

Progress in Discovery and Evaluation of Treatments to Prevent Bronchopulmonary Dysplasia

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Key Words

Bronchopulmonary dysplasia · Chronic lung disease · Pulmonary disease · Newborn infant · Evidence-based medicine

Abstract

Background: Recent improvements in the survival of extremely preterm infants have been accompanied by evolution in the pathogenesis and histopathology of bronchopulmonary dysplasia (BPD). Although oxygen and barotrauma-induced injury remain important contribut-

ing factors, pulmonary developmental arrest appears to play an equally important causal role in prolonged respiratory illness, especially among the most immature surviving preterm newborns. To date, clinical trials have failed to demonstrate a substantial benefit of a single treatment or preventive strategy for BPD. **Objectives:** To evaluate the current evidence in favor of treatments that might prevent BPD. **Methods:** Review of clinical studies of preventive treatment strategies for BPD. **Results:** High frequency oscillatory ventilation, permissive hypercapnea, and inhaled nitric oxide might offer benefit to infants at risk of BPD. These and other potential preventive therapies for BPD, such as superoxide dismutase, inositol, and α_1 -proteinase inhibitor, deserve further study. **Conclusions:** Although some current treatments offer promise, no preventive therapy for BPD has proven safe and effective, except for intramuscular vitamin A. Additional studies of respiratory technologies, management strategies, and protective molecules are needed.

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Abbreviations

α -1PI	alpha-1-proteinase inhibitor
BPD	bronchopulmonary dysplasia
CI	confidence interval
CPAP	continuous positive airway pressure
F _i O ₂	fraction of inspired oxygen
HFOV	high-frequency oscillatory ventilation
iNO	inhaled nitric oxide
NICU	neonatal intensive care unit
PaCO ₂	partial pressure of carbon dioxide
PMA	postmenstrual age
RD	risk difference
RR	risk ratio

Introduction

In the seminal description of the pulmonary disorder they termed 'bronchopulmonary dysplasia' (BPD), Northway et al. [1] implicated the barotrauma and oxygen toxicity of mechanical ventilation as the primary causal fac-

tors of lung injury among surviving preterm infants with hyaline membrane disease. Later advances in neonatal therapies, including exogenous surfactant and newer modes of mechanical ventilation, led to improved survival of extremely preterm infants. Rates of BPD, however, have remained relatively constant [2, 3] or have increased and the disorder is no longer limited only to the most severely ill preterm infants [4, 5]. The evolution in the pathogenesis and histopathology of BPD might explain why the search for the optimal preventive strategy for the disorder has proven elusive [6].

The earliest report of BPD [1] described pathognomonic findings of overdistended terminal pulmonary air spaces alternating with areas of atelectasis, prominent interstitial fibrosis, and airway changes of smooth muscle hyperplasia and squamous metaplasia. As increasing numbers of extremely preterm infants survived, the pathologic hallmarks of 'new' BPD became evident: arrested pulmonary development characterized by impaired alveolarization, vascular development [7] and airway growth – findings also observed in the very preterm (125 day) baboon model of BPD [8].

Clinical and laboratory evidence suggest that both prenatal (i.e. the fetal inflammatory response) and neonatal infection and/or inflammation may be involved in the pathogenesis of BPD [9–11]. Chorioamnionitis [12, 13], funisitis [14, 15] and inflammatory markers in amniotic fluid [16–18], cord blood [19] and tracheal secretions of intubated infants [20–23] have repeatedly been linked with BPD. Inflammation might injure the developing lung by a number of potential mechanisms: inflicting direct parenchymal biochemical injury, disrupting the developmental milieu, inhibiting angiogenesis [24, 25] and/or priming the lung for an exaggerated injury in response to subsequent insults such as postnatal infection or prolonged mechanical ventilation [26, 27].

Potentially Modifiable Antecedents

Respiratory Management

The principal goal in supporting the preterm infant with respiratory failure is to provide adequate oxygenation and ventilation without associated pulmonary injury [28]. The advent of exogenous surfactant therapy reduced respiratory associated mortality yet the use of surfactant has not led to lower rates of BPD. Other respiratory technologies and treatment strategies have been designed to offer optimal respiratory support with minimal lung injury, including: continuous positive airway

pressure (CPAP), conventional pressure-limited ventilation with or without synchronization, neonatal pressure-support, volume-targeted, high-frequency ventilation (HFV), permissive hypercapnea and inhaled nitric oxide. None of these technological advances has been shown conclusively to prevent BPD; however, several warrant consideration and further study.

