Bronchopulmonary Dysplasia: An Update of Current Pharmacologic Therapies and New Approaches

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ABSTRACT: Bronchopulmonary dysplasia (BPD) remains the most prevalent long-term morbidity of surviving extremely preterm infants and is associated with significant health care utilization in infancy and beyond. Recent advances in neonatal care have resulted in improved survival of extremely low birth weight (ELBW) infants; however, the incidence of BPD has not been substantially impacted by novel interventions in this vulnerable population. The multifactorial cause of BPD requires a multi-pronged approach for prevention and treatment. New approaches in assisted ventilation, optimal nutrition, and pharmacologic interventions are currently being evaluated. The focus of this review is the current state of the evidence for pharmacotherapy in BPD. Promising future approaches in need of further study will also be reviewed.

KEYWORDS: Long-term lung disease of prematurity, long-term pulmonary insufficiency

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Introduction

Neonatal preterm birth complications were reported as one of the three leading causes of death globally in children under 5 in 2016.[1] Although advances in neonatal care in the past 20 years have decreased, the frequency of several morbidities associated with prematurity, an increased incidence of bronchopulmonary dysplasia (BPD) is observed, due to, in part, increased survival of very low birth weight (VLBW) infants.[2] Specifically, from 2009 to 2012, BPD was the most common complication of preterm birth for all gestational ages (GAs) from 22 up to 28 weeks, overall affecting ~40% of infants born ⩽28 weeks. There are at least 10 000 new cases of BPD in the United States each year.[3]

Bronchopulmonary dysplasia is characterized by alveolar simplification, arrest in lung growth, impaired vascular development, and abnormal pulmonary function. It occurs in preterm infants receiving mechanical ventilation and supplemental oxygen and ultimately leads to long-term lung disease. Bronchopulmonary dysplasia remains firmly associated with repeated hospitalizations, neurodevelopmental impairment, and significant long-term pulmonary morbidities.[4] Infants with BPD exhibit abnormal pulmonary function and airway hyper-responsiveness and, in some cases, emphysematous changes that persist into adulthood.[5–7] Notably, pulmonary hypertension often complicates moderate to severe BPD and is associated with increased mortality.[8,9] Collectively, BPD is no longer considered a disease restrained to the neonatal period, but a condition with lifelong consequences.

The optimal definition of BPD has evolved as our understanding of pathology and pathophysiology has improved. Oxygen use at 36 weeks' postmenstrual age (PMA) is still the most commonly used criterion to define BPD based on its perceived high accuracy in predicting long-term respiratory outcomes.[10] Per the 2001 National Institute of Child Health and Human Development (NICHD) workshop, BPD is defined as oxygen use for 28 days and there are three severity categories (mild, moderate, and severe) based on oxygen use and/or respiratory support at 36 weeks' PMA (or 56 days of age for infants at ⩾ 32 weeks' GA).[11] More recently, the optimal definition of BPD has been questioned because in some instances, oxygen use at 36 weeks failed to predict long-term respiratory morbidities.[12–14] A recent study by the Canadian Neonatal Network, proposed oxygen/respiratory support at 40 weeks' PMA as the best predictor for serious adverse respiratory outcomes and neurosensory morbidities at 18-21 months.[15] Indeed, a definition accurately predicting long-term respiratory morbidities is critical in evaluating novel approaches for prevention and treatment and for providing optimal respiratory care, nutrition, and medications to these infants.

Multiple pharmacologic and non-pharmacologic treatment strategies have been proposed, aiming to not only support the survival but also minimize further lung injury and facilitate recovery.[16] Aside from protective ventilation strategies, optimal oxygen saturation goals, surfactant supplementation, and the use of antenatal corticosteroids, there has been a lack of efficacy of new therapies. Thus, a re-evaluation of previous therapies has emerged as our understanding of the pathobiology of the disease evolves. Several alternative drug approaches like inhaled nitric oxide and vitamin A supplementation have failed to consistently produce effective clinical outcomes, and most current therapies continue to be supportive.[17–20] Currently, multiple therapies are being studied to characterize their efficacy and safety profiles.

Table 1. Pharmacologic therapies in clinical use.

