive ventilation. Bjorklund and associates (35) demonstrated that just six large tidal volume breaths could injure the preterm lamb lung severely and that surfactant treatment prior to high tidal volume ventilation minimized the injury. Wada and colleagues (36) demonstrated that 30 minutes of tidal volume ventilation with 15 to 20 mL/kg was required to normalize PCO2 values using a ventilation rate of 30 breaths/min, but these tidal volumes also severely injured the preterm lamb lung. Injury was minimized by use of lower tidal volumes for initial ventilation after preterm birth, but the low tidal volumes resulted in hypercarbia. The use of low tidal volumes, but no PEEP, increases the injury that develops after preterm birth (Fig. 9). (37)

Other potential sources of injury to the preterm lung are the gases and the conditioning (temperature, humidity) of the gases used for resuscitation of the preterm. The new International Liaison Committee on Resuscitation (ILCOR) recommendations for neonatal resuscitation suggest that room air or an oxygen concentration of less than 100% are options, but caution is suggested for using less than 100% oxygen for the preterm infant. (38) However, the preterm infant may be more susceptible to oxidant-mediated injury than the term infant because protective antioxidant systems are less well developed. The term infant has delayed onset of spontaneous breathing and biochemical indicators of oxidant injury even after a brief exposure to 100% oxygen. The possible contribution of 100% oxygen to the initiation of lung injury in the preterm infant presently is not known. Many delivery rooms use only 100% oxygen that is neither heated nor humidified. There is no information about the potential of unhumidified and unheated air or oxygen to injure the airways of term or preterm infants.

Surfactant treatment before the initiation of breathing can decrease lung injury strikingly in preterm animals that have surfactant deficiency. (35)(36) The human situation is more complex because many preterm infants have some degree of early lung maturation, and intubation and ventilation, when not necessary, can increase the risk of injury to the preterm lung. The relative merits of early surfactant treatment are discussed in another article in NeoReviews. (39) The optimal timing of surfactant treatment for ELBW infants remains unresolved within the context of delivery room management.

Figure 9. Cytokine mRNA expression in lung tissue of preterm lambs 2 hours after delivery and ventilation. The animals were ventilated after surfactant treatment at birth with either 0 or 4 cm H2O positive end-expiratory pressure (PEEP) with a goal to keep the Pco2 greater than 50 mm Hg. The fetal lung expressed very low cytokine mRNA levels. Ventilation with PEEP resulted in increased IL-1beta and IL-6 mRNA levels, which were much higher when ventilation was without PEEP. Data redrawn from Naik (37). *P<0.05 versus fetal lung and **P<0.01 versus 4 cm H2O PEEP.
The recent ILCOR guidelines do not address resuscitation of the preterm infant other than to say that the lung can be easily injured, PEEP/CPAP may be helpful, and maintenance of body temperature is important. (38) The lack of specific guidelines results from the almost total lack of evidence-based information concerning resuscitation of the preterm infant. The results from animal models suggest strongly that PEEP/CPAP are important, as is limiting tidal volumes to perhaps no more than 5 mL/kg; 100% oxygen seldom is required. Avoidance of hyperventilation is an important first step in minimizing lung injury. The contribution of lung injury at delivery to the ultimate outcome of BPD may never be defined clearly because this brief opportunity to injure the lung soon is overtaken clinically by prolonged postnatal management. However, it is clear that in the extreme, pulmonary interstitial emphysema can be initiated in the delivery room and can be a strong indicator of subsequent poor lung function and ultimately BPD.

Ventilatory Support as a Cause of BPD

The two primary associations with the new BPD in ELBW infants are gestational age (birth-weight) and exposure to ventilatory support. The association of ventilatory support with BPD has been dominant since the initial description of the disease in 1967. (3) With each improvement in ventilatory technique, the new technique initially was believed to be a (partial) solution to the BPD problem. The introduction of CPAP and PEEP improved mortality, and negative pressure ventilation was promoted as the solution to lung injury. Unfortunately, small infants who have significant lung disease cannot be supported with negative pressure ventilators, and those are the infants now at significant risk of developing BPD. High-frequency oscillatory ventilation (HFOV) had been promoted as the solution to the BPD problem, initially because of the remarkable demonstrations of decreased injury relative to conventional ventilation of preterm baboons that had RDS. (40) However, the favorable BPD outcomes initially reported from clinical trials are much less compelling in more recent trials, and a meta-analysis demonstrates convergence of the BPD outcome for HFOV and conventional ventilation (Fig. 10). (41) Because the trials were conducted over about 15 years, the techniques, equipment, and clinical goals for all approaches to mechanical ventilation were improving, and survival of more immature infants was increasing. The incidence of BPD has not changed, but the severity of BPD has decreased. (42) Clark made the point in an editorial that outcomes with ventilatory support depend on “both the tool (ventilator) and the carpenter (clinician).” (43)

