Pharmacological Strategies in the Prevention and Management of Bronchopulmonary Dysplasia

Rajiv Baveja, MD, PhD, and Helen Christou, MD

Bronchopulmonary dysplasia (BPD) is a disease of complex and multifactorial etiology and a major cause of morbidity in premature infants. Contributing factors include infection, exposure to toxic oxygen levels, and ventilator-induced lung injury, resulting in arrested lung development and impaired lung function. Several preventive and therapeutic strategies have been employed and include lung protective ventilator strategies, pharmacological and nutritional interventions. These strategies target different components and stages of the disease process, and their success has been variable. This review intends to bring together prior and current pharmacological interventions and future therapeutic modalities that appear promising in the prevention and management of BPD. Better understanding of the pathogenesis has given hope for newer treatment options. Newer studies need to be designed to assess the efficacy of combination therapies that target multiple steps of the disease process.

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Despite recent advances in newborn medicine, little progress has been made in prevention and treatment of bronchopulmonary dysplasia (BPD). BPD, primarily a disease of extremely low birth weight (ELBW) infants in the surfactant era, evolves over the first few months of life following treatment with mechanical ventilation and oxygen. Although essential for the survival of the premature infant, these therapies are detrimental to normal lung development. Various pharmacological and nonpharmacological approaches have been proposed to prevent or limit the extent of injury. However, none has created a significant impact to limit or cure BPD. Transient responses together with unacceptable side effects make most of the therapies controversial.

The pathophysiology of BPD involves interaction of multiple factors, including toxic oxygen free radicals, ventilator-induced lung injury, and release of inflammatory cytokines and cytotoxic enzymes such as proteases and elastases. Injury at the early developmental stage leads to an arrest of both alveolar and vascular growth. Histopathological changes encompass fewer, larger alveoli and fewer capillaries (alveolar simplification). Compared with "old" BPD described by Northway, "new" BPD is characterized by less airway injury, such as fibrosis, epithelial metaplasia, and scarring. The pharmacologic strategies used in BPD can be categorized based on the process they target: some provide antioxidant protection, others minimize specific aspects of inflammation, reduce proteolytic and elastolytic injury, or regulate growth. In addition, supportive pharmacologic treatments target the development of pulmonary edema, bronchoconstriction, and impaired gas exchange. A comprehensive list of the drugs used in BPD is shown in Table 1. The efficacy of these pharmacologic treatments, mechanism(s) of action, and potential side effects remain incompletely understood. For the purpose of this review, we have examined pharmacologic modalities in published meta-analyses, randomized controlled trials, systematic reviews, and individual clinical studies. We aim to bring together current and potential future pharmacologic approaches in the prevention and management of BPD.

Oxygen

A complicated relationship exists between vascular growth and alveolar development. Judicial use of oxygen to maintain oxygen saturations and pO₂ levels within target range is important in preventing pulmonary hypertension and cor pulmonale in infants with BPD. Although there is general
acceptance that oxygen should be used and monitored as a medication with strict guidelines, there is no agreement on the acceptable level of oxygen saturation below which oxygen should be administered to preterm infants at risk for BPD or to maintain oxygenation in infants with established BPD. Inappropriately high concentrations of oxygen predispose to free radical-induced injury, whereas low oxygen saturations may be associated with poor weight gain and increased pulmonary vascular and airway resistance in infants with established BPD.3

Since oxygen therapy starts in the delivery room, it is worth examining whether the fractional inspired concentration of oxygen used during resuscitation may be related to pulmonary outcome. Beyond the delivery room, controversies further exist regarding acceptable level of oxygenation in preterm infants with established BPD. Askie and colleagues showed in a double-blind randomized trial (BOOST) that there is no benefit in maintaining high oxygen saturation (95% to 98%) compared with standard (91% to 94%) oxygen saturation level in preterm infants.4 There were no differences in growth, neurodevelopmental outcome, or frequency of rehospitalizations at 1 year of age between the two groups. The higher saturation group required longer hospitalization and longer home oxygen therapy. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial indicated a trend toward adverse pulmonary sequelae in patients who were targeted to higher oxygen saturation parameters.5 A higher proportion of infants had longer hospital stays and home oxygen therapy to maintain high saturations at 36 weeks postmenstrual age (PMA) that led to higher cost of care compared with lower saturation group. Because there is lack of consensus among neonatologists regarding criteria for oxygen therapy in infants with BPD, it would be extremely useful to perform further double-blind randomized controlled trials to compare the outcome in low and high saturation groups in terms of evolution of