CLASS	RECOMMENDED DOSE AND DURATION OF TREATMENT	INDICATIONS
Caffeine[21]	Caffeine citrate Loading dose: 20 mg/kg/day IV/PO Maintenance dose: 5-10 mg/kg/day IV/PO Continuation until after discontinuation of respiratory support	Apnea of prematurity Prevention of BPD
Diuretics[22,23]	Furosemide: 1 mg/kg IV or 2 mg/kg PO Hydrochlorothiazide: 20-40 mg/kg/day PO Duration guided by clinical response and adverse effects	Loop: evolving BPD Thiazides: established BPD especially if long-term use is needed
Bronchodilators[24]	Guided by clinical response and adverse effects	Infants with bronchospasm and acute clinical response
Systemic corticosteroids[25–28]	Hydrocortisone: 1.25 mg/kg/day IV/PO Taper based on individual patient Dexamethasone: 0.075 mg/kg/dose IV/PO BID for 3 days (total 0.89 mg/kg over 10 days) Taper based on individual patient Prednisolone: 1 mg/kg PO Prolonged course based on clinical status	Infants older than 14 days with ⩾60% risk for BPD per NICHD outcome estimator Infants with severe BPD, requiring invasive mechanical ventilation beyond 36 weeks' PMA Infants with severe BPD, requiring respiratory support beyond 40 weeks' PMA
Vitamin A[29]	5000 IUs IM thrice weekly for 4 weeks	To ELBW infants requiring ventilator support

Abbreviation: BID, bis in die; BPD, bronchopulmonary dysplasia; ELBW, extremely low birth weight; IM, intramuscular; IV, intravenous; IU, international units; NICHD, National Institute of Child Health and Human Development; PO, per os; PMA, postmenstrual age.

In this review, we present an update in pharmacologic approaches for the prevention and management of BPD and discuss approaches with future potential. We have included data from preclinical studies, human pilot studies, randomized controlled trials (RCTs), meta-analyses, and systematic reviews. In addition, we queried ClinicalTrials.gov for current clinical trials investigating pharmacologic therapies for BPD. Table 1 lists pharmacologic approaches currently in use, and Table 2 contains approaches with future potential in need of further study.

Methylxanthines

Caffeine

The RCT of Caffeine for Apnea of Prematurity (CAP) trial provided unequivocal evidence for the beneficial effects of caffeine in prevention of BPD (reduction of BPD by 36% in infants with VLBW).[21] Moreover, a post-hoc analysis demonstrated that the timing of treatment was also important: BPD was decreased by 52% if caffeine was given on postnatal days 1-3 in comparison with 23% reduction if given after day 3.[49] Although the mechanisms underlying caffeine's protective effect in BPD are incompletely understood, potential contributors include stimulation of breathing, decrease need for mechanical ventilation, and anti-inflammatory and diuretic effects.[50] Of note, Australian former CAP study participants who received caffeine had better lung function test results at 11 years of age compared with controls, suggesting that respiratory benefits are sustained beyond the neonatal period.[51] Caffeine is standard of care for the prevention and treatment of BPD. Dosing is based on the CAP trial (Table 1) and treated infants are being monitored for tachycardia, irritability, feeding intolerance, jitteriness, or seizures. At the time of this review, a phase IV clinical trial is evaluating if administration of caffeine at an earlier time point (2 vs 12 h of life), in infants born ⩽32 weeks, will have an effect on intubation rates.[30]

Pentoxifylline

Pentoxifylline decreases the production of inflammatory cytokines and has significant immunomodulatory properties.[52] In a hyperoxia-induced lung injury rodent model of BPD, animals treated with pentoxifylline had improved survival, increased antioxidant lung enzymes, decreased lung infiltration of inflammatory cells, and improved vascular growth.[53] A pilot study of 150 VLBW infants had shown that nebulized pentoxifylline reduced the risk of BPD.[54] However, a recent RCT in 81 preterm neonates (23-28 weeks GA), demonstrated that nebulized pentoxifylline did not reduce duration of oxygen supplementation.[55] The conflicting data regarding the efficiency of pentoxifylline require large, well-designed clinical trials with standardized ventilation strategies and adjuvant therapies to determine whether there is benefit in the application of pentoxifylline to prevent BPD.

Diuretics. Diuretics are used as symptomatic therapy in the management of BPD. Between 1997 and 2011, about 37% of preterm infants <32 weeks gestation and <1500 g birth weight were exposed to at least one diuretic during their hospital stay in 333 neonatal intensive care units (NICUs) in the United

Table 2. Therapies currently under evaluation.