CPAP

Two decades of observational studies have failed to resolve the debate regarding the merits of CPAP with respect to BPD prevention [29, 30]. The deficit in clinical evidence is explained by the lack of completed large-scale clinical trials needed to inform an evidence-based approach to the question of optimal application of the various forms of CPAP technology [31] with or without pretreatment with surfactant [30].

A number of observational studies suggest the use of CPAP rather than mechanical ventilation for neonatal respiratory support might reduce the risk of BPD among preterm infants. Following the report by Avery et al. [29] of substantial variation in crude and risk-adjusted rates of BPD among tertiary care centers and the investigators' suggestion that differential use of CPAP might explain the variability, observational studies were conducted that appeared consistent with this speculation. DeKlerk and DeKlerk [32] reported significantly improved 28-day outcomes (chronic lung disease and death or chronic lung disease) in the era in which CPAP was more often used. Narendran et al. [33] studied the impact of the introduction of bubble CPAP among 171 infants of 401–1,000 g birth weight born at a tertiary care unit during sequential eras (1998–1999 and 2000–2001) and documenting a trend toward 10% improvement in the composite outcome of death or oxygen requirement at 36 weeks with initiation of early nasal bubble CPAP (68 vs. 78%) that did not achieve statistical significance.

Finer et al. [34] recently demonstrated both the feasibility and the challenges of a clinical trial of CPAP initiation in the delivery room among infants born <28 weeks' gestation. Conducting the study at one of the NICHD Neonatal Network centers, the investigators found that 45% required delivery room intubation for resuscitation and 80% required intubation sometime during the first postnatal week; only 20% were not intubated between birth and 7 days of age.

Laboratory evidence provides additional support for the use of CPAP. In a study using the extremely preterm baboon model of BPD, Thomson et al. [35] demonstrated the beneficial effects of chronic CPAP vs. mechanical

ventilation. Electively delivered at 125 days' gestation (after completing two-thirds of the normal 185 days' baboon gestation), the preterm baboon infants were given two doses of surfactant, daily caffeine and were extubated to CPAP at 24 h of age. In contrast to the previously observed evidence of marked pulmonary injury occurring among 125-day premature baboons treated with mechanical ventilation, evaluations at 28 days of the CPAP-treated animals showed very little evidence of pulmonary injury with minimal fibrosis or inflammation and internal surface area, surface-to-volume ratio dimensions and pulmonary compliance similar to 156-day baboon infants.

Permissive Hypercapnea

Barotrauma, volutrauma, and oxygen toxicity are inherent risks of mechanical ventilation. Permissive hypercapnea was conceived as a surrogate indicator of gentle mechanical ventilation. A small randomized controlled clinical trial of permissive hypercapnea to minimize barotrauma and volutrauma, conducted by Mariani et al. [36, 37] studied the effects of 96 h of permissive hypercapnea in 49 infants of 601–1,250 g birth weight with respiratory distress syndrome at <24 h of age. The investigators compared outcomes after hypercapnea [PaCO_2 between 45 and 55 mm Hg (5.9 and 7.2 kPa) and $\text{pH} > 7.20$] vs. normocapnea [PaCO_2 35–45 mm Hg (4.6–5.9 kPa) and $\text{pH} > 7.25$] and detected no differences in respiratory or other clinical outcomes.

