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Bronchopulmonary Dysplasia in Preterm Infants

Pathophysiology and Management Strategies

Carl T. D'Angio and *William M. Maniscalco*

Strong Children's Research Center, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

Contents

Abstract

Bronchopulmonary dysplasia (BPD) has classically been described as including inflammation, architectural disruption, fibrosis, and disordered/delayed development of the infant lung. As infants born at progressively earlier gestations have begun to survive the neonatal period, a 'new' BPD, consisting primarily of disordered/delayed development, has emerged. BPD causes not only significant complications in the newborn period, but is associated with continuing mortality, cardiopulmonary dysfunction, re-hospitalization, growth failure, and poor neurodevelopmental outcome after hospital discharge.

Four major risk factors for BPD include premature birth, respiratory failure, oxygen supplementation, and mechanical ventilation, although it is unclear whether any of these factors is absolutely necessary for development of the condition. Genetic susceptibility, infection, and patent ductus arteriosus have also been implicated in the pathogenesis of the disease.

The strategies with the strongest evidence for effectiveness in preventing or lessening the severity of BPD include prevention of prematurity and closure of a clinically significant patent ductus arteriosus. Some evidence of effectiveness also exists for single-course therapy with antenatal glucocorticoids in women at risk for delivering premature infants, surfactant replacement therapy in intubated infants with respiratory distress syndrome, retinol (vitamin A) therapy, and modes of respiratory support designed to minimize 'volutrauma' and oxygen toxicity. The most effective treatments for ameliorating symptoms or preventing exacerbation in established BPD include oxygen therapy, inhaled glucocorticoid therapy, and vaccination against respiratory pathogens.

Many other strategies for the prevention or treatment of BPD have been proposed, but have weaker or conflicting evidence of effectiveness. In addition, many therapies have significant side effects, including the possibility of worsening the disease despite symptom improvement. For instance, supraphysiologic systemic doses of glucocorticoids lessen the incidence of BPD in infants at risk for the disease, and promote weaning of oxygen and mechanical ventilation in infants with established BPD. However, the side effects of systemic glucocorticoid therapy, most notably the recently recognized adverse effects on neurodevelopment, preclude their routine use for the prevention or treatment of BPD.

Future research in BPD will most probably focus on continued incremental improvements in outcome, which are likely to be achieved through the combined effects of many therapeutic modalities.

This article presents a critical review and discussion of the pathophysiology and effective preventive and treatment strategies for bronchopulmonary dysplasia (BPD) in preterm infants. Issues relating to glucocorticoid therapy of BPD are also discussed. It is not possible within a single article to review fully all the issues surrounding BPD. Where applicable, the reader is referred to recent, authoritative and systematic reviews of specific topics. The article concludes with recommendations for clinicians, based on the evidence available.

The articles reviewed for this work were selected on the basis of Medline searches including 'bronchopulmonary dysplasia' in combination with MeSH headings closest to the subtopics within the article. Both review articles and original articles were sought. For discussion of pathophysiology, representative articles to illustrate the major points were chosen. For discussion of treatment, all relevant articles from the Medline search were augmented with systematic reviews of the topics culled from the Cochrane Database of Systematic Reviews.

1. Background

Northway and colleagues[1] first described BPD over 30 years ago. The name described the lung pathology, which included injury and partial repair affecting both the airways and parenchyma of the developing lung.[2] The disease was not recognized prior to the availability of mechanical ventilation, as children with respiratory distress syndrome (RDS) had previously either died or recovered without pulmonary sequelae.[2]

Four major risk factors for BPD have been suggested.[2] These include:

- premature birth
- respiratory failure
- oxygen supplementation
- mechanical ventilation.

It is unclear whether any of these factors is absolutely necessary for the development of the condition. Premature infants certainly comprise the majority of children who develop BPD. However, full-term children with severe respiratory failure who require prolonged mechanical ventilation can also develop chronic pulmonary disease. Careful morphometric studies performed in the 1980s suggested that premature infants who survived without needing mechanical ventilation had normal alveolar numbers and fewer morphologic airway abnormalities compared with ventilated infants (figure 1).[3-5] Recent reports of the occurrence of BPD in significant proportions of infants <1kg in birthweight with initially minimal needs for ventilator and oxygen support suggest that neither oxygen supplementation nor mechanical ventilation may be absolutely required for the development of BPD.[6-9]

The advent of surfactant use and other more sophisticated neonatal care has led to little change in the incidence of BPD.[2] This may be because this same revolution in neonatal care has led to increased survival of extremely premature infants.[8] As more of these infants have survived, the face of BPD has changed. At present, it is largely a disease of very small infants. Even as early as 1987, the incidence was reported as 50% among infants born at a weight of 700–900g, but only 5% among infants born at a weight of >1250g.[11]

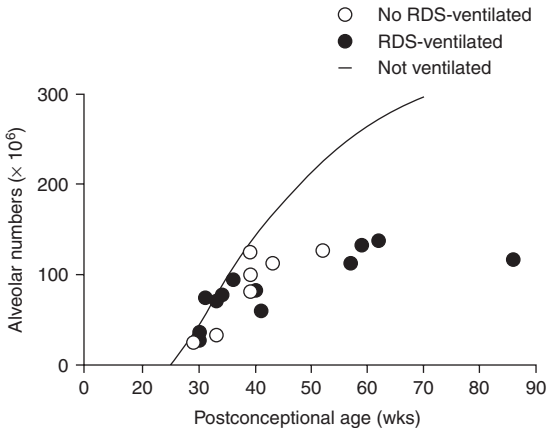

Fig. 1. Alveolar numbers measured in human infants either exposed or unexposed to mechanical ventilation. Mechanical ventilation inhibits the normal increase in alveolar number seen in nonventilated infants.[3,4] Reproduced from Jobe and Ikegami,[10] with permission. **RDS** = respiratory distress syndrome.

1.1 Pathology

The pathology of BPD has changed over time (figure 2), leading some authors to discriminate between an 'old' and a 'new' BPD.[9] Classic pathologic descriptions of BPD from the era before surfactant treatment include abnormalities at all levels of the tracheobronchial tree. Marked inflammation, edema, fibroproliferation, and hypercellularity, with destruction of alveolar septa and eventual fibrosis were described.[12] In addition, muscular hyperplasia surrounding the bronchi and bronchioles was reported, with increased goblet cell number, submucosal gland hypertrophy, excessive mucus production, and mucosal squamous metaplasia.[5,13] The vascular bed also underwent muscular hypertrophy, fibrosis, and endothelial cell hyperplasia, with decreased total arterial number.[13,14] In recent years, however, pathologic examinations of infants who have died following surfactant treatment have shown less marked fibrosis and inflammation, although the numbers of alveoli remain decreased.[15] The lung architecture appears consistent with the saccular stage of development, that typical of a fetus during most of the third trimester of pregnancy.[9] At the start of the third trimester, although respiratory airway division is nearly complete and the acinar limits have been defined, the distal saccules of the lung have not yet begun to be subdivided into alveoli.[16] It has been hypothesized that the 'new' BPD represents an arrest of lung development at the time the fetus becomes an infant.[9]

The majority of our understanding of the pathology of BPD comes from infants who have died from their disease, who may represent the most severe form of their disease. However, some information has also been gleaned from lung biopsy specimens of low birthweight infants requiring ventilatory support. These biop-

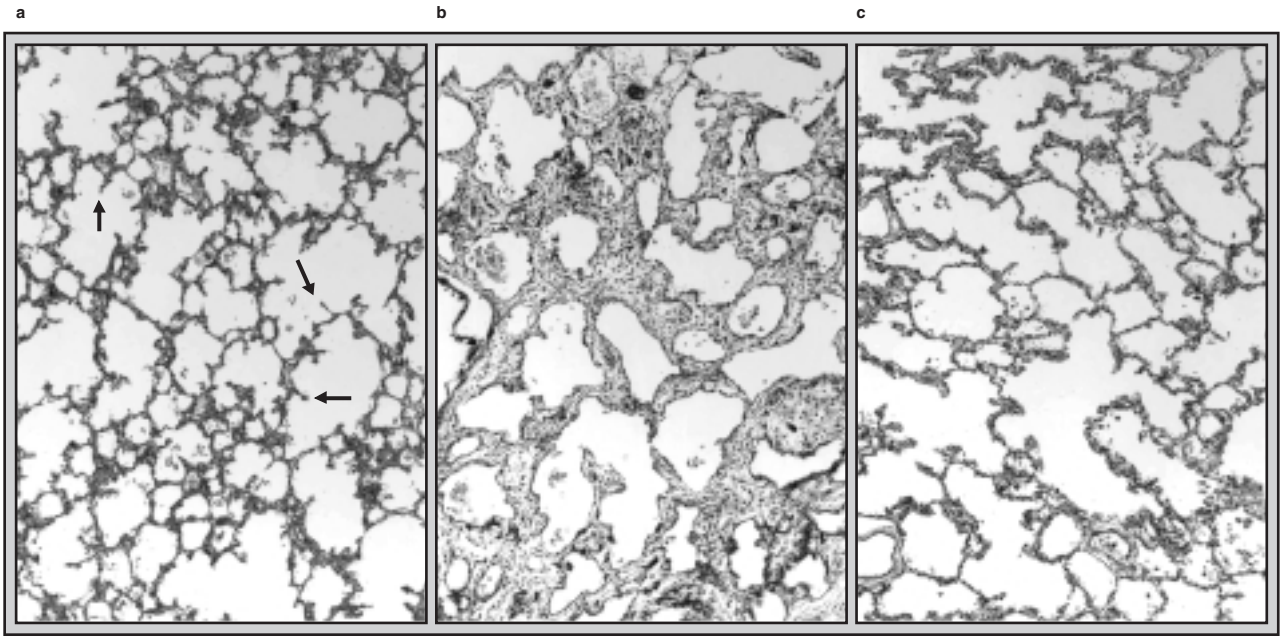

Fig. 2. Histologic appearance of bronchopulmonary dysplasia (BPD). (**a**) Normal alveolarizing lung with no inflammation, thin alveolar septa, and abundant secondary crests partitioning alveoli (arrows). (**b**) 'Old' BPD with intense inflammation, marked septal thickening, and lack of alveolarization. (**c**) 'New' BPD with much less inflammation and septal thickening, but with fewer mature alveoli and fewer secondary crests than a normal lung. Photomicrographs are of inflation-fixed, trichrome-stained lung specimens from human autopsy samples (original magnification 10×).