CLASS	STATUS	INDICATIONS
Caffeine[30]	Phase IV trial in progress evaluating intubation rates if administered at 2 versus 12 HOL	
Furosemide[31]	Phase II trial in progress	Currently in use for evolving BPD
Systemic corticosteroids[32]	Phase II clinical trial evaluating low-dose hydrocortisone in infants requiring mechanical ventilation on DOL 7-14	Routine use not recommended
Inhaled corticosteroids[33]	Phase I/II trial in progress evaluating the safety of escalating doses of budesonide suspended in calfactant	Routine use not recommended. Follow-up on survival and neurodevelopmental outcomes of previous trials have not been reported yet
rhCC10[34]	Phase II trial in progress evaluating survival in ELBW infants	
Surfactant[35–38]	Mode of delivery and combination with other drugs (budesonide/iNO) are currently under investigation	
Inositol[39]	Phase III trial in progress	Preliminary studies showed a reduction in mortality
Cell therapy[40–48]	Five ongoing clinical trials, using mesenchymal stem cells. Three have been completed	Phase I trial demonstrated the drug to be safe with no adverse events when followed at 1 year of age

Abbreviation: BPD, bronchopulmonary dysplasia; DOL, day of life; ELBW, extremely low birth weight; HOL, hours of life; iNO, inhaled nitric oxide; rhCC10, recombinant human club cell 10-kilodalton protein.

States.[56] Premature infants with BPD often experience interstitial and/or alveolar edema due to, at least in part, iatrogenic fluid overload to maintain adequate hydration and nutrition, capillary leak due to pulmonary inflammation or ventilator-induced lung injury, or a patent ductus arteriosus leading to pulmonary overcirculation.[22,57–61] Diuretics improve pulmonary edema and lead to decreased pulmonary vascular resistance and improved lung compliance. The two most commonly used classes in this patient population are loop diuretics and thiazides. Loop diuretics (furosemide most commonly used) cause increased re-absorption of the interstitial fluid, pulmonary vasodilation, decreased filtration of transpulmonary fluid, and systemic vasodilation,[22,62–67] and, via their diuretic function, reduce extracellular volume and ultimately promote fluid re-absorption in the pulmonary capillaries.[65,68–70] Enteral or aerosolized administration of furosemide has been studied. In a Cochrane meta-analysis, enteral administration of furosemide in preterm infants at 3 weeks of age resulted in minimal effect on the incidence of BPD.[22,71–73] In addition, a Cochrane meta-analysis of eight trials of a single dose of aerosolized furosemide in preterm infants >3 weeks of age found only a transient improvement in pulmonary function.[74] Long-term outcomes like duration of mechanical ventilation, oxygen requirement, length of stay, incidence of BPD, mortality, and complications of treatment have not been addressed. In addition, the potential risks of loop diuretics such as electrolyte imbalance, ototoxicity, nephrocalcinosis, and osteopenia, are not negligible and render furosemide usage problematic in this patient population.

Thiazides are less potent than loop diuretics, and trials examining their use in BPD were not always accompanied by improvements in pulmonary mechanics.[75,76] A Cochrane meta-analysis of six studies on the use of thiazides in preterm infants demonstrated improvement in lung mechanics and decreased need for supplemental furosemide boluses.[23] Addition of potassium-sparing diuretics such as spironolactone does not offer improvement to compliance or oxygen requirement compared with thiazides alone and is not recommended.[76] Future trials are warranted to justify the long-term use in current clinical practice and to provide definitive evidence of their clinical usefulness. At the time of this review, an ongoing multicenter clinical trial is studying the safety of furosemide in infants born at <29 weeks GA.[31] In conclusion, current evidence does not support routine use of furosemide for the prevention of BPD. However, symptomatic improvement in the acute management of pulmonary edema justifies its use for selected patients. Similarly, long-term thiazides use for ventilator-dependent infants with established BPD may be warranted on a case-by-case basis.