Table 1  Pharmacological Interventions in the Prevention and Management of BPD

<table>
<thead>
<tr>
<th>Class of Drugs</th>
<th>Effect on</th>
<th>Major Clinical Responses</th>
<th>Major Side Effects</th>
<th>Recommended use in BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Hypoxemia</td>
<td>Improved oxygenation</td>
<td>Longer hospital stay, home oxygen therapy</td>
<td>Maintain saturations &lt;95%</td>
</tr>
<tr>
<td>Diuretics (loop, thiazides)</td>
<td>Pulmonary Edema</td>
<td>Decreased pulmonary edema</td>
<td>Electrolyte imbalance, osteopenia, ototoxicity</td>
<td>Loop: use sparingly in early evolving BPD Thiazides: Consider for judicious chronic use</td>
</tr>
<tr>
<td>Bronchodilators (albuterol, ipratropium)</td>
<td>Bronchospasm</td>
<td>Bronchodilation</td>
<td>Tachycardia, arrhythmias</td>
<td>Limit use in infants with bronchospasm and acute clinical response</td>
</tr>
<tr>
<td>Steroids (early, moderately early, late, inhaled)</td>
<td>Inflammation</td>
<td>Improved oxygenation, earlier extubation</td>
<td>Short term: hyperglycemia, GI perforation Long term: increased risk for cerebral palsy</td>
<td>Last resort therapy for rapidly deteriorating pulmonary status</td>
</tr>
<tr>
<td>Mast cell stabilizer (cromolyn)</td>
<td>Inflammation</td>
<td>No clinical benefit</td>
<td>None reported</td>
<td>Not for routine use</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Impaired lung development</td>
<td>Small reduction in incidence of BPD</td>
<td>None reported</td>
<td>Used in some centers</td>
</tr>
<tr>
<td>Inositol</td>
<td>Impaired lung growth</td>
<td>Decreased incidence of BPD</td>
<td>None reported</td>
<td>Not for routine use</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Impaired lung growth</td>
<td>No clinical benefit</td>
<td>None reported</td>
<td>Not for routine use</td>
</tr>
<tr>
<td>Antioxidants (SOD, NAC, Vitamin E, vitamin C, allopurinol)</td>
<td>Oxidant injury</td>
<td>Delayed benefit from SOD</td>
<td>None reported</td>
<td>Not for routine use</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Inflammation</td>
<td>Ongoing evaluation of safety and efficacy</td>
<td>Ongoing evaluation</td>
<td>Not for routine use</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Infection</td>
<td>No clinical benefit</td>
<td>None reported</td>
<td>Not for routine use</td>
</tr>
<tr>
<td>Antiproteinases ($\alpha1P1$)</td>
<td>Inflammation</td>
<td>No clinical benefit</td>
<td>None reported</td>
<td>Not for routine use</td>
</tr>
</tbody>
</table>
BPD and pulmonary hypertension, growth, and neurodevelopmental outcome. Given the current knowledge, it is probably prudent to restrict oxygen use to maintain oxygen saturations below 95%. Proper arrangements should be made for monitoring and delivery of oxygen at home.

**Diuretics**

Diuretics constitute one of the most common classes of drugs used in the management of BPD. BPD in premature infants is complicated by interstitial alveolar edema. Iatrogenic increase in the fluid intake, capillary leak from inflammation due to infection or from ventilator-induced lung injury, or volume overload due to left to right shunting through a patent ductus arteriosus (PDA) are some of the factors that contribute to pulmonary edema.\(^9\)\(^{\text{-10}}\) The excessive interstitial edema leads to decreased lung compliance and poor lung function.\(^11\) Diuretics potentially benefit by increasing reabsorption of fluid from the lung. The two most common diuretics used in BPD, loop diuretics and thiazides, differ in their primary site of action on the nephron.