sies also show a simplified distal lung acinus, lack of alveolarization, abnormal capillary configuration, and an adaptive dysmorphic pattern of vascular organization.[13]

1.2 Clinical Definition

Since most infants with BPD do not die from their disease, the definition of BPD is largely a clinical one. This clinical definition has evolved over time. The original description of BPD was as "a new chronic pulmonary syndrome associated with the use of intermittent positive pressure respirators (IPPR) and high oxygen for longer than 150 hours (6 days)".[1] No mention was made of the need for, or length of, subsequent oxygen therapy. Later definitions included the need for positive pressure ventilation for at least 3 days during the first 2 weeks of life, clinical signs of respiratory compromise, supplemental oxygen requirement extending beyond 28 days of age, and a characteristic chest radiograph.[17] Subsequently, as the number of very small infants requiring supplemental oxygen at 28 days increased, the oxygen requirement and/or the need for respiratory support at 36 weeks' postmenstrual age (PMA) was suggested as an alternative definition.[18] Recently, a workshop convened by the US National Institutes of Health (NIH) proposed a definition that divides BPD into mild, moderate, and severe categories, based on gestational age and length and amount of oxygen support (table I).[19]

Two other matters of definition bear mentioning. The first is that several authors had proposed re-labeling the respiratory difficulties facing extremely premature infants as chronic lung disease of prematurity. The use of this term was discouraged by the NIH Consensus Conference as being insufficiently descriptive and because of the potential for confusion with the many causes of chronic lung disease in adults.[19] Secondly, even the graded definition recently proposed does not adequately categorize that significant minority of extremely premature infants who initially need no supplemental oxygen ('honeymoon'), but subsequently develop clinical and radiologic disease consistent with BPD.[7,8]

2. Burden of Disease

BPD results in significant short- and long-term sequelae (table II).[20] Many of the long-term data reviewed in this section focus on the outcome of the 'old' BPD. Although data have recently become available on the sequelae of the 'new' BPD, continued research will be needed to define the burden of disease in infants currently being diagnosed with BPD.

2.1 Newborn Period

In the newborn period, by virtue of the abnormal immaturity of the gas-exchanging surface in the lung, BPD prolongs infants' requirements for mechanical ventilation and supplemental oxygen therapy (table II). Infants with BPD also express heightened

Table I. Suggested definition and classification of bronchopulmonary dysplasia (BPD) from National Institutes of Child Health and Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases workshop (reproduced from Jobe and Banclari,[19] with permission)

	Gestational age	
	<32wk	≥32wk
Time point of assessment	36wk PMA or discharge to home, whichever comes first	>28d but <56d postnatal age or discharge to home, whichever comes first
Severity of BPD[a]		
mild	Breathing room air at 36wk PMA or discharge, whichever comes first	Breathing room air by 56d postnatal age or discharge to home, whichever comes first
moderate	Need for <30% oxygen at 36wk PMA or discharge, whichever comes first	Need for <30% oxygen at 56d postnatal age or discharge to home, whichever comes first
severe	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36wk PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56d postnatal age or discharge to home, whichever comes first

a All infants must be breathing >21% oxygen for at least 28 days and have persistent clinical features of respiratory distress, in addition to other criteria.

NCPAP = nasal continuous positive airway pressure; **PMA** = postmenstrual age; **PPV** = positive-pressure ventilation.

airway reactivity, leading to bronchospasm.[21] Airway hyperreactivity can be seen in infants as young as 1 week of age, before the onset of clinically apparent BPD.[21] Airway resistance is increased and lung compliance is decreased.[22] The functional residual capacity, initially decreased due to atelectasis, can later become increased due to air trapping.[23] The pulmonary hypertension experienced by children with BPD also complicates the respiratory course, and can result in life-threatening cor pulmonale.[23,24]

BPD is a major cause of prolonged neonatal hospitalization in premature infants, and remains a major cause of death among premature infants.[23] Infants with BPD may also suffer a higher incidence of prematurity-related conditions such as gastroesophageal reflux, apnea, or oxygen desaturation episodes.[23] Infants with BPD often grow poorly due to the increased metabolic demands imposed by their increased work of breathing.[23] This can also lead to prolonged hospitalization.

Table II. Burden of disease

Short term sequelae (neonatal period)	Prolonged mechanical ventilation and supplemental oxygen
	Airway reactivity
	Pulmonary hypertension
	Systemic hypertension
	Prolonged hospitalization
	Poor growth
	Death
Long term sequelae	Late mortality
	Abnormal cardiopulmonary function
	Decreased exercise tolerance
	Re-hospitalization
	Growth failure
	Poor neurodevelopmental outcome

2.2 Mortality

In the pre-surfactant era, mortality from BPD was significant, estimated to be 20–40% over the first few years after birth.[25] Most deaths occurred during the initial hospitalization, but up to 20% of deaths occurred after hospital discharge.[25,26] Mortality from BPD appears to have fallen since the introduction of surfactant therapy, although precise estimates are difficult to obtain.[23] In a small population of 137 infants born at <29 weeks' gestation in the early surfactant era, 18% of whom had BPD (defined as oxygen requirement at 36 weeks' PMA), 4% of children died between hospital discharge and school age.[27] The rate did not differ between children with and without BPD. However, a population-based study in Wales attributed 32% of postneonatal deaths in infants born at <1500g to BPD, and cited the condition as a coexisting factor in an additional 36% of deaths.[28]

Although most deaths from BPD are due to complications of the disease, it appears that BPD may also increase the risk of sudden, unexplained death.[23] Several instances of this have been described in hospitalized infants with severe BPD.[29] The incidents did not seem to be due to worsening of the infant's pulmonary status. Studies of infants after discharge have yielded mixed results, but also appear to suggest that BPD poses an independent risk for sudden infant death.[30,31]

2.3 Cardiopulmonary Structure and Function

Animal data suggest that BPD leads to a permanent loss of alveoli.[32] In human infants dying of BPD at 14–34 months of age, alveolar numbers may be only 25% of normal and alveolar surface area is markedly decreased.[4,33,34] If this were also true in surviving infants, it is unlikely that alveolar numbers would ever reach normal adult levels.

The hyperexpansion, atelectasis, and interstitial thickening so prominent in radiographs of infants with 'old' or severe BPD tend to resolve over the first few years of life.[2] However, subtle plain film abnormalities can persist into adulthood.[20,35] High resolution CT scans reveal abnormalities in over 90% of children and adolescents who survive BPD.[36]

The pulmonary function in survivors with BPD has been recently and comprehensively reviewed by Eber and Zach.[20] Premature infants of low birthweight, and especially children with BPD, can have pulmonary function abnormalities that persist at least to mid-adult life.[37] During infancy, these children have lower lung volumes, poorer lung compliance, decreased functional residual capacity, and outflow obstruction.[20] Although many of these abnormalities resolve over the first months or years of life, evidence of small airway obstruction and air trapping persists into late childhood or adolescence in about half of children.[38,39] Long-term survivors with BPD are also commonly described as having airway hyper-responsiveness.[20,40] Wheezing with acute respiratory illnesses is common in children with BPD.[41,42] However, this may be related to a smaller airway caliber, rather than to atopy.[43] Some investigators have not found BPD to be a risk factor for clinically diagnosed asthma by late childhood or adolescence.[44]

Cardiovascular function is also affected in survivors of BPD. Up to 50% of schoolchildren with BPD have right ventricular hypertrophy present on ECG.[20,40] Among ten children with severe BPD who underwent cardiac catheterization, pulmonary arterial pressures were increased.[45] Among those children who were re-catheterized, these abnormalities gradually improved, but did not resolve, over an average follow-up interval of 4 years. In another group of 26 adolescents and young adults with a history of BPD, only one had any evidence of right ventricular hypertrophy, and none had evidence of pulmonary hypertension.[35] Infants with BPD may also develop systemic hypertension, either before or after hospital discharge.[23] This is usually relatively mild, and often resolves by 1 year of age.[23]

The effect of these cardiopulmonary function abnormalities on children's exercise tolerance and activities of daily living is controversial. A follow-up of adolescents and young adults with a history of BPD found that while 76% of the individuals studied had measurable pulmonary dysfunction, the majority of these (about 75%) were clinically asymptomatic.[35] While some investigators report diminished exercise tolerance in child or adolescent survivors of BPD,[46,47] others report no differences in exercise capacity from children born at full term.[48-50] However, children with BPD with normal exercise tolerance appear to attain that capacity by using a greater percentage of their respiratory reserve and/or by tolerating lower arterial oxygen saturation and higher arterial CO_2 values.[49,50]

2.4 Re-hospitalization

Children who apparently recover well from their BPD in early infancy remain at significant risk for re-hospitalization with intercurrent illnesses in the first 1–2 years of life.[51,52] This risk is further increased if children have persistent clinical signs of BPD. Infants with BPD are at particular risk for severe disease with respiratory virus infections such as those caused by respiratory syncytial virus (RSV) and rhinovirus.[53,54] Up to 50% of children with BPD will require re-admission to a hospital within the first year of life.[41,42,52] Although the incidence of clinically significant respiratory disease decreases thereafter, one long-term follow-up study of adolescents and adults who survived BPD found that up to 25% had continuing respiratory symptoms, including wheezing and frequent pneumonia.[35]

2.5 Growth Failure

Infants with BPD are at risk for growth failure both before and after hospital discharge.[20,52] Both linear and weight growth can be affected, although weight gain often suffers disproportionately.[20,42,52] Growth failure is likely to be more severe in those with significant pulmonary symptoms, and is related in part to the increased metabolic demands imposed by respiratory distress.[42] Infants with BPD are also likely to experience undetected episodes of hypoxia; these may also contribute to growth failure.[55,56] Growth improves as pulmonary symptoms resolve.[42] Infants with BPD, like other very low birthweight infants, are likely to remain shorter than full-term children through school age.[57] Some children may continue to have continued poor growth into adulthood.[35]