Bronchodilators. Bronchopulmonary dysplasia has a component of airway pathology, due to hyper-reactivity and airway smooth muscle cell hypertrophy that leads to elevated airway resistance.[11] Since bronchodilators are used to relieve bronchospasm in asthmatic patients and improve dynamic compliance by lowering pulmonary resistance, they have also been used to treat bronchospasm in BPD.[24,77–81] However, the response to treatment is heterogeneous and may be genetically determined or depend on mode of administration.[82–86] Inhaled beta agonists and anticholinergics acutely improve pulmonary function, but two systematic reviews investigating bronchodilator therapy in BPD concluded that there is insufficient evidence to prove long-term pulmonary benefits.[24,87] One trial investigated

prophylactic aminophylline, resulting in significant reduction in BPD at 28 days of life and shorter duration of supplemental oxygen but no significant difference in mortality.[88] Careful interpretation of these data is advised, and additional clinical trials are necessary to assess the role of bronchodilator agents in prophylaxis or treatment of BPD. Moreover, relevant clinical outcomes in addition to pulmonary mechanical outcomes should be addressed in future investigations. Administration should be followed by meticulous assessments of clinical response by examination and measured changes in pulmonary mechanics in conjunction with careful monitoring for tachycardia and arrhythmias.

Corticosteroids. Corticosteroids have been used in BPD as a means to curb inflammatory processes that contribute to disease pathogenesis. Early and late treatment protocols with systemic steroids, different compounds, and alternative modes of delivery have been extensively studied in the preterm population to prevent BPD.[32,89–91]

Systemic corticosteroids

Early <8 days. A meta-analysis of 32 RCTs of early systemic corticosteroids to prevent BPD included in a Cochrane review, revealed that treatment is associated with lower rates of failure to extubate, lower risk of BPD, patent ductus arteriosus, and retinopathy of prematurity (ROP) compared with placebo. Short-term adverse effects included growth failure, gastrointestinal perforation and bleeding, hyperglycemia, hypertension, and hypertrophic cardiomyopathy. Long-term follow-up reports revealed increased risk of abnormal neurodevelopment including cerebral palsy. In subgroup analyses based on the type of corticosteroid used, dexamethasone was shown to have both the most beneficial respiratory effects but also was the most harmful in neurodevelopment. Early systemic hydrocortisone was associated with increased rates of spontaneous intestinal perforation especially when used in combination with indomethacin.[92] The effect of early low-dose hydrocortisone on survival without BPD in extremely preterm infants (PREMILOC study) was assessed in an RCT. Infants born at 24-27 weeks of gestation were randomized to either receive 2×0.5 mg/kg/day hydrocortisone on days 1-7 followed by 3 days 1×0.5 mg/kg/day or placebo in the first 10 days of life.[25] An increased survival without BPD was observed in infants receiving low-dose hydrocortisone compared with infants who received placebo. The beneficial effect of hydrocortisone was more pronounced in female infants. Of note, hydrocortisone was not associated with an increase in adverse events. However, the low dose used in this study mimics physiologic changes through regulating the infants' cortisol concentrations within a normal range.[93] The 2-year follow-up showed no difference in the rates of moderate-to-severe neurodevelopmental impairment or cerebral palsy between the two groups.[94] These studies point to the importance of long-term follow-up into late childhood for the assessment of important effects like neurodevelopment or other effects that cannot be assessed until later in childhood.[26,90]

Late >7 days. A total of 21 RCTs enrolling a total of 1424 participants were included in a Cochrane review assessing late corticosteroid treatment. In these trials, steroid treatment was associated with reductions in extubation failure, BPD, and neonatal mortality. Hyperglycemia, glycosuria, and hypertension were the short-term side effects. In turn, increased rates in severe ROP with no significant increase in blindness were observed long term. There was no difference in the combined rate of death or cerebral palsy, major neurosensory disability, or long-term respiratory health or function, blood pressure or growth between steroid and control groups. Trends toward an increase in cerebral palsy or abnormal neurological examination findings were partly offset by a trend of decreased mortality.[91]