The largest study of minimal ventilation to date was reported by Carlo et al. [38] in the NICHD Neonatal Network. Using a factorial design they randomized 220 infants of 501–1,000 g birth weight who required mechanical ventilation at <12 h of age (751–1,000 g birth weight infants also received $\text{F}_i\text{O}_2 \geq 0.30$) to dexamethasone or placebo and minimal ventilation [$\text{PaCO}_2 > 52$ mm Hg (>6.8 kPa)] versus routine ventilation [$\text{PaCO}_2 < 48$ mm Hg (<6.3 kPa)] for 10 days or until extubation. This study had a primary outcome of death or BPD at 36 weeks' postmenstrual age (PMA). The study was terminated at approximately half of the projected enrollment due to gastrointestinal complications attributed to corticosteroid treatment. The reduction in study power might explain the failure to demonstrate a benefit of permissive hypercapnea in BPD prevention; the relative risk of death or BPD at 36 weeks' PMA was 0.93 (95% CI = 0.77–1.12). Post hoc analyses showed that ventilator support was significantly reduced at 36 weeks in the hypercapnea group (1 vs. 16%; $p < 0.01$).

Data from the preterm lamb model of BPD suggested permissive hypercapnea might confer protection not only

by diminished barotrauma but also through anti-inflammatory properties. In laboratory studies of two groups of ventilated preterm lambs subjected to identical peak inspiratory pressures, tidal volumes and inspired oxygen, those that were exposed to supplemental exogenous carbon dioxide to reach targeted PaCO_2 levels ~ 100 mm Hg (13.2 kPa) compared with control lambs [$\text{PaCO}_2 \sim 40$ –50 mm Hg (5.3–6.6 kPa)] showed fewer indicators of pulmonary inflammation (i.e. white blood cells, hydrogen peroxide and IL-1 β and IL-8 mRNA expression), suggesting a beneficial effect of higher PaCO_2 independent of indicators of barotrauma [39].

Volume-Targeted Ventilation

Ventilator modifications introduced in an effort to improve the mechanics of intermittent mandatory ventilation (IMV) include synchronized and assist-control modes as well as volume-targeted ventilation. None has yet consistently proven efficacy in reducing death or BPD. A recent Cochrane meta-analysis of four studies of volume-targeted versus pressure-limited ventilation [40], however, revealed important benefits of volume-targeted ventilation with respect to secondary morbidities. In the meta-analysis of 178 preterm infants, volume-targeted ventilation was associated with a trend toward reduction in BPD that was of borderline statistical significance (RR 0.34; 95% CI 0.11–1.05) and significant reductions in duration of mechanical ventilation, risk of pneumothorax and severe (grade 3 or 4) intraventricular hemorrhage.

High-Frequency Ventilation

Like permissive hypercapnea the two forms of HFV, jet (HFJV) and oscillatory ventilation (HFOV), were developed in an effort to minimize pulmonary injury associated with mechanical ventilation. Large multicenter trials by Courtney et al. [41] and Johnson et al. [42] and a single center study by Van Reempts et al. [43] have made important contributions to the evaluation of high frequency oscillatory ventilation. The three study designs differed substantially and the results of the studies varied. Courtney et al. [41] conducted a multicenter randomized clinical trial of 500 infants of 601–1,200 g birth weight who were hospitalized at one of 26 tertiary neonatal care units in the United States. In this study randomization to HFOV before 4 h of age was associated with a modest improvement in survival without the need for supplemental oxygen at 36 weeks' PMA (i.e. 56% in the HFOV group compared with 47% in infants who received conventional ventilation). No improvements in the composite outcome death or BPD at 36 weeks' PMA were ob-

Table 1. Cochrane systematic reviews of preventive treatments for BPD designated at 36 weeks PMA: all comparisons are with a control or placebo treated group, unless otherwise specified