The physiologic model for ventilator-induced lung injury in the adult lung is shown in Figure 11. (44)
pressure-volume curve for the normal lung has regions of injury on the inflation and deflation limbs. Lung injury occurs below a normal FRC of about 30 mL/kg and for volumes approaching or above a normal TLC. Less pressure is required to ventilate the lung on the deflation limb of the pressure-volume curve than on the inflation limb. The preterm lung is a challenge to ventilate because the TLC is low, and although FRC also is less (15 to 20 mL/kg) than in the adult lung, there is a much smaller volume range in which injury will not occur. (45) This model is oversimplified primarily because lung inflation is not uniform if the lung is diseased or injured. Surfactant deficiency increases the pressures needed to achieve the volumes in the preterm lung and cause nonuniform inflation. The assumptions of this model and the clinical experiences in older children and adults are that if mechanical ventilation occurs in the safe pressure-volume range on the deflation limb of the pressure-volume curve, no lung injury occurs. The goal of HFOV is to keep the lung volume relatively high on the deflation limb of the pressure-volume curve and use small tidal volumes that do not approach TLC. Conventional ventilation of the preterm infant with sufficient PEEP to hold the lung at or above FRC and with the use of small tidal volumes may result in a risk of ventilation-mediated injury that is similar to that of HFOV.

CPAP is the ventilatory support technique now claimed to decrease BPD when used to avoid intubation and mechanical ventilation. (46) CPAP should recruit and maintain the FRC and allow the infant to breathe, presumably using tidal volumes that do not approach TLC. With experience, CPAP can be used to transition infants successfully from the delivery room to the neonatal intensive care unit, and many such infants do not require intubation and surfactant treatment. The clinical experience of Aly and colleagues (47) is shown in Figure 12. The larger infants usually required only CPAP. The
incidence of BPD was higher in infants who were intubated in the delivery room than in infants managed by CPAP. However, the occurrence of BPD was still 28% in infants who were extubated to CPAP soon after delivery. The infants were not randomized to care strategies, so this and other clinical experiences do not demonstrate that CPAP can “prevent” BPD.

Some experimental observations indicate that a CPAP strategy preserves lung structure and allows alveolarization to occur. Thomson and associates (48) demonstrated preservation of lung structure for preterm baboons supported with CPAP after an initial period of surfactant treatment and stabilization with mechanical ventilation. Preterm lambs have fewer biochemical indicators of lung injury on CPAP than on conventional ventilation. (49) These experimental results are “proof of principal” that CPAP can cause less injury to the preterm lung than conventional ventilation. However, similar models were used to show that HFOV was superior to conventional ventilation, an outcome that has not translated to clinical practice.

My assessment of the controversies about the best ways to avoid BPD combines concepts of lung injury, lung development, and reasonable clinical care strategies. Important advantages of CPAP are the avoidance of overinflation and inflation without control of PEEP, especially in the delivery room. The preterm lung is easy to injure, and the more injury, the more likely that BPD will develop. However, CPAP, PEEP, and the higher mean airway pressures used for HFOV stretch the lung, and stretch can transduce inflammation. The requirements for an FRC and a tidal volume sufficient for gas exchange, no matter how accomplished, may be sufficient to alter the subsequent development of the saccular lung. Injury and the other associations with BPD only make the developmental abnormalities worse.

Oxygen and BPD
In the clinical setting, oxygen has not been disentangled from ventilation in terms of relative importance for causing BPD. Infants who require ventilatory support also usually receive supplemental oxygen. The anatomic changes of delayed alveolar septation and an arrest in microvascular development occur simply with oxygen exposure in newborn rodents. (50) There is no information on the importance of oxygen to lung injury immediately after delivery or within the first days after birth in infants. However, infants who had retinopathy of prematurity and were randomized to a high oxygen saturation target had more severe BPD that persisted for a longer period of time than infants randomized to a lower oxygen saturation range in one study. (51) The recent emphasis on keeping oxygen saturations to a reasonable range (perhaps 85% to 95%) for oxygen-exposed ELBW infants should help decrease the severity of BPD, although the optimal oxygen saturation range remains unknown.

Sepsis and BPD
As reviewed previously, chorioamnionitis is an association with BPD. Infants exposed to chorioamnionitis range in exposure from mild lung inflammation to a systemic inflammatory response and sepsis. The lung inflammation prior to birth is the start of an inflammatory response that can be amplified by postnatal care that includes ventilation and oxygen. Infants exposed to chorioamnionitis also have early tracheal colonization with organisms, which also is an association with BPD. (52) Postnatal sepsis is a similar insult that occurs after the lung injury/developmental abnormality sequence has been initiated. The experimental literature clearly demonstrates that most any cause of inflammation can stop alveolar septation in newborn rodents. Whenever it occurs, infection with its associated inflammation is likely to interfere with lung development. Postnatal sepsis is an important variable that confounds studies of the relative benefits of different ventilatory support strategies because infection is so common in ELBW infants.