**Loop Diuretics**

Loop diuretics act principally by blocking the luminal Na-K-2Cl transporter in the thick ascending limb of the loop of Henle. They appear to compete for the chloride site on this carrier, thereby diminishing net reabsorption, resulting in negative fluid balance. Loop diuretics may improve pulmonary mechanics in patients with lung edema through both diuretic-independent and diuretic-dependent responses.\(^9\) The diuretic-independent response is of immediate onset and occurs through cyclooxygenase-mediated pulmonary vasodilation, decrease in the transpulmonary fluid filtration, increase in interstitial fluid reabsorption, and systemic vasodilation that decreases pulmonary fluid load.\(^9\)\(^{\text{-12-17}}\) Later, the diuretic-dependent response reduces extracellular volume by an increase in the urine output, which, along with higher capacitance of the systemic vessels, decreases filling pressure of the left heart and pulmonary capillaries.\(^9\) A lower hydrostatic pressure and a higher oncotic pressure promote fluid reabsorption in the pulmonary capillaries.\(^9\)\(^{\text{-13,18-20}}\)

Furosemide is the most widely studied loop diuretic in neonates, yet its use remains controversial. A recent meta-analysis has reviewed several trials that studied the risks and benefits of systemic furosemide on preterm infants with BPD.\(^9\) Minimal effect was observed with enteral furosemide in preterm infants <3 weeks of age.\(^21\) Chronic administration of furosemide for a week improved pulmonary compliance, oxygen requirement, and minute ventilation in preterm infants >3 weeks of age with BPD.\(^22,23\) Despite these responses, no beneficial effect was observed in duration of oxygen requirement, weaning off mechanical ventilation, duration of hospital stay, incidence of BPD, long-term outcome, and mortality.

Administration of aerosolized furosemide has also been explored in an effort to minimize systemic side effects in preterm infants with established or developing BPD. A single dose of 1 mg/kg of aerosolized furosemide improved lung compliance at 1 to 2 hours compared with intravenous furosemide or placebo.\(^24,25\) According to the Cochrane meta-analysis of 8 trials with aerosolized furosemide, a single aerosolized dose of furosemide may transiently improve pulmonary mechanics in preterm infants >3 weeks of age.\(^26\) There was no significant pulmonary improvement with chronic administration of aerosolized furosemide. None of these studies examined delivery of the drug to the distal airways or serum levels. Furthermore, the studies had inadequate assessment of clinical outcomes, such as duration of mechanical ventilation, oxygen requirement, length of stay, incidence of BPD, mortality, and complications of treatment.

Furosemide has also been studied in combination with other diuretics. The rationale for combination therapy is that the addition of a second diuretic that acts on a different part of the nephron may overcome the resistance that is seen with long-term use of diuretics due to renal and hormonal compensatory responses. Segar and colleagues compared administration of metolazone and furosemide to furosemide alone.\(^27,28\) Furosemide plus metolazone decreased extracellular fluid similar to the group receiving furosemide alone. The treatment group had a better urine output and lower weight gain, suggesting a lower interstitial fluid volume. Even though a better diuresis was shown in the combined diuretic therapy group, no data exist to show changes in the primary pulmonary and other secondary outcomes. In conclusion, the data on the use of furosemide alone (parenteral or aerosolized) or in combination with other diuretic is limited. Potential risks, such as electrolyte imbalance, ototoxicity, nephrocalcinosis, higher incidence of PDA, and osteopenia, along with inconclusive data on long term primary and secondary outcomes warrant future trials to justify the chronic use of furosemide in current clinical practice. Use of furosemide sparingly to acutely treat pulmonary edema is currently preferred.

**Thiazides**

The second group of diuretics localizes its effects to the early portion of the distal tubule. Benzothiadiazines (thiazides) exert their action by binding to the chloride site of the electroneutral sodium chloride channel. The thiazide diuretic effect is limited since only a very small fraction of filtered sodium absorption occurs in the distal tubule. However, the risk of electrolyte abnormalities is far less with thiazide compared with loop diuretics, which makes it preferable for chronic use.