The American Academy of Pediatrics issued a policy statement in 2010 regarding the use of different postnatal steroids in the prevention of BPD, advising against the use of early high-dose dexamethasone, with insufficient data to recommend low dose. At the time, there was insufficient evidence to recommend low-dose hydrocortisone for all infants at risk of BPD or to make a recommendation regarding treatment with high-dose hydrocortisone.[27,95] A short course of prednisolone in preterm infants with established BPD who continue to require invasive or non- invasive ventilation, may be beneficial in weaning off supplemental oxygen. Cessation of supplemental oxygen was possible in a high percentage of infants with a pulmonary acuity score <0.5 or baseline capillary $Pco_2 < 49$ mm Hg treated with prednisolone (16 mg/kg total over 14 days).[28] Notably, infants with a higher pulmonary acuity score or baseline Pco_2 also responded to this therapy 40%-50% of the time. A useful approach for the use of a proven beneficial drug therapy that has a safety concern is to reserve this therapy for those patients at higher risk for moderate to severe BPD, thus minimizing the risk-benefit ratio from the specific treatment. To this end, the BPD predictor described by Laughon et al[20] provides a useful tool to calculate the risk for moderate to severe BPD in individual patients based on the amount of respiratory support at the first week of life and beyond.

At the time of this review, an ongoing clinical trial (StoP-BPD: systemic hydrocortisone to prevent BPD) is evaluating the use of low-dose hydrocortisone between 7 and 14 days after birth in mechanically ventilated preterm infants over a 22-day period.[96]

Topical corticosteroids

Inhaled and intratracheal mode of drug delivery has also been evaluated in an effort to optimize the benefits and minimize the systemic side effects of corticosteroids. A Cochrane review

of early administration of inhaled steroids to VLBW neonates showed decreased incidence of death or long-term lung disease.[97] In addition, a reduction in death/BPD and BPD alone was found in a meta-analysis by Shinwell et al.[98] A multicenter RCT (NEuroSIS: neonatal european study of inhaled steroids) aiming to examine the effect of early administration of inhaled budesonide in preterm infants also showed reduction in death/BPD among budesonide compared with placebo-treated infants.[99] However, there was increased mortality at 2 years of age (19.9% vs 14.5%) in treated infants, with no difference in neurodevelopmental disability.[100] A phase II single-center pilot trial will evaluate if treatment with inhaled budesonide of infants at less than 30 weeks gestation who are on continuous positive airway pressure (CPAP) with ⩾25% FiO2 on day 14 of life or later has any effect on duration of oxygen supplementation, BPD, re-intubation rates, days on mechanical ventilation, and days on CPAP as well as adverse outcomes.[35]

Intratracheal administration of budesonide combined with exogenous surfactant has also been investigated in a randomized study of 265 VLBW premature infants comparing the effects of surfactant or a combination of surfactant and budesonide mixture on BPD. The group receiving surfactant and budesonide had lower rate of death or BPD compared with the control group.[101] Long-term neurodevelopmental outcomes and confirmation of these data in other settings is necessary before recommending this approach. Moreover, currently a trial is evaluating the optimal dose of budesonide re-suspended in calfactant in extremely low gestational age newborns (ELGANs).[33]

Macrolide Antibiotics

Meta-analyses support the association between *Ureaplasma spp.* infection and the development of long-term lung disease in preterm infants hence, the use of antibiotics such as azithromycin, erythromycin, and other macrolides in clinical practice.[102,103] Macrolide antibiotics also have immunomodulatory properties, suppressing lung inflammation.[104] In clinical trials, intubated infants receiving erythromycin did not have reduced risk of BPD.[105] Treatment with azithromycin, a newer macrolide, has shown promise in a meta-analysis demonstrating reduction in BPD and BPD/death in preterm infants when given prophylactically.[106] Clarithromycin treatment was also associated with lower incidence of BPD in premature infants with a BW between 750 to 1250 g in an RCT.[107] Studies combining use of all macrolides in *Ureaplasma*-colonized ventilated preterm infants did not show reduction in BPD or the composite outcome of BPD/death, and routine use of the macrolides for the prevention of BPD is not recommended.[106]

Recombinant Human Club Cell 10-Kilodalton Protein

CC10 is a 10-kD Club cell (previously called Clara cell) secretory protein (CCSP) secreted by bronchiolar epithelial cells. It is one of the most abundant proteins within the fluid lining the lung epithelium and has been shown to be significantly lower in tracheal aspirates of premature infants who subsequently died or developed BPD.[108] In preclinical studies, recombinant human CC10 (rhCC10) is protective in rodent models of lung injury by modulating inflammation, increasing the expression of surfactant proteins and vascular endothelial growth factor and improving respiratory function.[109,110] Levine et al,[111] in a pilot study of 22 VLBW ventilated preterm infants with respiratory distress syndrome (RDS), found no difference in the BPD rates between rhCC10 treated and control infants. Intratracheal administration of rhCC10 was well tolerated and was associated with significant reduction in inflammatory markers in tracheal aspirates.[111] The properties of rhCC10 were further investigated in a multicenter randomized, controlled trial evaluating survival without BPD, but the results have not been reported at the time of this review.[34]