Postnatal Corticosteroids
Corticosteroids have pleotropic effects on the fetus and newborn, and the lung is a target of corticosteroid action. Corticosteroids mature the fetal lung, primarily by decreasing the amount of mesenchymal tissue and increasing potential airspace volume. Such anatomic changes result in an arrest in alveolar (saccular) septation in fetal monkeys and sheep. (27) Similarly, postnatal corticosteroids arrest alveolar septation and microvascular development in rodents. (19) Thus, corticosteroids induce the anatomic equivalent of a mild new BPD. The fetal exposures are of low dose and short duration relative to the exposures often provided postnatally. The maternal benefits exceed the risks for fetal exposures. Postnatal treatments to prevent or treat BPD are primarily used for anti-inflammatory effects. Postnatal corticosteroids are controversial and generally not recommended because of concerns about adverse effects on neurodevelopment. The recent meta-analysis by Doyle and colleagues (21) demonstrated that for infants at high risk of developing BPD, corticosteroid treatments after approximately 1 week of age may be of benefit (Fig. 13).
Outcome of Infants Who Have BPD

The long-term lung outcomes for ELBW infants are a concern. ELBW infants who do not have BPD require frequent hospitalizations and lung-related medications in the first 2 postnatal years. (53) ELBW infants who have BPD have increased pulmonary problems and poorer neurodevelopment than unaffected ELBW infants. My interpretation is that all ELBW infants have some degree of abnormal lung development, and BPD is the clinical manifestation of increased severity of developmental abnormalities. Preterm infants have more airway restriction than term infants at term, and the preterm infant has more airway reactivity later in life. Children who survived the old BPD have some restrictive airway disease and increased airway reactivity. (54) There is very little information about if and how infants who have the new BPD remodel their alveoli and microvasculature with growth. Of concern is the observation that adolescent monkeys that were ventilated after preterm birth continued to have lungs that had decreased alveolar numbers (Fig. 14). (55) Most infants who have milder forms of BPD seem to have minimal residual lung disease, but normally there is a large respiratory reserve that decreases after adolescence throughout life. A concern is how such BPD lungs will age.

ACKNOWLEDGMENTS. This work was supported in part by grants HD-12714 and HL-65397 from the National Institutes of Health.

References

4. Bancalari E. Changes in the pathogenesis and prevention of
39. Jobe AH. Pharmacology review: why surfactant works for respiratory distress syndrome. *NeoReviews.* 2006;7:e95–e106. Available at: http://neoreviews.aappublications.org/cgi/content/full/7/2/e95
43. Clark RH. Both the tool and the carpenter are important. J Pediatr. 1997;131:796–798
NeoReviews Quiz

9. In contrast to “classic” bronchopulmonary dysplasia (BPD), initially described in 1967, the “new” BPD in the more contemporary clinical setting is characterized by different histopathologic findings on examination of the lung tissue. Of the following, the most striking abnormality in the lungs of infants who have new BPD is:
   A. Decrease in alveolar septation.
   B. Diffuse leukocytic infiltration.
   C. Epithelial squamous metaplasia.
   D. Hypertrophy of airway smooth muscle.
   E. Lung parenchymal fibrosis.

10. Maternal chorioamnionitis, defined as inflammation of the fetal membranes and the presence of inflammatory cells or organisms in the amniotic fluid, often is a pathway for the development of BPD in preterm infants. Of the following, the most frequent organism associated with maternal chorioamnionitis as a cause of neonatal BPD is:
   A. Escherichia coli.
   B. Group B Streptococcus.
   C. Listeria monocytogenes.
   D. Staphylococcal species.
   E. Ureaplasma urealyticum.

11. The pathogenesis of new BPD in extremely low-birthweight (ELBW) infants involves a complex interplay of several factors. Of the following, one of the primary associations with the development of new BPD in ELBW infants is:
   A. Exposure to ventilator support.
   B. Genetic predisposition.
   C. Nutritional deficit.
   D. Postnatal sepsis.
   E. Surfactant deficiency.

12. Corticosteroids have pleiotropic effects on the fetus and newborn, and the lung is a target of corticosteroid action. Of the following, the most striking anatomic change in the lung in relation to postnatal corticosteroid treatment is:
   A. Arrested microvascular development.
   B. Decreased airspace volume.
   C. Dysplastic epithelial type 2 cells.
   D. Increased mesenchymal tissue.
   E. Infiltration with inflammatory cells.
The New BPD
Alan H. Jobe
NeoReviews 2006;7:e531
DOI: 10.1542/neo.7-10-e531

Updated Information & Services
including high resolution figures, can be found at:
http://neoreviews.aappublications.org/content/7/10/e531

References
This article cites 52 articles, 9 of which you can access for free at:
http://neoreviews.aappublications.org/content/7/10/e531#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Psychiatry/Psychology
http://classic.neoreviews.aappublications.org/cgi/collection/psychiatry_psychology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://classic.neoreviews.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://classic.neoreviews.aappublications.org/site/misc/reprints.xhtml
The New BPD
Alan H. Jobe
NeoReviews 2006;7;e531
DOI: 10.1542/neon.7-10-e531

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/content/7/10/e531