2.6 Neurodevelopmental Outcome

Prematurity is a risk factor for poor neurodevelopmental outcome. Although some studies have suggested no independent effect of BPD on this risk,[58,59] others have found that BPD is associated with poorer neurodevelopmental outcome at ages ranging from 3 to over 15 years.[27,60-66] This effect persists when other factors are controlled, and appears to persist in infants born in the surfactant era. There also appears to be a 'dose effect', with

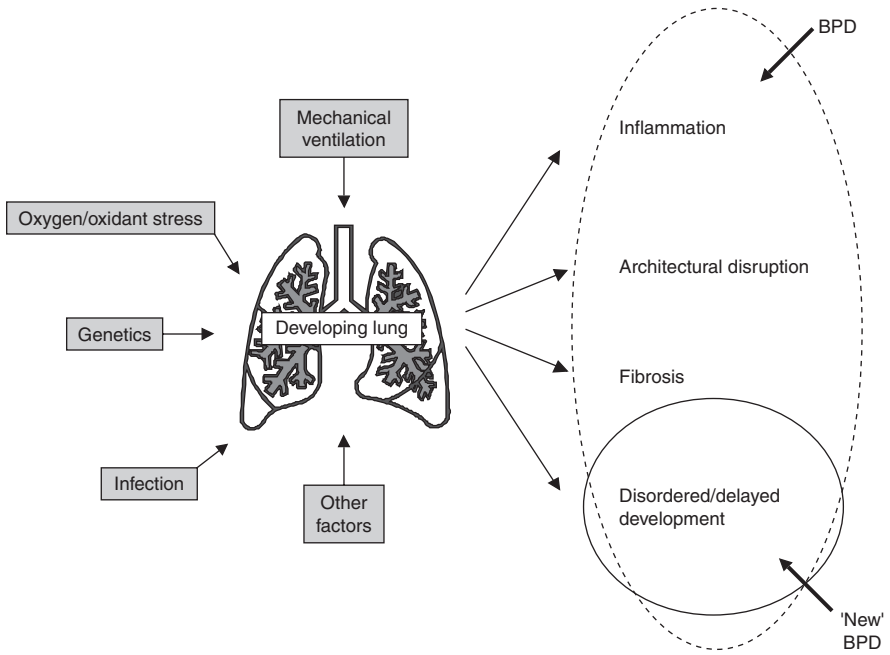

Fig. 3. Pathogenesis of bronchopulmonary dysplasia (BPD). BPD results from the interaction of several potentially injurious stimuli on the developing lung. The degree of injury needed to produce disease appears to diminish if the lung is extremely immature. Severe ('old' or 'classical') BPD involves significant amounts of inflammation and fibrosis, while the 'new' BPD, seen in extremely immature infants, is primarily an arrest of development.

oxygen requirement at 36 weeks' PMA predicting a poorer outcome than oxygen requirement at 28 days of age.[52]

3. Pathophysiology

Multiple pathophysiologic processes have been implicated in the eventual development of BPD (figure 3). Some of these, such as inflammation and fibroproliferation appear to be more active in the development of 'old' or severe BPD, while others, such as delayed or disordered development may be more germane to the 'new' BPD seen in extremely premature infants. All the processes, however, are likely to be active to a greater or lesser extent in all cases of neonatal lung injury.

3.1 Inflammation

Granulocyte infiltration into the lungs of infants developing BPD has been well described. Animal models of newborn lung injury support an active role for granulocytes in the pathogenesis of BPD.[67,68] Neutrophils appear rapidly in the bronchoalveolar lavage fluid of premature infants with RDS.[69,70] Neutrophil counts peak by the fourth day of life, and decline rapidly thereafter in infants who recover uneventfully.[70] The fall in neutrophil counts is delayed in infants who later develop BPD. In animal models, neutrophil depletion can limit the effects of hyperoxia-induced pulmonary injury, implying a role for the neutrophil in lung damage.[12] Although it has been suggested that the resident phagocyte of the lung, the alveolar macrophage, may also be crucial to the development of BPD, the evidence for this in human infants is limited.[8]

The role of proinflammatory mediators, such as cytokines, that attract inflammatory cells into the lung, has been extensively studied in premature newborns.[71] Elevated levels of the proinflammatory cytokines tumor necrosis factor-α (TNFα), interleukin (IL)-1β, IL-6, or IL-8 in amniotic fluid have been associated with the later development of BPD, as have elevated IL-6 levels in umbilical cord blood.[72-74] Similarly, the appearance in the first few days of life of TNFα, IL-1β, IL-6, IL-8, and monocyte chemoattractant protein-1, among other proinflammatory cytokines, in the airway fluid of premature infants are all associated with the later development of BPD.[69,75-80] Other, noncytokine, proinflammatory molecules, such as leukotrienes, thromboxanes, and complement components are also elevated within the first 7–10 days after birth in infants who later develop BPD.[76,81]

3.2 Architectural Disruption

One of the presumed results of the influx of granulocytes into the lung is cellular injury and destruction due to release of reactive oxygen species and proteases from the inflammatory cells. The lung protease/antiprotease balance appears to be tilted toward proteolysis in infants who develop BPD. Although lung fluid levels of elastase are increased in the first few days after birth in many premature infants with RDS, some investigators have found

that infants who will develop BPD have higher elastase levels.[70,82] In animal models of BPD, elastin deposition is also disturbed, with increased deposition and abnormal distribution.[83] In addition, α1-protease inhibitor levels rise concurrently with elastase levels in the infants who will recover from RDS, but are depressed in infants who go on to develop BPD.[70] Infants who later develop BPD also secrete higher amounts of elastin degradation products in their urine, indicating ongoing proteolysis.[84]

3.3 Fibroproliferation

The mechanism of fibrosis in BPD remains an active area of research. Mice that specifically over-express the fibrogenic growth factor, transforming growth factor (TGF)-β, in the lung epithelium during development have been shown to suffer an arrest of lung development in the pseudoglandular stage.[85] Smooth muscle actin (a marker for myofibroblasts) is increased in the lung mesenchyma and collagen I gene expression rises in the distal airways of these animals.[85] This suggests that TGFβ has a major inhibitory effect on lung development, in addition to any specific fibrogenic effect. TGFβ has been sought in the lung fluid of infants at risk for BPD. Some, but not all, studies have found evidence of increased levels of TGFβ in premature infants who go on to develop BPD.[86-88] Mice over-expressing another fibrogenic growth factor, TGFα, in the lung epithelium suffer progressive alveolar enlargement and fibrosis of the lung after birth.[89] Lungs of mice deficient for TGFα are protected from bleomycin-induced fibrosis.[90] Studies designed to detect this growth factor in human infants have not been performed.

3.4 Disordered/Delayed Development

The arrest of lung development in the absence of prominent signs of inflammation or fibrosis is one of the hallmarks of the 'new' BPD.[9] The process of lung development is thought to be controlled by a balance between stimulatory and inhibitory factors, two of the most prominent being endogenous glucocorticoids and TGFβ.[19,91] Glucocorticoids at physiologic levels encourage the maturation of parenchymal structures and lung functions such as surfactant production and lung water clearance.[91] Endogenous retinoids may also promote lung septation.[19] TGFβ appears to inhibit many of these same aspects of maturation.[85,92]

In experimental animal studies, any number of factors, including hyperoxia, hypoxia, mechanical ventilation, and poor nutrition, can decrease lung septation.[93] The final common pathway for these events is unclear. In mice, over-expression of a number of cytokines, including TNFα, TGFα, IL-11, and IL-6 can lead to a decrease in alveolar number.[89,94-96] Paradoxically, deficiency of the epidermal growth factor receptor (which binds, among other factors, TGFα) also leads to decreased alveolar numbers.[97] Unlike the apparently beneficial and important maturational effects of endogenous glucocorticoids, supraphysiologic doses of glucocorticoids also significantly inhibit alveolarization in experimental animal studies.[98] The administration of pharmacologic doses of tretinoin can ameliorate glucocorticoid- or oxygen-induced decreases in lung septation.[98,99] A great deal of work remains to delineate the interaction of signals that promote normal lung development, much less to understand the specific derangements of these signals that result in the altered alveolarization seen in BPD.

While the lung epithelium is derived from embryonic endoderm, the lung vasculature arises from the mesoderm.[100] The lung microvasculature arises *de novo* from the mesenchyme underlying the airways and apposes itself progressively more closely to the epithelium as development progresses. This process is guided in part by vascular growth factors, such as vascular epithelial growth factor (VEGF), elaborated by the epithelium.[100] Both in human infants with BPD and in animal models of BPD, vascular development is arrested in much the same way as is septation.[13,101,102] Epithelial VEGF expression is decreased in animal models and in humans with BPD,[102-104] and some studies have indicated that infants who later develop BPD have lower levels of VEGF in lung fluid during the first 10 days after birth.[105] Inhibitors of angiogenesis inhibit alveolarization of the lung, leading to the suggestion that inhibited angiogenesis may be one of the causes of inhibited septation in BPD.[19,106] Mesodermally derived myofibroblasts are also important in lung development. Myofibroblast-deficient animals do not alveolarize their lungs.[107]

Neuroendocrine cells in the developing lung, contributed by the embryonic ectoderm, are also affected by lung injury.[108] Neuroendocrine hyperplasia occurs in human infants with BPD and in animal models of BPD, suggesting that all tissue types in the lung may be affected in BPD.[19,108,109] Inhibition of neuroendocrine cell products known as bombesin-like peptides has been shown to inhibit lung injury in a baboon model of BPD.[109]

4. Etiology

The etiology of BPD is complex and multifactorial (figure 3). Several authors have recently reviewed in depth varying aspects of the etiology.[8,9,16,110-112] Some of the major factors involved are briefly outlined in this section.