Leukotriene Receptor Antagonist

Leukotrienes (LTs) are potent bronchoconstrictors, promote inflammation, microvascular permeability, and mucus secretion, thus their inhibition has been beneficial in respiratory diseases like asthma.[112] Montelukast, a LT inhibitor, was evaluated in its effect on development of BPD in a pilot clinical trial of 66 VLBW neonates. No difference was observed between the treated and untreated group in the rates of BPD or secondary respiratory outcomes.[113]

Vitamin A

The role of vitamin A in cell differentiation, integrity, and lung growth is well established. VLBW infants have low levels of vitamin A, and intramuscular administration in the first month of life has been confirmed to be beneficial in decreasing mortality and BPD. Neurodevelopmental assessment at 18-22 months of age showed no difference between the groups.[29] Application in clinical practice has been limited, possibly because it is costly and intramuscular administration is painful. Enteral Vitamin A is being studied in an RCT.[114] Infants born at less than 28 weeks' GA and less than 72 hours of life are randomized to receive either enteral water-soluble vitamin A (5000 IU once a day) or placebo, starting within 24 hours of introduction of feeds and continued until 34 weeks' PMA. The effect on the severity of BPD at 36 weeks' PMA based on right-shift of the peripheral oxyhemoglobin saturation versus partial pressure of inspired oxygen (SpO_2-PiO_2) curve will be assessed.

Surfactant

Exogenous surfactant replacement therapy has historically been used shortly after birth for the prevention and treatment of RDS. Recent efforts to further optimize the efficacy of surfactant have focused on preparation, timing, and modes of administration. Specifically, natural and synthetic preparations have been compared for efficiency, and natural surfactants have been shown to be superior.[115] Infants treated with natural surfactant had lower inspired oxygen concentration and ventilator

pressures, decreased mortality, and lower rate of RDS compared with infants treated with synthetic surfactant. In 2012, the US Food and Drug Administration (FDA) approved the first synthetic peptide-containing surfactant (lucinactant); however, the manufacturer has voluntarily discontinued production. Other synthetic surfactants are still in development and at the time of this review, a large multicenter phase II trial of another synthetic surfactant (CHF5633) was completed and is awaiting analysis of the primary outcomes (oxygen requirement, ventilatory support, incidence of BPD, and other major co-morbidities of prematurity).[36] Timing of administration (early vs late) is also of interest, and late surfactant administration continues to be evaluated. Moreover, the combination of surfactant with other drug therapies is being assessed. Notably, a large multicenter clinical trial evaluated 511 ELGANs, who were mechanically ventilated between 7 and 14 days of life and randomized to receive late surfactant for a maximum of 5 doses and inhaled nitric oxide (iNO) versus iNO-alone.[37] No differences were seen by treatment group for the primary outcome, survival without BPD at 36 weeks PMA.[116] However, at 1 year of age, infants who were randomized to receive surfactant and iNO had lower rates of home respiratory support.[117] Neurodevelopmental outcomes of infants in this study have not been reported at the time of this review.

Recognizing that the beneficial effects of surfactant may be offset by the detrimental effects of intubation and prolonged mechanical ventilation, efforts to avoid intubation have focused on alternative methods of delivery, including aerosolized, laryngeal mask airway-aided delivery, minimally invasive or less-invasive techniques via pharyngeal installation and the use of thin intratracheal catheters.[118–124] Administration of surfactant using a small catheter placed in the trachea of infants spontaneously breathing with the aid of Magill forceps under direct laryngoscopy is named less-invasive surfactant administration (LISA). LISA combined with antenatal steroids, early CPAP, and caffeine treatment in the delivery room led to an immediate increase in end-expiratory lung volume and oxygenation.[125–128] In preclinical models, LISA-treated animals had better lung compliance, and despite having lower surfactant deposition, with less being delivered to the right upper lung, oxygenation improved in a similar way to animals that got surfactant via intubation.[129,130] The first RCT of LISA (AMV: avoid mechanical ventilation study) in preterm infants demonstrated less need for mechanical ventilation in the first 72 h and less oxygen need compared with infants who were treated conventionally.[120] Infants treated conventionally in this trial received CPAP, rescue intubation and surfactant if needed. In turn, infants in the intervention group received the same care, but surfactant was administered while spontaneously breathing if they were stable on CPAP with FiO_2 more than 30%. Infants were recruited right after delivery, thus not all required surfactant administration.[120] In another RCT (nonintubated surfactant application [NINSAPP] study) although LISA did not result in a reduction in BPD and/or death, the LISA-treated infants showed a higher rate of survival without major complications (BPD, necrotizing enterocolitis [NEC], pneumothorax, and severe intraventricular hemorrhage [IVH] grade 3/4) compared with the control group.[131] Dargaville et al modified the procedure to a minimally invasive surfactant therapy (MIST), using a rigid adult vascular catheter to avoid the use of Magill forceps. In two observational trials MIST showed similar results to the LISA.[118,132] At the time of this review, a large international multicenter trial (OPTIMIST-A) using this method is currently recruiting.[38]