Therapeutic comparison	Cochrane author(s), year	Trials in meta-analysis	Participants in 36 weeks PMA analyses	BPD at 36 weeks PMA		Death or BPD at 36 weeks PMA	
				risk ratio (95% CI)	risk difference (95% CI)	risk ratio (95% CI)	risk difference (95% CI)
Antioxidants and antiproteinases							
α_1 -Proteinase inhibitor	Shah and Ohlsson, 2005 [103]	2	151	0.64 (0.35, 1.18)	-0.01 (-0.23, 0.03)	0.84 (0.53, 1.34)	-0.06 (-0.20, 0.09)
Superoxide dismutase	Suresh et al., 2001 [104]	1	33	1.0 (0.10, 9.86)	0.0 (-0.21, 0.21)	2.00 (0.25, 15.82)	-
Glucocorticoids							
Early inhaled steroids	Shah et al., 2000 [105]	5	429	0.94 (0.6, 1.48)	-0.009 (-0.076, 0.058)	0.83 (0.61, 1.13)	-0.050 (-0.130, 0.031)
Inhaled budesonide vs. systemic dexamethasone	Shah et al., 2003 [106]	1	278	1.45 (0.99, 2.11)	0.11 (0.00, 0.21)	1.09 (0.88, 1.35)	0.05 (-0.07, 0.16)
Early (<96 h) dexamethasone or hydrocortisone	Halliday et al., 2003 [107]	15	2,415	0.69 (0.60, 0.80)	-0.09 (-0.12, -0.05)	0.86 (0.79, 0.94)	-0.07 (-0.11, -0.03)
Moderately early (7-14 days) dexamethasone	Halliday et al., 2003 [108]	5	247	0.62 (0.47, 0.82)	-0.21 (-0.33, -0.09)	0.63 (0.51, 0.78)	-0.27 (-0.38, -0.15)
Delayed (>3 weeks) dexamethasone	Halliday et al., 2003 [109]	1	118	0.76 (0.58, 1.00)	-0.18 (-0.35, -0.01)	0.73 (0.58, 0.93)	-0.22 (-0.38, -0.07)
Nutritional							
Vitamin A (i.m. or p.o.)	Darlow and Graham, 2002 [74]	2	395	0.87 (0.77, 0.99)	-0.07 (-0.14, -0.01)	0.91 (0.83, 1.00)	-0.06 (-0.12, 0.00)
Respiratory technologies							
CPAP (prophylactic)	Subramaniam et al., 2005 [110]	1	230	2.0 (0.18, 21.75)	0.01 (-0.02, 0.04)	-	-
Synchronized IMV vs. CMV	Greenough et al., 2004 [111]	2	1,310	0.90 (0.75, 1.08)	-0.03 (-0.08, 0.12)	-	-
HFJV (elective) vs. CV	Bhuta and Henderson-Smart, 2000 [46]	2	170	0.59 (0.35, 0.99)	-0.14 (-0.27, -0.01)	0.88 (0.33, 2.34)	-0.03 (-0.22, 0.17)
HFOV (elective) vs. CV	Henderson-Smart et al., 2003 [112]	9	2,026	0.88 (0.79, 0.99)	-0.04 (-0.08, 0.00)	0.92 (0.85, 1.00)	-0.04 (-0.07, 0.00)
iNO	Barrington and Finer, 2006 [113]	7	748, 1,073 ^a	0.89* (0.78, 1.02)	-0.05 (-0.12, -0.01)	0.94 (0.88, 1.01)	-0.04 (-0.10, 0.01)
Respiratory management							
Permissive hypercapnea	Woodgate and Davies, 2001 [37]	1, 2	43, 269 ^a	1.05* (0.16, 6.77)	0.00 (-0.17, 0.18)	0.94 (0.78, 1.15)	-0.03 (-0.14, 0.08)
Antibiotics							
Erythromycin (prophylactic)	Mabanta et al., 2003 [114]	1	75	1.40 (0.72, 2.7)	0.17 (-0.44, 0.78)	1.06 (0.66, 1.69)	0.00 (-0.65, 0.65)

* Among survivors.

^a Risk difference.

served. In the study by Johnson et al. [42], of 797 preterm infants born at 23–28 weeks' gestation who were hospitalized at one of 25 centers in the United Kingdom, Australia and Singapore, no improvements in the composite outcome of death or BPD at 36 weeks' PMA were observed. Similarly, the single center study of 300 infants born before 32 weeks' completed gestation conducted in Belgium by Van Reempts et al. [43] showed no benefit of HFOV over conventional ventilation in ventilator and/or oxygen dependence at 28 days postnatal age or 36 weeks' PMA or secondary outcomes including early intracranial abnormalities, mortality and neurodevelopmental outcomes at 18 months. Differences in the patient population, severity of illness, study protocols, HFOV devices and experience of the operators have been proposed as potential explanations for the variability in results among studies [44].