Six studies on the use of thiazide in preterm infants were reviewed in the Cochrane meta-analysis, and the conclusion is that chronic use of thiazide improves lung mechanics and decreases the need for supplemental furosemide boluses.\(^29\) In a randomized double-blind placebo-controlled trial, thiazide and spironolactone were given to 43 nonintubated BPD patients until they no longer required oxygen supplementation.\(^30\) The study showed decreased oxygen requirement and improved lung function in the treatment group compared with placebo, but failed to show any improvement in the
survival rate, duration of oxygen requirement or length of hospital stay. In intubated patients, a study by Albersheim reported less oxygen requirement and better lung compliance in the treatment group compared with placebo, but with no change in airway resistance. The study further reported less need for furosemide boluses, decreased risk of failure to extubate, and an improvement in the overall survival rate. Administration of thiazide did not decrease the length of hospital stay, need for ventilator support or other long-term outcomes. Addition of potassium-sparing diuretics such as spironolactone, which act exclusively on the Na\(^+\)-K\(^+\)/H\(^+\) exchange mechanisms in the late distal tubule and cortical collecting duct did not alter the compliance or oxygen requirement compared with thiazides alone. More importantly, adding spironolactone did not decrease the risk for sodium or potassium supplementation in patients receiving thiazides. Most studies on the role of thiazide diuretics in the management of BPD were conducted in an era of rapidly changing neonatal practices. Further studies on the role of chronic diuretics in the treatment of BPD may be warranted in this era of antenatal steroids and surfactant therapy to provide definitive evidence of their clinical usefulness. Meanwhile, thiazides are the diuretics of choice in ventilator-dependent infants with evolving or established BPD. Care should be taken to avoid electrolyte abnormalities by appropriate electrolyte supplementation.

**Bronchodilators**

Patients with BPD have increased airway resistance due to smooth muscle hypertrophy and hyperreactivity. Bronchospasm in response to a hypoxic event could lead to sudden deterioration of pulmonary status. Bronchodilators have been used to relieve bronchospasm in asthmatic patients and the potential dilating effect of bronchodilators on hypertrophied muscle of the airways has validated their use in BPD patients. Studies have shown that bronchospasm contributes to elevated pulmonary resistance in preterm infants and bronchodilators improve dynamic compliance by lowering pulmonary resistance.

Bronchodilators have been broadly categorized into adrenergic and anticholinergic agents. Their effect is transient and both have been shown to acutely reduce pulmonary resistance and increase compliance in BPD patients. Variability in individual responsiveness to β-agonists may be genetically determined: β2-adrenergic receptor polymorphisms contribute to variability in responsiveness to β-agonists in children and adults with asthma; this has not been examined in infants with BPD. In the Cochrane database, only one trial addressed the use of bronchodilators for the prevention of BPD and measured long-term outcomes. The study enrolled 173 infants <31 weeks of gestational age who needed ventilatory support at the 10th postnatal day. They were randomized to four groups and received either placebo, placebo with salbutamol, beclomethasone, or both beclomethasone and salbutamol for 28 days. No significant effects of the treatment on incidence or severity of BPD, duration of ventilator support, or oxygen therapy were observed.

Bronchodilators may be administered via nebulizer or aerosol with a spacer device, orally or intravenously. The oral or intravenous route can lead to systemic side effects; therefore, the preferred mode of delivery has been locally via nebulizer or pressurized aerosol. Few trials have studied the most effective mode of delivery for albuterol and compared nebulator versus aerosol in spontaneously breathing or ventilated preterms. Fok and coworkers showed highest delivery to the lower respiratory tract using the ultrasonic nebulizer compared with jet nebulizer or metered dose inhaler with spacer device. Studies by Khalaf and Gappa demonstrated that both MDI-spacer and jet nebulizer are equally effective in improving the pulmonary mechanics. A smaller dose of albuterol and shorter treatment time was required for the MDI-spacer compared with jet nebulizer for a similar clinical response. Importantly, MDI-spacer is a more cost effective option. Irrespective of the mode of delivery, less than 2% of the dose reached the lung periphery. Factors that improved lung deposition included less humidification, use of spacer device with MDI and synchronizing nebulization with inspiration.

The two most widely used bronchodilators are albuterol and ipratropium. Potential side effects of β-sympathomimetic agents include tachycardia, hypokalemia, arrhythmias, and hyperglycemia. Inhaled anticholinergic agents, in addition, decrease gastrointestinal motility and dry and thicken respiratory secretions. Ipratropium has traditionally been used along with albuterol to provide synergism. No trials have yet investigated if a combination therapy of a beta agonist and anticholinergic serve better in BPD than albuterol alone. Future trials are required to study various modes of delivery of the different adrenergic and anticholinergic drugs alone or in combination. Due to paucity of trials and potential side effects, bronchodilator therapy should be limited to infants with evidence of bronchospasm and continued only if there is a clinical response to therapy. Even in these cases, there is no evidence that the long-term outcome is altered.