4.1 Animal Models

Much of our understanding of the etiologic agents of BPD has, of necessity, been gained from animal models of the disease. In newborn animals, oxygen exposure alone mimics many of the

pathologic findings of BPD.[112-117] However, it is unclear whether oxygen stress replicates the pathogenesis of BPD or merely produces similar effects through unrelated or partially related mechanisms. Other investigators have reported that hypoxia will also delay alveolar development.[118] Similarly, high-volume mechanical ventilation alone can reproduce some aspects of BPD.[119] On the other hand, administration of continuous positive airway pressure to weanling ferrets appears to accelerate normal lung growth, suggesting that the effects of respiratory support on lung injury may be complex.[120]

Animal models that combine the factors of prematurity, mechanical ventilation, and controlled oxygen exposure have made it possible to begin to separate out the various factors involved.[101] In a full-term, ventilated neonatal piglet model, Davis and colleagues[119] compared animals treated with hyperoxia and hyperventilation with those treated with hyperoxic/normocarbic ventilation, hyperventilation alone, or normoxic/normocarbic ventilation. After 48 hours of exposure to experimental conditions, the hyperoxic/hyperventilated animals showed the most biochemical and pathologic evidence of damage. Animals treated with hyperoxia alone displayed less damage than hyperoxic/hyperventilated animals, but more damage than animals treated with hyperventilation alone. Normoxic/normocarbic ventilated animals showed the least damage. Delemos and colleagues,[121] in a ventilated premature baboon model, showed that baboons delivered at 75% of gestation and exposed to ventilation with hyperoxia developed pathologic findings consistent with severe BPD. Animals ventilated with oxygen only as needed to maintain normal arterial oxygen concentrations had significantly less damage. However, baboons delivered at 67% of gestation will develop alveolar hypoplasia and variable saccular wall fibrosis even if managed with the minimum necessary mechanical ventilation and inspired fraction of oxygen.[122] The pathology is very similar to that seen in human infants born at <1000g, and may mimic the pathogenesis of the 'new' BPD.

In summary, the animal data support the contribution of each member of the triad of prematurity, mechanical ventilation, and oxygen administration implicated in the original description of BPD.[1] Extremes of either hyperoxia or hyperventilation are likely to be able to recreate the disease. As the degree of immaturity increases, lung injury is likely to occur with lower amounts of oxygen administration or mechanical ventilation. Lung injury models using extremely immature animals subjected to minimal ventilatory support may best replicate the pathogenesis of the 'new' BPD currently seen in premature infants.

4.2 Prematurity

Although full-term infants exposed to high levels of mechanical ventilation or oxygen can develop BPD, the disease is largely limited to premature infants, with smaller premature infants predominating.[11] This is particularly true of the 'new' BPD. The lung of an extremely premature infant born at 24–28 weeks' gestation is just leaving the cannalicular stage of lung development and entering the saccular stage.[16] True alveolarization has yet to occur. Injury during that stage of development appears very likely to lead to the arrest of development described as the hallmark of the 'new' BPD.[9]

4.3 Genetics

Genetic traits may either predispose certain infants to BPD or worsen the disease when it develops. Gender and racial differences have been described in airway function in preterm infants.[123] A family history of asthma is associated with symptomatic BPD, as is the presence of the HLA-A2 haplotype.[23,124] Recent studies suggest that a family history of asthma may exacerbate existing BPD, rather than being a separate causal factor.[125] Twin studies suggest a genetic predisposition to BPD (odds ratio of 12.3 for a second twin having BPD if the first twin was affected).[126] Genetic polymorphisms in the surfactant protein A gene are associated both with the development of RDS and with the presence of BPD at 28 days of age.[127,128] Levels of some cytokines, such as TGFβ, show sexual dimorphism in premature infants, and may affect the incidence or severity of BPD.[19,88]

4.4 Oxygen/Oxidant Stress

The evidence that higher levels of oxygen directly cause the development or worsening of BPD in humans has until recently been circumstantial. The presence of lipid peroxidation products in lung lavage has been linked to the later development of BPD.[129,130] However, other investigators have found that protein peroxidation products in tracheal aspirates are generally associated with very low birthweight, but not specifically with subsequent development of BPD.[131,132] In a comparison of practices among several centers, Van Marter and colleagues[133] reported that infants exposed to higher levels of inspired oxygen on the first day of life were more likely to develop BPD at 36 weeks' PMA. However, arterial oxygen measurements did not differ between infants who developed BPD and those who did not, suggesting that oxygen exposure may be a result of initial disease severity, making it difficult to isolate an independent causative effect of inspired oxygen concentrations on BPD.

A recent trial, STOP-ROP (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity), provided perhaps

the most direct evidence that inspired oxygen may be related to severity of BPD.[134] In this trial, 649 infants with pre-threshold retinopathy of prematurity were randomized to receive sufficient oxygen to maintain target arterial oxygen saturation at either 89–94% (conventional group) or 96–99% (supplemental group). Average inspired oxygen concentrations (FiO_2) rose 0.05–0.10 in the supplemental group following randomization. More infants in the supplemental than the conventional group required diuretics or supplemental oxygen therapy at 50 weeks' PMA. The different oxygen saturation targets did not explain the increased oxygen requirement at 50 weeks' PMA. Infants in the supplemental group were also more likely to develop exacerbation of their BPD.

4.5 Ventilator-Induced Lung Injury

In a study of human infants who died of BPD, the length of time on mechanical ventilation correlated better with severity of outcome than did either gestational age at birth or length of time with >60% oxygen.[135] Mechanical ventilation of the surfactant-deficient lung poses risks of both 'atelectrauma' from the repeated closing and opening of lung units with poor surface tension, and 'volutrauma' from overdistention and rupture of more compliant lung units.[10,136] The physiology of ventilator-associated lung injury in newborns has recently been reviewed extensively.[10,136,137] Aggressive ventilation may predispose to volutrauma.[137] In a multicenter study of 235 infants born at 751–1000g, the best predictors of the later development of BPD (defined as oxygen requirement at 30 days of age) were male sex and lower arterial partial pressure of CO_2 ($PaCO_2$) at 48 hours of age.[138] Infants whose highest $PaCO_2$ at 48 or 96 hours was <5.3 kPa (40mm Hg) were about 1.5 times as likely to develop BPD than infants whose highest $PaCO_2$ was >6.7 kPa (50mm Hg). In the same study, the center-to-center incidence of BPD was also correlated with mean $PaCO_2$ levels among infants in each center at 48 and 96 hours of age. Even short durations of low $PaCO_2$ have been associated with the later development of BPD. In a study that examined $PaCO_2$ levels in 188 infants born at ≤1700g with RDS in the hours (average, 6 hours) before they received surfactant, infants with a $PaCO_2$ ≤3.9 kPa (29mm Hg), 4.0–5.2 kPa (30–39mm Hg), and ≥5.3 (40mm Hg) had sequentially lower likelihoods of developing BPD at 36 weeks' PMA (odds ratios of 5.6, 3.3, and 1.0, respectively).[139] Evidence from human adults with acute RDS suggests directly that lower tidal volume ventilation (6 mL/kg, rather than 12 mL/kg) mitigates lung injury and decreases mortality.[140]

Animal studies have confirmed that increases in lung volume (volutrauma), rather than increased pressures used in ventilation ('barotrauma') result in lung injury. Young rabbits whose chest wall motion is limited by casting and who are subsequently exposed to high inspiratory pressure do not develop lung injury.[141] Even short periods (30 minutes) of high tidal volume ventilation produce lung injury in premature lambs.[142] Ventilation with low positive end expiratory pressure (PEEP) creates atelectrauma in animal models and also results in lung injury.[143] Premature lambs exhibit lung injury following as few as six high-volume manual breaths delivered without PEEP.[144]

4.6 Infection

Both prenatal and postnatal infections increase the risk of BPD.[6,81,145] Low-grade, ascending infection of the chorioamnion is likely a major cause of premature labor and birth.[146] Intrauterine infection appears to decrease the risk of RDS, but increases the risk of BPD in intubated premature infants.[81,147,148] This effect may be mediated through the production of IL-1, which may mature some lung functions, but also provides a powerful proinflammatory stimulus.[81] Similar accelerated lung maturation has been described in fetal animals exposed to intra-amniotic injection of either endotoxin or IL-1α.[149,150] Episodes of systemic sepsis in newborns have also been associated with the later development of BPD.[6,145]

Infection with the intracellular parasite *Ureaplasma urealyticum* appears specifically to be related to a risk of later development of BPD.[151] Several investigators have found an association between respiratory colonization of premature infants with *U. urealyticum* and later development of BPD, with the pooled odds ratio estimated at 1.7.[152-155] This association seems strongest in infants born at <1000g.[154] The organism often seems to be acquired *in utero*.[154] Like intrauterine infection in general, *U. urealyticum* colonization seems to confer protection against RDS while increasing the risk of BPD.[153] The relationship between *U. urealyticum* colonization and BPD seems to hold in the surfactant era.[156,157] Lending further credence to the hypothesis that the organism is indeed pathogenic, premature baboons experimentally infected with *U. urealyticum* developed a bronchiolitis similar to that seen in human infants with severe BPD.[151,158]

4.7 Other Factors

Symptomatic patent ductus arteriosus (PDA) has also been associated with the later development of BPD.[6,145] Both PDA and systemic infection increase serum levels of proinflammatory cytokines and prostaglandin F1α.[145] When these conditions are present together, the risk of BPD is further increased.[145] It has been suggested that lungs smaller than expected for age may be a risk factor for BPD.[159] Maternal tobacco use affects lung function in premature infants as young as 30–33 weeks' gestation, and may be

an exacerbating factor in BPD.[16,160] Even the plasticizers in endotracheal tubes, which can cause cellular toxicity, have been suggested as possible etiologic contributors to BPD.[161]

5. Strategies for the Prevention of Bronchopulmonary Dysplasia (BPD)

This section reviews therapies that may prevent the development of BPD. Some of these strategies, while not attaining the goal of complete prevention, may lessen the severity of the disease when it does develop.