Surfactant administration via a laryngeal mask versus intubate-surfactant-extubate (INSURE) has also been studied in infants with birth weights >1000 g. Treatment failure was decreased, although this might be due the definition of failure as the need for mechanical ventilation or antagonizing drugs.[112] In the quest for the least invasive method, administration by nebulization is an attractive alternative that may be effective. Minocchieri et al[133] performed a clinical trial randomizing 64 infants born between 29 and 34 weeks' GA to receive bubble nasal continuous positive airway pressure (nCPAP) or bubble nCPAP and nebulized surfactant demonstrating a reduction in intubation rates in the first 3 days of life in the infants receiving nebulized surfactant. Further studies are required to assess efficacy especially in smaller infants.

All in all, systematic reviews and meta-analyses comparing surfactant administration methods for preterm infants have shown that LISA/MIST are superior and associated with a reduction in BPD and/or death[134,135] and these approaches have gained wide acceptance in many NICUs predominantly in Europe. However, pre-medication is a matter of debate and may negate the positive effects of the less-invasive techniques.

Inositol

Inositol is an important component of surfactant; thus, postnatal inositol was given to preterm infants with RDS to support phosphatidylinositol in surfactant synthesis. A Cochrane meta-analysis showed a significant reduction in death compared with untreated controls.[136] The phase II clinical trial of inositol at multiple doses in preterm infants has shown that administration was safe and will proceed to phase III.[39] Inositol is not currently recommended for the prevention of BPD.

Antioxidants

Oxygen supplementation, inflammation, and reperfusion could lead to reactive oxygen species (ROS) production, and these are detrimental in respiratory health, contributing to the pathogenesis of BPD.[137] Intratracheal administration of recombinant human CuZnSOD in VLBW infants failed to demonstrate any difference in death, BPD, and respiratory or neurodevelopmental outcome.[138] However, long-term follow-up showed significant decrease in respiratory morbidities in the treatment group over the first year of life and fewer hospitalizations,

suggesting that the improvement in pulmonary outcomes may be delayed.[14]

Other antioxidants like N-acetyl-cysteine, Vitamins E and C, lutein and zeaxanthins supplementation were not found to be effective and are not currently being evaluated in clinical trials.[139–142]

Pulmonary vasodilators

Inhaled nitric oxide

Infants with BPD are at increased risk for secondary pulmonary hypertension, due to episodes of intermittent hypoxia, causing pulmonary vasoconstriction.[8,143,144] Inhaled NO, a selective pulmonary vasodilator, has gained interest due to its effects on immune modulation and alveolar and vascular growth.[145–148] In 17 clinical RCTs, iNO was administered as either treatment during the first three days of life, routine use in preterm babies along with respiratory support, or later treatment for infants at increased risk for BPD to test its effect on mortality or the incidence of BPD. In a Cochrane systematic review, there was no consistent long-term improvement in mortality or the incidence and severity of BPD when using iNO in preterm infants as a prevention or rescue therapy.[149] Of note, despite not reaching significance, early rescue treatment was associated with a 20% increase in severe IVH. A National Institute of Health (NIH) consensus panel in 2011 concluded that there is insufficient evidence to support the use of iNO in preterm infants in early routine, early rescue, or later rescue regimens.[150,151] In the most recent clinical trial, 451 VLBW neonates born at <30 weeks' GA receiving mechanical ventilation or positive pressure respiratory support on postnatal days 5 to 14 were randomized to be treated with either iNO or placebo. No differences were observed between the two groups at 36 weeks PMA in survival or rates of BPD. No differences were found in respiratory or neurodevelopmental outcomes at the 24 months PMA follow-up between infants treated with iNO or placebo.[152] These findings are consistent with the meta-analyses, the National Institutes of Health's consensus statement and the Committee on Fetus and Newborn statement. Whether iNO therapy has a beneficial effect in BPD-associated pulmonary hypertension requires further study.[143,144]