**Steroids**

Inflammation is a main contributor to the pathogenesis of BPD. Since corticosteroids are potent antiinflammatory agents, there was great promise in the use of steroids for the management of BPD. Systemic steroid administration reduces the inflammatory response, produces a rapid improvement in pulmonary function with better gas exchange, and facilitates weaning from mechanical ventilation. In addition to the antiinflammatory effects, steroids also enhance surfactant production, decrease airway edema, stabilize capillary leakage, augment β adrenergic activity, and decrease overall lung fibrosis. Both systemic and inhaled corticosteroids have been studied extensively in preterm neonates for prevention and treatment of BPD. The steroid trials may be categorized according to the time of administration. Early administration is defined as within 96 hours of birth, moderately early is at 7 to 14 days of life, and late administration is after...
3 weeks of life. Twenty-one randomized controlled trials evaluated effects of early treatment of dexamethasone on the incidence of BPD. Steroids facilitated extubation and decreased the incidence of BPD. However, adverse effects such as hyperglycemia, gastrointestinal perforation, hypertension, infection, steroid-induced cardiomyopathy, long-term neurodevelopmental effects, and growth retardation complicated the treatment. Moderately early administration of dexamethasone (between 7 to 14 days) led to similar decrease in the incidence of BPD and facilitated extubation. Nine trials studied late administration of dexamethasone usually after 3 weeks. These studies showed transient improvement in ventilator-dependent patients, leading to a better success rate at extubation, and reduced the need for later steroid and home oxygen therapy compared with the controls. Both moderately early and late treatments were complicated by short and long-term side effects. The most worrisome long-term effect was increased risk for poor neurological outcome including cerebral palsy. As a result, the European Association of Perinatal Medicine, the American Academy of Pediatrics and the Canadian Pediatric Society have advised against routine use of systemic dexamethasone for the prevention or treatment of BPD. A recently published study reported use of low dose dexamethasone (0.89 mg/kg over 10 days) in preterm infants who were ventilator dependent after 1 week of age. The study showed decreased ventilator requirement, improved oxygenation, and greater percentage of successful extubation in the treatment group compared with placebo. Although the study showed no short-term side effects, such as hypertension or intestinal perforation, it enrolled relatively "older" premature infants (mean gestational age 28-29 weeks). In addition, no data on the long-term neurological outcomes are available for this study. Given the concerns for increased likelihood of poor neurological outcome, dexamethasone is currently reserved for patients with BPD in whom weaning from high ventilator settings and oxygen support is unsuccessful or their respiratory status is rapidly deteriorating.

Recent arguments have questioned the use of dexamethasone in the steroid trials and the possible role of other steroids. Betamethasone, a stereoisomer of dexamethasone, may have a differential role in preterm infants. Both steroid substances act primarily at the nuclear steroid receptor level to modulate gene responses. It has been proposed that preservatives such as sulfites may cause direct neuronal injury and contribute to the neurological side effects associated with dexamethasone. More trials are required to study the role of betamethasone in the prevention and treatment of BPD. Watterberg and colleagues studied the effects of hydrocortisone prophylaxis for early adrenal insufficiency to prevent BPD. The rationale for this treatment was based on the premise that preterm infants are relatively cortisol-deficient and unable to mount an antiinflammatory response to acute stress. Therefore, hydrocortisone at a dose lower than the previous trials mimicking concentrations seen in stressed patients might prevent the development of BPD. Preterm infants weighing less than 1 kg and mechanically ventilated were randomized to receive placebo or hydrocortisone, 1 mg/kg/d for 12 days and then 0.5 mg/kg/d for 3 days. The study showed no significant differences in the survival rates between the two groups. However, among infants exposed to chorioamnionitis, the ones treated with hydrocortisone had significantly lower mortality and improved survival without BPD. There was no suppression of adrenal function or short-term growth but a higher rate of gastrointestinal perforation was seen in the hydrocortisone-treated group receiving indomethacin compared with the placebo group. Additional trials may be warranted to determine the role of low dose hydrocortisone therapy in the prevention of BPD especially in preterm infants born to mothers with chorioamnionitis.