5.1 Prevention of Prematurity

Given the importance of extreme prematurity in the pathogenesis of the 'new' BPD, the clearest preventive measure for BPD is the prevention of prematurity itself. Some approaches to this, such as treatment of bacterial vaginosis during pregnancy, have been shown to hold promise by some investigators, but have not been supported by others.[162-164] Treatment of maternal *U. urealyticum* colonization has also been unsuccessful in preventing preterm birth.[165]

Recently, weekly injections of 17 α-hydroxyprogesterone during pregnancy have been shown to reduce the risk of recurrent preterm delivery by about one third in women with a previous spontaneous preterm delivery.[166] However, secular trends, such as increasing numbers of multiple pregnancies, presumably due to assisted reproductive technologies, are driving up the overall rate of prematurity.[167] The proportion of the US birth cohort born prematurely in 2000 was 11.6%, part of a pattern of steady increase from 9.4% in 1981.[167] As a result, the major burden of prevention of BPD is likely to continue to lie in the treatment of infants with lung disease.

5.2 Prenatal Treatments

Several treatments have been used to promote lung maturation in fetuses at risk of lung injury. The prenatal administration of glucocorticoids promotes maturation of the surfactant system and decreases the risk of RDS by 40–50%.[168] However, although some investigators have shown a decrease in the incidence of severe BPD, it is less clear that prenatal glucocorticoid use affects the overall rate of BPD.[168,169] Van Marter and colleagues[169] found, in a retrospective analysis of 223 intubated infants of <1751g in birthweight, that infants whose mothers had not received antenatal glucocorticoids were at increased risk of developing BPD at 28 days of age compared with infants of those mothers who had received antenatal glucocorticoids (odds ratio of 3.0). Recent systematic review of the topic, however, has not substantiated this benefit.[168] More than one course of prenatal glucocorticoids during pregnancy does not appear to further decrease the rate of RDS.[170-172] Indeed, some studies suggest that multiple courses may lead to lower birthweights and may increase the incidence of severe BPD.[170,171] The apparently paradoxical effect of multiple doses of glucocorticoids is in keeping with animal data that suggest that while some glucocorticoid effect is needed for normal lung development, additional glucocorticoids inhibit normal lung maturation.[91,98,173-175] A recent NIH Consensus Conference recommended that a single antenatal course of betamethasone should continue to be used routinely in women at risk for preterm delivery, but that repetitive courses of glucocorticoids should not be used routinely outside of clinical trials.[176] These trials are currently underway.

Thyrotropin-releasing hormone (TRH) has also been proposed as a method of achieving accelerated intrauterine lung maturation. However, in a large clinical trial involving 996 women, prenatal TRH given in addition to prenatal glucocorticoids was no more effective in preventing RDS or the composite outcome of death or BPD at 28 days of age than using glucocorticoids alone.[177]

5.3 Surfactant Therapy

Exogenous surfactant replacement significantly improves pulmonary mechanics in the surfactant-deficient lung, and protects the lung against ventilator-induced lung damage.[142] Exogenous surfactants have significantly decreased the severity of and mortality from RDS among intubated infants.[178]

However, this major improvement in the treatment of acute lung injury has not been fully reflected in the incidence of BPD.[10] Several early trials of exogenous surfactant found an improvement in the likelihood of survival without BPD among surfactant-treated infants, a finding supported by systematic review.[178-181] However, some of these infants were relatively large (over 1000–1250g). More recent estimates of BPD at 28 days of age have continued to place the rate at about 40% among surviving infants born at 500–1000g who initially required mechanical ventilation.[6,10] Although this represents an improvement over the 72% rate of BPD at 28 days reported in one study among 177 surviving nonsurfactant-treated infants born at 600–1000g, surfactant therapy clearly has not abolished the disease.[179] It has been argued that since surfactant has disproportionately improved the survival of the smallest premature infants, who are at the greatest risk for BPD, the population of infants with BPD has been shifted toward smaller infants.[10,179] Surfactant therapy may also reduce the severity of BPD in those infants who develop the disease.[10,111] This has been difficult to quantify, as the effects on survival have altered the demographics of babies with BPD.

5.4 Postnatal Glucocorticoids

The use of glucocorticoids postnatally to prevent the development of BPD is a tale of triumph and tragedy. In a landmark study in 1989, Cummings and colleagues[182] treated 36 infants with a high risk of BPD (≤1250g in birthweight and ≤ 30 weeks' gestation), who remained on mechanical ventilation at 14 days of age. A prolonged, 42-day, tapering course of dexamethasone resulted in faster weaning from the ventilator and supplemental oxygen. Their results also suggested improved long-term developmental outcome. Prolonged courses of glucocorticoids, however, result in significant adverse effects, including hypertension, hyperglycemia, gastrointestinal bleeding, hypertrophic cardiomyopathy, and infection.[183]

Subsequent studies focused on earlier, less intense, and shorter courses to try to obtain the same benefit with fewer adverse effects.[184,185] Courses begun either in the second week of life or as early as the first day after birth were effective in decreasing BPD.[184,185] Even systemic courses as short as two doses given over the first 36 hours after birth spared the later use of prolonged courses of glucocorticoids.[186] However, the improvement in the rate of BPD came at a high cost in other areas. A study in 220 infants 501–1000g in birthweight of stress-dose dexamethasone beginning within the first 24 hours after birth and weaning over 10 days revealed an increased incidence of gastrointestinal perforation and poorer growth in dexamethasone-treated infants.[187] Follow-up studies of both prolonged (42 days) and shorter courses of glucocorticoids revealed a more than 2-fold increased risk of neurodevelopmental abnormalities, especially cerebral palsy.[183,185,188,189] Even a 3-day course of dexamethasone 0.25 mg/kg/dose twice daily beginning at 12 hours of age in infants 500–2000g in birthweight resulted in an increased risk of cerebral palsy (odds ratio of 4.6) in treated infants among 159 survivors studied at a mean age of 53 months.[190] A recent preliminary report of a school-age follow-up of 158 premature infants from a trial of a tapering 28-day course of dexamethasone begun at <12 hours of age showed that poorer somatic growth and poorer neuromotor and cognitive outcomes persisted through to 8 years of age in dexamethasone-treated children.[191,192] Animal data also suggest that postnatal glucocorticoid treatment limits lung growth and maturation, perhaps adversely affecting the very organ the drugs are being used to treat.[98,175,193] As a result, the American Academy of Pediatrics currently does not recommend the routine use of systemic dexamethasone for the prevention or treatment of BPD outside of the context of randomized, controlled clinical trials.[183]

The search for a method to capture the beneficial effects of glucocorticoids without also garnering the adverse effects continues. Success has been reported in decreasing death or BPD at 36 weeks' PMA in a study of 78 infants ≤1500g in birthweight using short, 3-day 'pulses' of dexamethasone beginning at 7 days of age, with minimal acute adverse effects.[194] However, a long-term follow-up of the cohort in which that regimen was tested is lacking, and a similar 'pulse' given in the first 3 days of life has been shown to result in an increased risk of cerebral palsy.[190]

Adrenal insufficiency in preterm infants has been linked to an increased incidence of BPD, again reinforcing the concept of a 'correct' amount of glucocorticoid effect for normal lung function and development.[195] A pilot trial in 40 infants born at <1000g using low doses of hydrocortisone designed to replace deficient adrenocortical output resulted in an improvement in survival without BPD at 36 weeks' PMA in treated infants.[196] However, a multicenter trial underway to test this concept further was recently stopped early due to concerns about glucocorticoid-related complications. Inhaled glucocorticoids have also been used in an attempt to gain local effects while sparing systemic effects. Although a recent systematic review found no effect of inhaled glucocorticoids initiated within the first 2 weeks of life on the incidence of BPD, they did appear to decrease the use of later systemic glucocorticoids.[197]

5.5 Anti-inflammatory Agents/Bronchodilators

One of the major proposed mechanisms for the actions of glucocorticoids has been their anti-inflammatory properties. Viscardi and colleagues[198] evaluated the anti-inflammatory agent, cromolyn sodium (sodium cromoglycate), begun at 3 days of age in a study of 26 infants at high risk for BPD. Although cromolyn sodium treatment decreased levels of lung proinflammatory cytokines, it did not affect the incidence of BPD at 28 days of age. Although both systemic and inhaled bronchodilators have been used extensively in the treatment of established BPD (see section 6.3), there are few studies examining their use for BPD prophylaxis. A recent systematic review identified only one randomized controlled trial of a bronchodilator, inhaled albuterol (salbutamol), for BPD prevention.[199,200] Among 173 infants born at <31 weeks' gestation at risk for BPD, albuterol was ineffective in preventing BPD at 28 days of age.

5.6 Closure of the Ductus Arteriosus

Premature infants who develop a persistently PDA are at increased risk for BPD.[6,145] Early studies comparing surgical ligation of the PDA to expectant management showed improved lung compliance after PDA ligation, and shorter hospital and ventilator courses in infants undergoing ligation.[201,202] Systematic review confirms the effectiveness of indometacin (indomethacin)-induced

PDA closure in preventing the development of BPD, and also suggests that earlier therapy (when symptoms of PDA first appear) may be more effective in preventing pulmonary morbidity than therapy commencing after signs of congestive heart failure are present.[203] Prophylactic therapy with indometacin did not appear to decrease the incidence of oxygen requirement at 36 weeks' PMA in a study of 1202 infants of 500–999g in birthweight, despite reducing the incidence of symptomatic PDA.[204] With the easy availability and high efficacy of indometacin for PDA closure, prompt medical or surgical closure of symptomatic PDA is a reasonable method of BPD prevention.

5.7 Fluid Management

Capillary leak and pulmonary edema are part of the constellation of neonatal lung injury. Both retrospective studies and a controlled clinical trial have suggested that fluid limitation may help to prevent BPD at 28 days of age.[205,206] However, the peak fluid intake in the controlled trial 'high fluid group' (200 mL/kg/day after the first week) was quite elevated, while the fluid-restricted group was allowed an intake (150 mL/kg/day after the first week) that many might consider standard rather than restricted.[206] It is difficult to predict whether additional benefit would accrue from further fluid restriction.