Substantial heterogeneity among studies of HFOV and/or HFJV versus conventional ventilation has con-

founded the interpretation of meta-analyses. The Cochrane meta-analysis of a group of clinical trials that randomized 1,771 preterm or low-birth-weight infants with respiratory failure to HFOV versus conventional ventilation revealed a reduction in BPD at 36 weeks' PMA of borderline significance (random effects model RR = 0.70; 95% CI = 0.46–1.06) [45] (table 1). Meta-analysis of the three prophylactic studies of HFJV versus conventional ventilation incorporating only 84 subjects from two studies in assessment of 36 weeks' PMA outcomes did show a significant reduction in BPD (RR 0.59, 95% CI 0.35–0.99) [46]. A third meta-analysis of studies of both HFOV and HFJV versus any form of conventional ventilation incorporated 17 randomized trials and a total of 3,776 subjects [47]. The overall analyses showed no benefit of HFV in the composite outcome of death or BPD (RR 0.87; 95% CI 0.75–1.00) or severe intraventricular hemorrhage (RR 1.14, 95% CI 0.96–1.37); the risk of air leak, however, was increased with HFV (RR 1.23, 95% CI

0.96–1.44). Thus, we lack a clear understanding of the population of infants most likely to benefit from HFOV and/or HFJV and the optimal bedside management of HFV technologies.

Inhaled Nitric Oxide

Nitric oxide's capacity to improve ventilation:perfusion (V:Q) matching and its anti-inflammatory [48–54] and antioxidant [55] properties offer potential benefit to the preterm infant at risk of BPD. Early studies of inhaled nitric oxide (iNO) by Kinsella et al. [56], Mercier et al. [57] and Subhedar et al. [58] showed no benefit of iNO for prevention of BPD, either independently or in a Cochrane meta-analysis [59]. Schreiber et al. [60], however, evaluated iNO therapy for BPD prevention in a randomized clinical trial of 207 infants and found a significant reduction in the composite outcome of death or BPD at 36 weeks' PMA among the iNO-treated infants (49 vs. 64%). The magnitude of this effect was greater among infants whose respiratory illness was less severe (oxygenation index <6.94) than others. No adverse effects of iNO were detected with respect to rates of severe intraventricular hemorrhage or periventricular leukomalacia, although the study protocol did not provide standardized assessment of these outcomes. The mortality rates among control subjects in this study population, however, were higher than observed at many other tertiary centers, raising the possibility that the study results might not be generalizable to the wider population of preterm infants. In the 24-month follow-up of 138 (82%) of the 168 survivors to 2 years of age among this study cohort, Mestan et al. [61] found improved outcomes among the iNO-treated group: 24% abnormal neurodevelopment among iNO-treated vs. 46% among placebo-treated subjects. This result was due, in large part, to higher Bayley MDI scores among iNO-treated babies.

In the same journal issue, a report authored by Van Meurs et al. [62] summarized the initial clinical results of a multicenter randomized double-masked placebo-controlled clinical trial of iNO treatment of extremely preterm infants hospitalized at NICHD Neonatal Network centers. This study enrolled 420 newborns born before 34 weeks' gestation at birth weights of 401–1,500 g who exhibited signs of ongoing respiratory failure more than 4 h after receiving exogenous surfactant. The investigators found no difference in the primary outcome between study groups: 80% of the iNO treatment group and 82% of the placebo group died or had evidence of BPD at 36 weeks' PMA (RR: 0.97; 95% CI: 0.86–1.08). There were no apparent effects of iNO treatment on the rates of in-

traventricular hemorrhage or white matter disease. Post hoc analyses suggested that iNO effects differed by birth weight. Among infants above 1,000 g birth weight, iNO was associated with improved primary outcome (i.e. death or BPD); however, infants born at or below their 1,000 g who were treated with iNO had higher rates of mortality and intraventricular hemorrhage than their placebo treated counterparts.

The marked variability in existing study results, suggesting coexistence of beneficial and harmful effects of iNO treatment in the context of the known risks of iNO associated toxicities, warrant a prudent approach to iNO treatment of preterm infants [63, 64].