Inhaled steroids have also been tried in an effort to optimize the benefits of corticosteroids and minimize unacceptable systemic side effects. Inhaled steroids have been tried early (<2 weeks of age) to prevent BPD and later to treat established BPD. None of the trials demonstrated significant change on the BPD rate at 28 days or 36 weeks PMA. Trials by Halliday, Suchomski, and Dugas studied the effectiveness of inhaled steroids administered to ventilator-dependent preterm infants after 2 weeks of life. These trials offered no advantage of aerosolized corticosteroids over systemic therapy. Aerosolized steroids did not have any significant effect on the mortality or incidence of BPD, duration of ventilatory support, and oxygen therapy. Major concerns with inhaled corticosteroids included the type of steroids, their dosages, and uncertainty regarding drug delivery. Studies have suggested that delivery of aerosolized particles is limited by the size of the particles, presence or absence of endotracheal tube to facilitate delivery, differences in delivery device (ie, MDI versus spacer), and use of nebulizers. There is some evidence that inhaled steroids are absorbed systemically and thus carry risks similar to systemic steroids. Due to their multiple mechanisms of action, steroids continue to offer promise in the prevention and management of BPD; however, the appropriate dose, timing and size of the glucocorticoid molecule need to be further studied to maximize benefit and minimize risks. These studies must include long-term pulmonary and neurodevelopmental follow-up to determine whether the intervention is safe and effective.

Mast Cell Stabilizer

Cromolyn, a mast cell stabilizer, is the first nonsteroidal antiinflammatory drug used in asthmatic patients. It targets both sensitized and nonsensitized mast cells and prevents degranulation and release of histamine. Mast cell stabilizers have been shown to decrease neutrophil migration and activation, thus minimizing inflammation. Two trials studied the possible role of cromolyn in prevention and treatment of evolving BPD. In the Watterberg study, cromolyn was given 12 hours after intubation, and in the Viscardi study, it was given on the 3rd postnatal day. Although the sample sizes were small, both studies showed no improvement in mortality, days on mechanical ventilation, or incidence of BPD. Cytokine levels were lower in the lung lavage fluid in the treatment group compared with the placebo. These studies, similar to other aerosolized drug studies did not assess drug
delivery, thus failing to provide evidence for effective drug deposition. Currently, cromolyn is not recommended for the prevention or treatment of BPD, but further studies may be warranted.

**Vitamin A**

Vitamin A is essential for the optimal growth of cells and tissues. It is comprised of a group of compounds, which include retinal, retinaldehyde, and retinoic acid. Evidence for low levels of vitamin A in BPD patients along with its role in tissue differentiation and growth supported the hypothesis that vitamin A deficiency may contribute to the development of BPD. Details of the use of vitamin A in BPD have been discussed by Biniwale and Ehrenkrantz elsewhere in this issue. Some units have adopted vitamin A prophylaxis because of the small but significant reduction of the incidence of BPD in very LBW (VLBW) infants. Although the response has been minimal despite a well-characterized mechanism of action and proven deficiency of vitamin A, optimal supplementation may potentially complement a host of other measures to reduce BPD.

**Inositol**

Inositol is a phospholipid that enhances the synthesis and secretion of surfactant phospholipids thereby improving pulmonary function. Hallman and coworkers demonstrated lower oxygen and airway pressure requirements with the use of intravenous inositol in a randomized controlled trial with only few patients receiving surfactant. Cochrane meta-analysis showed that infants who received inositol treatment had significant reduction in death or BPD. No further studies to confirm these findings have been reported. Inositol is not currently recommended for prevention of BPD, but further trials may be warranted in the surfactant era to confirm these preliminary findings and to study the long-term effects.

**Thyroxine**

Preterm infants often have low thyroxine levels detected at the time of initial newborn screening. Since thyroid hormone is essential for the structural and cellular differentiation of the lung and enhances surfactant production, it was hypothesized that thyroxine supplementation would enhance pulmonary maturity, thus lowering the incidence and severity of BPD. A trial conducted by Smith and colleagues administered 10 to 20 μg/kg of thyroxine or placebo to infants <32 weeks gestational age within 48 hours after birth. The study reported no difference in the incidence of BPD or any other benefit with thyroxine replacement compared with the placebo group. As a result, routine treatment with thyroxine is not recommended at present.