Loop diuretics, such as furosemide (frusemide), have been evaluated for their ability to prevent BPD. Furosemide appears to have a direct effect on pulmonary fluid balance in addition to its renal effects.[207] Systemic administration of furosemide has favorable acute effects on pulmonary mechanics and the alveolar-arterial oxygen gradient, but when given to premature infants <3 weeks old it has no consistent effect on the later incidence of BPD.[208] Aerosolized furosemide also improves pulmonary compliance, but its prophylactic use to prevent BPD has been insufficiently studied to draw any conclusions.[209,210] The data on distal tubular diuretics, such as chlorothiazide and spironolactone, are insufficient to determine whether they effectively prevent the later development of BPD.[211]

5.8 Treatment of Infection

Systemic sepsis increases the risk of BPD.[6,145] Since systemic sepsis also carries significant morbidity and mortality, treatment is justified, regardless of the effects on the later development of BPD. More contentious is the issue of whether treatment of neonatal colonization with organisms associated with BPD, such as *U. urealyticum*, will prevent later development of the disease. A recent controlled study of 7 days of prophylactic intravenous erythromycin from the day of birth in 75 ventilated, premature infants born at <30 weeks' gestation and at risk for *U. urealyticum* infection showed no effect of erythromycin treatment on BPD at 36 weeks' PMA.[212] However, the incidence of *U. urealyticum* colonization in the study population was only 13%, making the power to detect a difference in BPD quite low. Further research is needed in this area.

5.9 Nutrition

Premature infants are born with limited caloric and micronutrient reserves. Undernutrition in animal models impairs lung growth and repair, tolerance of oxidant stress, and resistance to infection, all crucial elements in the development of BPD.[213] While adequate caloric intake is likely to be important for lung growth, a recent study of aggressive enteral and parenteral nutrition did not support a preventive effect on BPD.[214] Among 125 infants <1500g at birth, the risk of BPD at 28 days of age did not differ between the 'aggressive nutrition group' (which received an average of about 100 kcal/kg/day by 7 days of age) and the control group (about 65 kcal/kg/day at 7 days of age). Early administration of intravenous polyunsaturated fatty acids in a study of 133 infants born at 600–1000g also failed to protect against BPD (defined as oxygen requirement for at least 28 of the first 60 days after birth).[215]

Two more specific nutritional interventions have shown some promise for preventing BPD. In animal models, retinoids preserve alveolarization in the face of lung injury.[99] Premature infants who develop BPD have lower retinol levels compared with control individuals.[216] Clinical trials of retinol supplementation (intramuscular 2000–5000IU three to four times a week) in premature infants have suggested that it can lower the incidence of the later development of BPD.[217,218] A recent study showed a decrease in death or BPD at 36 weeks' PMA from 62% to 55% among 807 initially ventilated infants of 401–1000g in birthweight.[217] A systematic review of the retinol data concluded that the therapy was associated with reductions in death or oxygen requirement in very low birthweight infants at 1 month of age, and in oxygen requirement among infants born at <1000g who survive to 36 weeks' PMA.[219] Inositol supplementation has also been reported to increase survival without BPD at 28 days among infants <2000g in birthweight with initial respiratory distress.[220,221] This conclusion was supported by a systematic review of inositol therapy.[222] However, the effects on respiratory function were seen only among infants who had not received surfactant therapy, suggesting that the effects of inositol were overshadowed by the improvements engendered by surfactant.[221]

5.10 Antioxidant Therapy

The use of antioxidants has been proposed as a method to counteract the oxidant stress that may contribute to BPD. Recombinant human copper-zinc superoxide dismutase (SOD) has been administered intratracheally to 33 premature infants of 700–1300g in birthweight, beginning shortly after initial surfactant treatment and continuing for up to 14 days.[223] Although the treatment increased lung SOD levels and decreased markers of acute lung injury, it had no effect on clinical outcomes during the initial hospitalization. Preliminary re-evaluation of the same infants at 1 year of age suggested that the SOD-treated infants had a decreased need for respiratory medications.[224]

Tocopherol, administered parenterally to premature infants, also does not reduce the risk of BPD.[225] Although the use of other antioxidants, such as glutathione, has been suggested, there are no human trials of these agents for the prevention of BPD.[19]

5.11 Strategies of Mechanical Ventilation

Despite extensive research, the definition of the 'best' way to manage ventilation of the premature infant remains elusive. Jobe and Ikegami[226] have commented that "the field is clouded by strong opinions and weak experimental observations that have not been blinded." Indeed, many strategies have been suggested, but few have withstood the rigor of randomized clinical trials.

5.11.1 Limitation of Inspired Oxygen

The results of the STOP-ROP study suggest that elevation of FiO_2 may result in an increase in BPD.[134] A comparison between British centers that used FiO_2 sufficient to keep infants' pulse oximetry values between 88–98% and those using target levels of 70–90% showed that, among infants born at <28 weeks' gestation, the incidence of continued supplemental oxygen use at 36 weeks' PMA was 48% in 'high target' centers and 18% in 'low target' centers.[227] However, it is also clear that chronic hypoxia can be associated with cor pulmonale and poor growth.[23] The ideal target for oxygenation in infants at risk for BPD remains to be determined.

5.11.2 Positive End Expiratory Pressure

The ideal PEEP in a patient on positive-pressure ventilation maintains an adequate functional residual capacity without risking chronic overdistention of lung units. In preterm lambs treated with exogenous surfactant, a PEEP of 0.4 kPa (4cm H_2O) was less injurious than a PEEP of 0 kPa (0cm H_2O) or a PEEP of 0.7 kPa (7cm H_2O). Whether the same is true in human premature infants remains unknown. Limited human studies performed on 12 mechanically ventilated premature infants with RDS in the pre-surfactant era showed that systemic oxygen delivery and arterial oxygenation were optimal at a PEEP of 0.6 kPa (6cm H_2O).[228] However, there are no data on the effect of PEEP changes alone on human lung injury.

5.11.3 Patient Triggered/Synchronized Ventilation

With the introduction of microprocessor-controlled ventilators and flow transducers sensitive enough to sense a premature infant's respiratory effort, it became possible to synchronize ventilator breaths to an infant's breathing pattern. These modes have been variously called 'synchronized' or 'patient-triggered'. Early studies suggested that synchronized ventilation speeded weaning from the ventilator compared with nonsynchronized ventilation.[229,230] However, both a recent systematic review and a large, international, randomized controlled trial detected no difference in the incidence of BPD at 28 days between synchronized and nonsynchronized modes of ventilation.[231,232] Although continued improvements in conventional mechanical ventilator design may eventually yield improvements in the incidence of BPD, the promise of this technology has not yet been realized.

5.11.4 Low-Tidal-Volume Ventilation

A number of animal studies have suggested that high-tidal-volume ventilation is injurious to the lung.[142,233] This has led to the suggestion of 'gentle' ventilation, with tidal volumes limited to 5–7 mL/kg in premature infants.[8] A recent publication compared methods of ventilation between two groups of preterm lambs during a 3-week study.[234] 'High-tidal-volume animals' were ventilated with 15 mL/kg at 20 breaths/minute, while 'low-tidal-volume animals' received 6 mL/kg at 60 breaths/minute. Both groups developed classic histologic evidence of BPD. Lung elastin deposition was heavier and secondary saccular crest formation poorer in high-tidal-volume animals, but atelectasis was more pronounced in low-tidal-volume animals. There may be no 'appropriate' tidal volume during mechanical ventilation of the premature infant; all mechanical ventilation may cause lung injury.

5.11.5 High-Frequency Ventilation

Early animal studies suggested that high-frequency ventilation (HFV) in RDS might decrease the incidence of BPD.[235] Recent systematic reviews of both high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) have concluded that both modes of HFV, when used as initial therapy in premature infants with respiratory distress, result in lower incidences of BPD at 36 weeks' PMA compared with conventional mechanical ventilation (CMV).[236,237] However, both modes of HFV, when used according to strategies that promoted atelectasis ('low-volume' strategies), were seen in some,[238,239] but not all,[240,241] studies to result in higher rates of intraventricular hemorrhage (IVH) and/or periventricular leukomalacia (PVL). When used with a 'high-volume' strategy, designed to maintain adequate

lung volumes, both modes appeared largely to avoid higher incidences of IVH and/or PVL.[242-250] In addition, the high-volume strategy appeared to account for most of the effect of HFV on prevention of BPD.

The 9-year pulmonary outcome of a subset of infants from an early low-volume-strategy HFOV trial did not differ between children who had been treated with HFOV or CMV.[251] However, the school-age pulmonary outcome from a high-volume-strategy trial showed that peak expiratory flow, residual lung volume, and distribution of ventilation were closer to normal in HFOV-treated children compared with CMV-treated children.[252] Long-term neurodevelopmental follow-up of an early low-volume-strategy HFOV study suggested that neurodevelopmental outcomes were worse in the HFOV-treated group than in the CMV-treated group.[238] However, subsequent evaluations of long-term neurodevelopmental outcomes from smaller high-volume-strategy HFOV trials at 1 year[236,244] and 5–8 years[252] have not found any differences between infants who received HFOV and CMV. No long-term neurodevelopmental follow-up is available for HFJV studies.

Two recent multicenter trials of high-volume-strategy HFOV came to differing conclusions about BPD prevention. Courtney and colleagues,[253] in a study of 500 infants weighing 601–1200g who had received surfactant and required mechanical ventilation, showed that 56% of infants in the HFOV-treated group and 47% of infants treated with conventional ventilation were alive without BPD at 36 weeks' PMA ($p = 0.046$). Johnson and colleagues,[254] among 797 infants of 23–28 weeks' gestation assigned to HFOV or conventional ventilation within an hour of birth, showed no difference between groups (34% in the HFOV-treated group and 32% in the conventional ventilation group were alive without BPD at 36 weeks' PMA). In neither trial was an increase in intracranial pathology seen in the HFOV-treated group. Other HFV trials have been completed and are awaiting publication.[255] Long-term follow-up of these infants will be crucial.