Antioxidants

Superoxide Dismutase and N-Acetylcysteine

The immature infant's deficiency in endogenous pulmonary antioxidants [65, 66] and multiple sources of exposure to oxidative stress [67] led to consideration of a number of antioxidant therapies to prevent or ameliorate BPD. Human studies of antioxidants have failed to show a benefit in BPD prevention. Although the antioxidant and free radical scavenger N-acetylcysteine recently has been shown to reduce markers of injury in a rat model of endotoxin-mediated acute lung injury [68], a Nordic randomized placebo-controlled clinical trial of 6 days of intravenous treatment with N-acetylcysteine in mechanically ventilated infants of 500–999 g birth weight showed no significant improvement in lung function [69] or reduction in mortality or requirement for supplemental oxygen at 28 days or 36 weeks' PMA [70]. Similarly, in a multicenter randomized clinical trial of intratracheal human copper-zinc superoxide dismutase (CuZnSOD) administered every 48 h for up to a month in mechanically ventilated, extremely preterm infants [71] there was no difference in mortality or 36-week oxygen dependence between the two study groups at 1 year of age. However, the treated infants had lower rates of hospitalization, emergency room visits and treatment with asthma medications, suggesting a potential CuZnSOD-mediated pulmonary benefit that was not evident on the early assessments.

More effective antioxidant therapies now being tested in animals might offer greater short-term benefits. In the moderately preterm baboon model of BPD induced by oxygen toxicity, Chang et al. [72] found that an intravenous infusion of a catalytic antioxidant, metalloporphyrin (AEOL 10113) partially reversed the morphological

changes induced by 100% oxygen exposure and inhibited hyperoxia-induced increases in pulmonary neuroendocrine cells and urine bombesin-like peptide. This compound has yet to be evaluated in clinical trials.

Nutritional Treatments

Vitamin A

Vitamin A enhances epithelial integrity and immunocompetence. In the preterm newborn parenteral vitamin A supplementation by a series of injections three times a week for four weeks conferred a modest reduction (i.e. 7% in the study by Tyson et al. [73]) in rates of supplemental oxygen administration at 36 weeks' PMA. Among infants born at or below 1,000 g an improvement in the composite outcome of death or supplemental oxygen at 36 weeks' PMA [73, 74] was also observed. The benefits of vitamin A in BPD prevention are biologically plausible because retinoic acid regulates both pulmonary development and response to injury. Both normal alveolarization in the mouse [75] and resumption of alveolarization after dexamethasone exposure in the rat [76] appear to be retinoic acid dependent. Furthermore, recent data in the preterm lamb model of BPD suggest that the abnormal proliferation of elastin in response to pulmonary injury is partially antagonized by retinoic acid treatment [77].

Inositol

Endogenous levels of inositol, an essential nutrient, correlate inversely with severity of respiratory distress syndrome in preterm infants. A meta-analysis [78] of three relatively small clinical trials [79–81] in which a total of 307 infants were enrolled suggested that enteral or intravenous inositol supplementation from 5 to 20 days is associated with a reduced rate of BPD (i.e. oxygen dependence at 28 days postnatal age) or mortality and other neonatal complications such as severe retinopathy of prematurity and grade III-IV intraventricular hemorrhage. Larger multicenter clinical trials are needed, however, to more fully evaluate the effectiveness of inositol in BPD prevention.

Proteinase Inhibitors

Alpha-1 Proteinase Inhibitor

Lung injury by proteolytic enzymes accompanies unopposed antioxidant stress, and pulmonary inflammation and disruption of the pulmonary BPD proteinase:

antiproteinase balance has been associated with occurrence of BPD [82, 83]. Rigorously conducted studies of α_1 -proteinase inhibitor (α -1PI), using two different treatment regimens [84, 85], failed to show a benefit of α -1PI as regards mortality or oxygen requirement at 36 weeks' PMA, independently or in a meta-analysis of all 195 infants studied [86]. These results might reflect developmental regulation of matrix metalloproteinases (MMPs) and tissue inhibitor of MMPs (TIMP) that may or may not have a causal relationship to BPD [87, 88]. A number of investigators have suggested that an excess of neutrophil elastase and proteinase:antiproteinase imbalance might be of diminished importance in the pathogenesis of 'new' BPD [89, 90]. However, the benefits of antiproteinase therapy are biologically plausible, the number of infants studied to date is small and no adverse effects of α -1PI treatment have been observed, making α -1PI a preventive therapy for BPD worthy of larger-scale clinical trials.