**Antioxidants**

**Superoxide Dismutase (SOD)**

Free radicals have been implicated in the pathogenesis of BPD. Premature infants are susceptible to oxidant injury since they are relatively deficient in antioxidant enzymes while being exposed to toxic oxygen levels. Preliminary animal and human studies have provided evidence for a protective action of antioxidants such as SOD in hyperoxia-induced acute and chronic lung injury. A randomized controlled trial studied if recombinant CuZnSOD would decrease the incidence of BPD in ventilated and surfactant-treated preterm infants. This trial enrolled 302 patients and showed that CuZnSOD can be given safely and is well-tolerated intratracheally but found no difference in the primary outcome of BPD at 28 days of life or 36 weeks PMA. The striking result was a significant decrease in several indicators of lung disease over the first year of life. Infants <27 weeks gestation who received CuZnSOD required fewer medications for asthma, had fewer emergency department visits, and fewer hospitalizations, suggesting a delayed beneficial response at 1 year of age. The mechanism underlying this SOD-mediated delayed benefit is unclear, but presumably involves the interruption of a pathogenic cascade that involves reactive oxygen species (ROS). It appears that the role of SOD in the management of BPD may warrant further study. The long-term effect of SOD in other neonatal morbidities as well as the effects of dosage, mode of delivery, frequency, and type of preparation of SOD need to be addressed in future trials.

**N Acetyl-Cysteine (NAC)**

Glutathione is an endogenous scavenger of free radicals, which is relatively deficient in premature infants with decreasing gestational age. Ahola and coworkers proposed use of NAC, a precursor of glutathione, to ameliorate cellular injury from free radicals. Intravenous NAC was administered for the first six postnatal days in a multicenter double blind placebo-controlled trial. In a group of 391 infants weighing under 1000g, no significant differences were found in incidence or severity of BPD between the NAC and placebo groups. A follow-up study showed no significant difference in the lung function between the two groups. Long-term follow-up of these infants will be required to determine potential delayed benefits.

**Tocopherol (Vitamin E) and Ascorbic Acid (Vitamin C)**

Both Vitamins E and C could serve as scavengers of ROS produced during high oxygen exposure and prevent lipid peroxidation. Randomized controlled trials have shown no evidence that vitamin E supplementation alone or in combination with vitamin C offers protection against BPD.

**Allopurinol**

Xanthine oxidase, a key enzyme in purine metabolism, produces ROS during oxidation of hypoxanthine. Allopurinol competitively inhibits the action of xanthine oxidase and effectively counters oxidative stress. In a randomized control trial of 400 infants <32 weeks gestational age, allopurinol given enterally for 7 days showed no improvement in the incidence of BPD at 28 days of age. Although the mechanism is ostensibly well established,
limited success has been achieved using antioxidants therefore their routine use is not recommended at present. Potential limiting factors include radical formation restricted to subcellular compartments, timing, dose and delivery of the drug, or perhaps a need for multiple agents blocking different pathways of ROS. Alternatively, as the SOD trial has shown, lack of acute benefit does not preclude delayed beneficial effects on pulmonary outcome. This underscores the importance of including long-term outcomes in the design of randomized trials of pharmacologic interventions for BPD.

Nitric Oxide
Nitric oxide (NO) is synthesized by nitric oxide synthase found primarily in endothelial and epithelial cells. The role of endogenous NO in the perinatal adaptation of the pulmonary circulation is well established. Inhaled NO has additional beneficial effects, such as bronchodilation and inhibition of pulmonary inflammation, which may potentially contribute to prevention of BPD. The randomized trials of inhaled NO for prevention of BPD in preterm infants have so far yielded conflicting results. Mestan and coworkers reported reduced rate of death or BPD in premature infants treated with inhaled NO and improved cognitive neurodevelopmental outcome at two years of age. Instead, Van Meurs and coworkers reported no significant beneficial response of inhaled NO compared with placebo. In contrast, the study demonstrated worse outcomes with inhaled NO in a subgroup of neonates with birth weights of less than 1000g. Differences in the outcome were attributed to dissimilar patient population in the two studies with sicker and smaller population in the group with no or deleterious effect versus the group that showed beneficial response. More trials are underway to further define the potential role of inhaled NO in preventing BPD and more studies are likely needed to determine the optimal dose, frequency and duration of the therapy. Until these issues are addressed, routine use of inhaled NO in premature infants is not recommended.

Erythromycin
Tracheal colonization with Ureaplasma urealyticum has been linked to inflammation and later development of BPD in mechanically ventilated VLBW infants. Clinical trials of erythromycin in intubated preterm infants to eradicate these organisms and potentially minimize lung injury and reduce the incidence of BPD failed to demonstrate a beneficial effect. A subsequent report suggests that 5 to 10 days of systemic erythromycin treatment often fails to eliminate the organism from the trachea. The question of whether effective elimination of tracheal Ureaplasma urealyticum will reduce the incidence of BPD remains to be answered. Routine use of erythromycins is not recommended.