Although HFV shows some promise for the prevention of BPD, the findings of intracranial pathology and poor neurodevelopmental outcome in survivors of some of the early trials are concerning. Continued attention to long-term follow-up of infants in more recent trials will be needed to confirm that a high-volume strategy obviates concerns about neurodevelopmental outcome.

5.11.6 Nasal Continuous Positive Airway Pressure

Nasal continuous positive airway pressure (NCPAP) has been used as a therapy to treat RDS for decades. It has come into prominence as a possible method for the prevention of BPD based on the low rates of BPD in centers that use NCPAP preferentially for respiratory support in premature infants.[11] At present, studies of its use have been limited to inter-center comparisons and uncontrolled reports of clinical experience.[256-260] Some of these studies have indicated a decrease in the relative rate of BPD by nearly 40% in comparison with retrospectively determined incidence rates.[260] A recent comparison between a center that used NCPAP as the preferred mode of support for premature infants and two other centers that used mechanical ventilation preferentially found, in a multivariate regression, that the best predictor of BPD at 36 weeks' PMA was mechanical ventilation on the day of birth (odds ratio of 13.4).[133]

Other investigators have pointed out that not only NCPAP, but also the type of NCPAP, may be an important variable.[111] 'Bubble' continuous positive airway pressure (CPAP), generated by bubbling gas under a water seal, produces chest wall vibrations that have been likened to those with HFV.[261] Although a small study of intubated infants suggested that 'bubble' CPAP improved respiratory parameters when compared with ventilator-generated CPAP,[261] others have not supported this contention.[262] Despite the circumstantial evidence suggesting that NCPAP may prevent BPD, randomized, controlled clinical trials will be required before the therapy can be recommended. Such trials, including trials where this strategy is begun in the delivery room, are being planned or are underway in the US and internationally.[257,263]

5.11.7 Permissive Hypercapnia

One of the cornerstones of many of the 'gentle ventilation' strategies is to provide adequate oxygenation while providing less ventilation, and presumably, less volutrauma. In a recent study, infants managed at a center preferentially using NCPAP for respiratory support had a higher $PaCO_2$ than infants managed at those tending to use mechanical ventilation.[133]

The effects of varying levels of $PaCO_2$ on the lung and other organ systems have been a topic of some debate. $PaCO_2$ levels below the normal physiologic range of 4.7–6.0 kPa (35–45mm Hg) appear to be highly associated with the development of periventricular leukomalacia and neurologic injury.[137,264,265] $PaCO_2$ levels above the normal physiologic range have been associated with increased intraventricular hemorrhage in uncontrolled human trials and increased proliferative retinopathy in animals.[266-268] However, other investigators have reported brain and lung protection in animals with hypercapnia.[269,270] Sporadic neonatal experience and controlled adult experience have suggested that a strategy of 'permissive hypercapnia' (allowing the $PaCO_2$ to rise above physiologic levels) protects the lung from ventilator-induced injury.[265]

Against this backdrop, two controlled trials of permissive hypercapnia in premature infants have been performed. One small trial enrolled 49 infants 601–1250g at birth, and randomized them

to ventilation that maintained normocapnia ($PaCO_2$ target 4.7–6.0 kPa or 35–45mm Hg) or to permissive hypercapnia ($PaCO_2$ target 6.0–7.3 kPa or 45–55mm Hg).[271] The second study enrolled 220 individuals 501–1000g, who were randomly assigned to routine ventilation ($PaCO_2$ target <6.4 kPa or 48mm Hg) or minimal ventilation ($PaCO_2$ target >6.9 kPa or 52mm Hg).[272] This second study was stopped short of its original intended sample of 532 individuals due to unanticipated adverse events related to dexamethasone therapy in a nested portion of the study. Although the larger trial showed a decrease in the number of individuals requiring ventilator support at 36 weeks' PMA (from 16% in the routine ventilation group to 1% in the minimal ventilation group), neither study showed a difference in the rate of BPD between routine ventilation and permissive hypercapnia. A systematic review of the same data also did not show an effect of permissive hypercapnia on BPD at 36 weeks' PMA.[273]

6. Strategies for the Treatment of BPD

Most strategies for the treatment of established BPD are aimed at relieving symptoms. However, many of the treatments have significant side effects of their own, including the potential to worsen the very disease they are aimed at managing. As a result, the management of established BPD becomes a complex act of balancing risk and benefit, with treatment strategies tailored to the stage and severity of the disease in each patient.

6.1 Oxygen/Vasodilators

Infants with severe BPD have an element of pulmonary hypertension, which can in extreme cases lead to cor pulmonale and death.[23] Oxygen is a well described pulmonary vasodilator. In 15 individuals with severe BPD studied by cardiac catheterization, oxygen therapy decreased pulmonary artery pressures, resulting in normal pressures in five children.[24] Limited evidence suggests that PaO_2 levels >7.3 kPa (55mm Hg) may be most effective in avoiding pulmonary hypertension in infants with established BPD.[274] Oxygen therapy may also alleviate respiratory symptoms and promote growth in chronically hypoxic infants with BPD.[23]

Systemic administration of nifedipine in six infants with BPD and pulmonary hypertension decreased pulmonary vascular resistance and improved cardiac output.[275] In a phase II trial, inhaled nitric oxide, which acts as a specific pulmonary vasodilator, improved oxygenation in 11 of 16 intubated infants with severe BPD.[276]

6.2 Diuretics

Diuretics have been used for decades to manage the pulmonary edema that is part of BPD. A single dose of systemic furosemide improves airway resistance and lung compliance in infants with BPD.[208,277] Chronic administration of furosemide improves oxygenation and lung compliance in infants with established BPD.[208] A small study of 17 infants with BPD suggested that furosemide (1 mg/kg/12 hours intravenously or 2 mg/kg/12 hours orally) may also hasten ventilator weaning when compared with placebo.[278] However, in light of the paucity of controlled trials in this area, a recent systematic review concluded that routine use of furosemide could not be recommended in BPD.[208] A single dose of inhaled furosemide also improves pulmonary mechanics, but data are lacking on its long term administration.[210] Furosemide also has significant metabolic side effects, ranging from displacing bilirubin from albumin at high doses to decreased weight gain, ototoxicity, hypercalciuria, and electrolyte abnormalities.[23,279]

Distal tubular diuretic (thiazides and spironolactone) use in BPD has also been the subject of recent systematic review.[211] A 1-week course of these diuretics was shown to improve pulmonary function in some studies, but not in others.[280,281] A 4-week course improved pulmonary function and decreased the need for concomitant furosemide use in a study of 43 infants with BPD.[282] In addition, in a study of 19 intubated patients, oxygen requirement and survival improved in those infants receiving a 4-week course of a thiazide diuretic and spironolactone.[283] Although distal tubular diuretics may also cause significant electrolyte abnormalities, the incidence rates of nephrocalcinosis and hearing loss do not appear to be increased by these drugs.[23,282]

6.3 Anti-inflammatories/Bronchodilators

Both systemic and inhaled bronchodilators are often used in established BPD. However, most of the literature on these drugs deals with their short-term effects on pulmonary function, and little new research has been done in the past decade.[23,284] A recent systematic review found no eligible studies examining the long-term outcome of their use in BPD.[199]

The inhaled bronchodilators that have been used in BPD include β-agonists and anticholinergic agents. The inhaled β-agonists isoproterenol (isoprenaline), albuterol, metaproterenol (orciprenaline), and isoetarine all result in acute improvement in airflow.[284-289] Terbutaline, another β-agonist, improved short-term pulmonary mechanics when given subcutaneously to eight premature infants with severe BPD.[290] The inhaled anticholinergic agents atropine and ipratropium bromide also cause bronchodilation and improve pulmonary function in patients with BPD in the short term.[285,287] Long-term efficacy has not been studied for any of these drugs.[199,284]

The inhaled anti-inflammatory agent cromolyn sodium has been studied to a limited extent in intubated infants with establish-

ed BPD. Although cromolyn sodium decreased leukocyte concentrations in lung fluid and improved pulmonary function, there have been no long-term studies of its use in BPD.[291]

The systemic methylxanthines, theophylline and caffeine, have multiple effects, including bronchodilation, respiratory stimulation, a weak diuretic effect, and improvement of muscle contractility.[284] Like other drugs that inhibit phosphodiesterases, they may also have anti-inflammatory effects. These drugs have been shown to improve pulmonary function in infants with BPD, and this improvement is additive with the effects of diuretics.[292,293] Although there have been case reports attributing improved weaning of infants from mechanical ventilation to the use of theophylline, long-term studies of methylxanthine effectiveness in BPD have not been performed.[294,295] The respiratory stimulatory effects of the methylxanthines can obscure underlying apnea and complicate decisions regarding the discontinuation of cardiorespiratory monitoring.[23] In addition, methylxanthines may have significant side effects, such as gastroesophageal reflux that may complicate the management of premature infants.

6.4 Mucolytics

There have been several case reports of the use of the mucolytic DNase (dornase-α) intratracheally or by nebulization to relieve the mucus plugging that occurs in BPD. Dornase-α appears to improve radiographic evidence of plugging and to decrease oxygen requirements.[296,297] No randomized trials of this therapy have been performed.

6.5 Nutrition

Although undernutrition and poor protein intake may increase susceptibility of the premature lung to injury, it is less clear that achieving optimal nutrition can speed lung repair.[19] Infants with BPD often need caloric intakes of 120–180 kcal/kg/day to achieve optimal growth.[23] In small premature infants whose parents choose not to breastfeed, calorically dense infant formulas lead to faster growth than routine formulas.[298,299] Similar formulas do not always promote sustained growth improvement in infants with BPD. In a study of 60 infants with established BPD, Brunton and colleagues[300] provided infants with a high-calorie formula (910 kcal/L), and either protein and mineral intake similar to standard infant formula or an intake enriched in protein and minerals. Infants on the protein- and mineral-enriched formula had better growth during the study period, which lasted until about 3 months of corrected age. However, both groups failed to maintain normal growth after the study period ended.[301] The effect of the regimen on pulmonary recovery was not evaluated. The optimal composition and duration of enriched feedings in infants with BPD remains to be determined.