Glucocorticoids

Low-Dose Hydrocortisone

Antenatal maternal treatment with betamethasone enhances fetal and neonatal surfactant production and reduces the rates of respiratory distress syndrome and other complications of prematurity. The benefits of postnatal dexamethasone treatment however, are substantially offset by complications of treatment (e.g. hypertension, hyperglycemia, growth failure, intestinal perforation) and long-term neurodevelopmental disabilities and therefore they are no longer recommended for routine treatment of preterm infants with evolving BPD [91].

Watterberg and co-workers were the first to report cortisol deficiency [92] and inadequate responses to corticotropin [93] in preterm infants at highest risk of BPD. These investigators conducted a pilot clinical trial showing that early low-dose hydrocortisone treatment [94] was associated with a reduction in BPD among the treated infants [95]. Watterberg et al.'s [96] larger multicenter randomized clinical trial of low-dose hydrocortisone treatment was halted as a result of a higher rate of neonatal complications attributable to the therapy. There was no difference in the BPD-free survival at 36 weeks among the 360 ventilated infants weighing between 500 and 999 g who were enrolled. A beneficial effect of hydrocortisone treatment was observed, however, within the subgroup of infants exposed to chorioamnionitis. Recent data suggest that pretreatment corti-

sol values might be useful to identify infants most likely to benefit from hydrocortisone treatment [97]. It is uncertain whether considerations of safety and research ethics will permit the studies of low dose corticosteroid treatment that are needed to better assess the risks and benefits of this therapy.

Promising Potential Therapies

Late Surfactant Treatment

Secondary surfactant deficiency appears to play a role in the evolution of BPD. Most infants ventilated for a week or more exhibit periods in which dysfunctional surfactant and transient deficiency of surfactant proteins B and C are associated with respiratory deterioration [83]. Late administration of surfactant might ameliorate respiratory signs and reduce the barotrauma, oxygen toxicity and inflammation associated with periods of respiratory deterioration in preterm infants with evolving BPD.

Data from a primate model of lung disease suggest that one of the benefits of iNO treatment is enhanced surfactant protein function [98]. However, it remains to be seen whether this effect will be observed among preterm infants treated with iNO or whether other respiratory therapies such as late surfactant or combined surfactant and iNO treatment might prove useful in preventing BPD.

Cytokines and Other Humoral Factors

Future preventive therapies for BPD are likely to include targeted cytokine or anti-cytokine therapies aimed at upregulating beneficial and blocking harmful humoral factors. An example of one such therapy is antimacrophage chemokine (anti-MCP-1). In a report of anti-MCP-1 treatment in a newborn rat model of lung injury [99] at 1 week, anti-MCP-1-treated rats showed reduced pulmonary macrophages and neutrophils in bronchoalveolar la-

vage fluid, suggesting suppression of harmful inflammatory factors. Other candidates for future therapies include: anti-inflammatory agents (e.g. interleukin-10), surfactant proteins [100], Clara cell secretory protein [101] and bombesin-blocking molecules [72, 102].

Conclusion

The recognition that BPD has evolved from a disorder of pulmonary injury to one with likely prenatal contributions characterized by pulmonary developmental arrest offers new insights and challenges in BPD prevention. We have yet to discover a single highly effective preventative therapy for BPD. Of the currently available alternatives that have been evaluated in single studies and meta-analyses, intramuscular supplementation of vitamin A is the safest treatment proven to be effective. Meta-analysis of pilot studies suggest that inositol is another nutrient that might prove useful in BPD prevention should larger trials support the encouraging early results. Promising potential preventive respiratory therapies warranting further study include: CPAP (i.e. comparison among CPAP devices and against alternate forms of mechanical ventilation), HFOV, permissive hypercapnea and iNO. Larger clinical trials of superoxide dismutase and α -1PI should be considered yet the current data in favor of these therapies are less convincing. Although potentially useful, safety concerns and research ethics currently present substantial obstacles to further study of early low-dose glucocorticoid treatment.

Acknowledgement

The author thanks Jennifer Goode for her assistance in preparing the manuscript.

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