Antiproteinases
Alpha-1 Proteinase Inhibitor (α1P1)
The rationale for a therapy with exogenous protease inhibitors is to restore protease/antiprotease balance and prevent the development of BPD. Neutrophil-derived elastase has been implicated in the inflammatory process leading to BPD. Influx of neutrophils and increased neutrophil-derived elastases were detected in tracheal aspirates of preterm infants who later developed BPD. The proteinases in the lung tissue can hydrolyze extracellular matrix, and digest surfactant proteins and protective immunoglobulins. Their function is opposed by antiproteases such as α1P1. α1P1 forms a complex with neutrophil elastase and leads to its inactivation through oxidation of a methionine residue. Low functioning levels of α1P1 were detected in preterm infants with RDS who later developed BPD. A single randomized controlled trial conducted to study the effectiveness of α1P1 in preventing BPD enrolled 106 patients weighing 600 to 1250 g. Systemic treatment was initiated in the first week of life (4 doses of intravenous α1P1), and the infants were followed for oxygen dependence at 28 days of age or 36 weeks PMA. No statistically significant difference in the incidence of BPD was found between the treated and the placebo groups. A subsequent report by the same group suggests that a high plasma clearance rate of α1P1 in the neonate may result in inadequate plasma concentrations. In addition, it is unknown whether a delayed benefit might have been observed if the patients were followed longer. α1P1 is currently not recommended for clinical use. Additional studies with varying doses and routes of administration as well as long-term follow-up may be worth pursuing.

Other Potential Therapies
Pentoxifylline
Pentoxifylline is a methylxanthine derivative that has been used in the treatment of peripheral arterial diseases because it improves capillary blood flow by reducing blood viscosity and improving erythrocyte deformability. Pentoxifylline is also a phosphodiesterase inhibitor with antiinflammatory effects that decreases neutrophil sequestration and inhibits neutrophil-derived oxidation products. In rat pups, pentoxifylline reduced fibrin deposition and prolonged survival in experimental hyperoxic lung injury. Lauterbach and coworkers reported a tendency for less oxygen requirement within 3 days of nebulized pentoxifylline in 5 patients. To date no randomized controlled trial has been conducted to study the effects of pentoxifylline in human preterm infants; therefore, this modality is not recommended for clinical use.

Stem Cell Therapy
The therapeutic potential of stem cells is currently being explored for a variety of disorders. Intrinsic qualities of stem cells, such as their capacity to respond, migrate and replace damaged tissue make them an attractive candidate for prevention and repair of neonatal lung injury. In animal models, bone marrow-derived stem cells have been shown to ameliorate injury in heart, brain, kidney, and lung. Transplantation of adult stem cells in mice were shown to differentiate into bronchiolar epithelia and Type 2 pneumocytes. Further studies in animal models of BPD are needed to
address whether stem cells can provide protection by releasing specific growth factors and anti-inflammatory molecules or by repleting different cell types in the developing lung.

**Conclusion**

Well-conducted clinical trials and meta-analyses have demonstrated no significant impact of several pharmacologic therapies. Yet, an alarming number of pharmacologic therapies are currently practiced because of transient beneficial effects and lack of alternatives. The complex and multifactorial nature of BPD makes it unlikely that targeting individual pathways will have a significant impact on outcome. Rather, a multi-drug regimen addressing several pathways simultaneously may have an impact on the incidence and progression of the disease. These pathways are identified through ongoing research focusing on the response of the developing lung to injury. In addition, better understanding of host factors may provide the basis for better patient selection in which a particular therapy may be effective. Strategies to minimize ventilator-induced lung injury, oxygen toxicity and infection as well as ways to optimize nutrition should also continue to be pursued. Finally, long-term pulmonary and general outcomes are essential in the evaluation of potential new therapies.

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**References**

15. Silke B: Central hemodynamic effects of diuretic therapy in chronic heart failure. Cardiovasc Drugs Ther 7:45-53, 1993 (suppl 1)
35. Gappa M, Gartner M, Poets CF, et al: Effects of salbutamol delivery from a metered dose inhaler versus jet nebulizer on dynamic lung...


80. Davis JM, Parad RB, Michele T, et al: Pulmonary outcome at 1 year