6.6 Treatment of Infection

In a study of 28 infants born at <30 weeks' gestation colonized with *U. urealyticum*, although erythromycin treatment was effective in reducing colonization, there was no evidence that treatment altered the severity of lung disease.[302]

6.7 Glucocorticoids

The uses of both systemic and inhaled glucocorticoids in infants with established BPD have recently been systematically reviewed.[189,303] Avery and colleagues[304] first reported in 1985 that, among infants with established BPD, intravenous dexamethasone dramatically improved pulmonary function and allowed rapid ventilator weaning. Multiple studies since then have used glucocorticoids in infants with continued ventilatory requirements at 3 weeks of age or older, usually beginning with dexamethasone 0.5–1.0 mg/kg/day, followed by a tapering course, for total durations ranging from 6 to 42 days.[189,305,306] These studies have confirmed improved rates of extubation by 7 or 28 days of treatment, lower rates of death or BPD at 36 weeks' PMA, and fewer dexamethasone-treated babies requiring home oxygen.[189]

Since many of the studies were quite small, it is difficult to determine whether the length of glucocorticoid therapy affected the outcome. The most commonly reported acute adverse effects of therapy included hyperglycemia, glycosuria, and hypertension.[189] Even the largest of the studies lacked the statistical power to detect differences in less common adverse effects such as gastrointestinal bleeding or necrotizing enterocolitis. However, a systematic review showed that severe retinopathy of prematurity was increased in infants who received glucocorticoids.[189] The incidence of abnormal neurologic examination at follow-up was higher in glucocorticoid-treated infants, although cerebral palsy was not significantly increased in glucocorticoid-treated infants.[189] Although systemic glucocorticoids improve lung function and may be life-saving in some instances, the risk of long-term neurodevelopmental sequelae precludes their routine use in BPD.

Inhaled glucocorticoids have been explored as a potential method for delivering anti-inflammatory activity locally without the risks associated with systemic administration. When given to intubated infants with BPD for periods of 1–4 weeks, inhaled glucocorticoids significantly improved the rate of successful extubation during treatment (with a meta-analysis estimating a summary relative risk of remaining intubated of 0.38).[303] Although the studies that measured adrenal function, infection, retinopathy

of prematurity and/or intraventricular hemorrhage generally did not find adverse effects in glucocorticoid-treated infants, the studies were small and lacked the power to detect clinically significant rises above background rates.[307-309] A recent study of adrenal function in premature infants being treated with inhaled glucocorticoids showed decreases in basal cortisol levels, but normal responses to stimulation.[310] Given that there appears to be at least some systemic absorption of inhaled glucocorticoids by premature infants, long-term studies of neurodevelopmental outcomes of treated infants will be of critical importance.

6.8 Prevention of Secondary Disease

Premature infants in general, and infants with BPD in particular, are at increased risk for severe disease with a number of respiratory infections, including pertussis, influenza, RSV infection, and pneumococcal disease.[311] In most cases, premature infants mount an adequate immunologic response to vaccines given at the same postnatal ages as those recommended for full-term infants.[311] Due to the increased risks of vaccine-preventable disease in premature infants, it is particularly important that these infants receive their routine infant vaccines at the recommended postnatal ages, without adjustment of dose or timing (with the exception of the hepatitis B vaccine, for which a differing schedule exists).[312]

The influenza vaccine has recently been added to the list of routine infant immunizations for infants aged 6–24 months.[313] In a study of 1502 children, the monoclonal antibody to RSV (palivizumab) reduced hospitalization from RSV disease by 55% in premature infants under 35 weeks' gestation, and by 39% (from 12.8% to 7.9%) in infants with BPD.[314] Administration of the antibody, which requires monthly injections during the RSV season, should be considered until up to 2 years of age in children with BPD who have required medical therapy for their disease within the 6 months prior to the RSV season.[315]

6.9 Home Care

The home care of infants with BPD is beyond the scope of this review and has been well summarized recently by Farrell and Fiascone.[23]

7. Emerging Therapies

Many promising therapies for BPD prevention or treatment have undergone preliminary testing in animals and/or humans. In addition, modifications of many existing strategies are being tested in ongoing clinical trials. These studies cannot be fully reviewed here. A few agents with specific effects will be mentioned to illustrate active areas of investigation.

7.1 Animal Studies

Treatments aimed at decreasing inflammation by blocking the actions of cytokines, such as the chemokines, which cause neutrophil influx during lung injury in neonatal animals, can result in a striking preservation of lung architecture.[316-318] Agents that promote vascular development, such as IL-13 and VEGF, protect animals from hyperoxia-induced lung injury.[319] The premature baboon model of BPD continues to be used to test potential therapies. Recent studies with an antioxidant metalloporphyrin in premature baboons exposed to 100% oxygen during ventilation showed improvement of the severe architectural derangement those animals otherwise suffer.[320]

7.2 Human Studies

Nitric oxide is an endogenous vasodilator. When inhaled, it acts locally to produce selective pulmonary vasodilation, and may improve ventilation-perfusion matching.[321] The drug may also have anti-inflammatory effects. Several small studies and one large European study have tested the hypothesis that inhaled nitric oxide will prevent BPD in premature infants with respiratory failure.[322-324] A recent systematic review of these studies suggested that inhaled nitric oxide has no effect on the prevention of BPD.[325] However, several other large trials of the therapy are underway.

There are several reports in the literature of the use of ambroxol, a drug with mucokinetic, secretagogue and surfactant stimulatory effects, for the prevention and treatment of BPD. It has been used, with some reports of success, in a manner analogous to antenatal glucocorticoids to stimulate surfactant maturation and prevent RDS.[326,327] There is one report of the use of ambroxol in a study of 148 infants born at <30 weeks' gestation who had RDS, which showed a decrease in BPD at 28 days among treated infants.[328]

Pentoxifylline is a methylxanthine with anti-inflammatory and anticytokine effects. In a randomized, controlled trial of 100 individuals, the drug improved survival in newborns with sepsis.[329] A small, uncontrolled trial reported improvement in oxygenation in five infants with BPD.[330]

8. Conclusions

BPD remains one of the major sequelae of premature birth. Despite decades of concerted research, the incidence of the disease has changed little. Some of the lack of improvement in the BPD rate is likely to be explained by the emergence of a 'new', less severe form of the disease that preferentially affects the extremely premature infants now frequently surviving.

Table III. Degree of effectiveness of selected therapies for the prevention or treatment of bronchopulmonary dysplasia (BPD)[19a]

Degree of effectiveness	Strategies for prevention and/or decreasing severity of disease	Treatment strategies
Consistent evidence of beneficial effect[b]	Prevention of prematurity	Oxygen therapy[c]
	Prenatal glucocorticoids, single course (decreases severity)	Inhaled glucocorticoids[c] (earlier extubation)
	Surfactant replacement (decreases severity)	Vaccines against respiratory pathogens (prevents exacerbation)
	Closure of patent ductus arteriosus	
Possible beneficial effect[d]	Low-tidal-volume ventilation	Diuretics (systemic)
	High-frequency ventilation ('high volume' strategy)	Mucolytics
	Improved general nutrition	
	Retinol (vitamin A)	
	Limitation of oxygen	
	Nasal continuous positive airway pressure	
Inadequate evidence to determine effectiveness[e]	Synchronized ventilation	Methylxanthines
	Permissive hypercapnia	Inhaled bronchodilators
	Inositol supplementation	Anti-inflammatory therapies
	Inhaled bronchodilators	Improved general nutrition
	Anti-inflammatory therapies	Treatment of *Ureaplasma urealyticum*
	Antioxidant therapies	Inhaled furosemide
	Treatment of *U. urealyticum*	Inhaled nitric oxide
	Diuretics	
	Fluid limitation	
	Inhaled nitric oxide	
	Inhaled glucocorticoids[c]	
	Systemic glucocorticoids[c] (replacement doses)	
Ineffective[f]	Antenatal TRH	
	Tocopherol (vitamin E)	
Evidence that harmful effects may outweigh benefits[g]	Systemic glucocorticoids (pharmacologic doses)	Systemic glucocorticoids (pharmacologic doses)

a The evidence summarized in this table comes from studies with varying definitions of BPD. The most commonly used definitions were oxygen requirement at 28 days of age and oxygen requirement at 36 weeks' postmenstrual age.

b Consistent controlled clinical trial data and/or very strong observational, animal, and epidemiologic data.

c Significant concerns about safety exist, but these may not outweigh potential benefit.

d Inconsistent controlled clinical trial data and/or strong observational data.

e Conflicting controlled clinical trial data, no evidence of effect in small trials and/or only short-term observational data.

f Controlled clinical trial data of no effect.

g Consistent evidence of harm, despite consistent evidence of benefit.

TRH = thyrotropin-releasing hormone.

The major therapies for the prevention or treatment of BPD focus on diminishing the effects of oxidant injury and mechanical ventilation in the immature lungs of infants with respiratory failure. Few therapies for the disease have 'miraculous' effects, and many of the commonly used therapies have been inadequately tested.

The future of research in BPD will most probably focus on continued, incremental improvements, which are likely to be achieved through the combined effects of many modalities of therapy.

Table III shows the degree of effectiveness of selected therapies for the prevention or treatment of BPD. As implied in the table, the

art of medicine involves the continual balancing of risks and benefits. It has become apparent in recent years, for instance, that the risks of high-dose systemic glucocorticoid therapy in premature infants may outweigh the very significant beneficial effects it has on respiratory parameters in infants at risk for or experiencing BPD. Although BPD is, in itself, a risk factor for poor outcome in premature infants, the application of a potentially injurious therapy may not be justified except in extreme circumstances. Several other therapies, including oxygen itself, are likely to require the clinician to consider both beneficial and detrimental effects. It is, therefore, important to continue to provide firm science, complete with long-term outcome data to aid in decision making.

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Correspondence and offprints: Dr *Carl T. D'Angio*, Box 651, Neonatology, Golisano Children's Hospital at Strong, 601 Elmwood Avenue, Rochester, NY 14642, USA.
E-mail: carl_dangio@urmc.rochester.edu