Sildenafil

Sildenafil promotes pulmonary vasodilation via selective inhibition of phosphodiesterase 5, resulting in increased cyclic guanosine monophosphate (cGMP) levels. Sildenafil treatment in animal models of BPD and diaphragmatic hernia has been shown to be beneficial through mediating alveolar growth, preserving vascular growth, and decreasing pulmonary hypertension.[153–155] Infants that had received sildenafil had reduced pulmonary vascular pressures, and improvement in gas exchange with no adverse effects.[156–159] Although these early studies show that sildenafil is well tolerated, there are concerns regarding drug safety due to increased mortality when administered at higher doses in older children.[160] In addition, prenatal administration of sildenafil in the setting of intrauterine growth restriction resulted in increased mortality in the STRIDER study.[161] It thus appears that there are many unanswered questions about the optimal dosing, timing, and patient selection in the use of sildenafil in this population. At the time of this review, a multicenter phase II clinical trial is being conducted.[162] Infants born at <29 weeks' gestation receiving either positive airway pressure or mechanical ventilation are randomized to receive either sildenafil or placebo for 28 days to assess safety.[162] Despite the lack of data evaluating the efficacy in infants with pulmonary hypertension associated with BPD, in the absence of alternatives, sildenafil still remains a promising therapy. Further studies to elucidate appropriate dose, formulation, and timing of administration in neonates with BPD are warranted.

Dietary Interventions

Omega-3 long-chain polyunsaturated fatty acids

Omega-3 long-chain polyunsaturated fatty acids (LCPUFA), such as docosahexaenoic acid (DHA), are abundant in fish and fish oil and have anti-inflammatory effects.[163] DHA supplementation in rodents has shown to attenuate hyperoxia-induced lung injury.[164] In addition, decreased levels of DHA have been associated with increased incidence of long-term lung disease in premature infants.[165] A meta-analysis that included 18 RCTs, showed that omega-3 LCPUFA supplementation was not associated with a decreased risk of BPD. However, when considering RCTs that included only infants less than 32 weeks GA, the authors found a trend toward reduced BPD rates (pooled relative risk (RR): 0.88, 95% confidence interval (CI): 0.74-1.05, 7 studies, n = 1156 infants).[166] In a recent multicenter RCT, 1273 infants, less than 29 weeks GA, received enteral DHA emulsion or control soy emulsion without DHA until 36 weeks PMA. The intervention did not reduce the risk of BPD; on the contrary, there was an increased risk of BPD using the physiologic definition (need for oxygen supplementation or respiratory support at 36 weeks PMA or discharge home) (RR adjusted for randomization strata: 1.13, 95% CI: 1.02–1.25, $P = 0.02$).[167] Given the biological plausibility of this intervention, it is reasonable to evaluate its role in additional studies.

Citrulline

L-citrulline is an amino acid that is produced from ornithine and carbamoyl phosphate in the urea cycle and as a byproduct of L-arginine metabolism during endogenous NO production in endothelial cells. L-citrulline supplementation ameliorates pulmonary hypertension in both hypoxia and hyperoxia-induced lung injury rodent models.[168,169] In a recent case report of a premature infant born at 25 weeks GA with severe

BPD, L-citrulline supplementation facilitated weaning of respiratory support.[170] There is currently an ongoing phase I clinical trial of L-citrulline for BPD-associated pulmonary hypertension to assess the pharmacokinetic and safety profile in premature infants.[171] At this time, further studies are warranted before L-citrulline can be recommended as a routine treatment for BPD.

Estradiol and Progesterone

Estrogen and progesterone play an important role in lung development and alveolar formation.[172,173] In rodent models, ovariectomy induces loss of alveoli with subsequent reduction of the alveolar surface area and these changes can be rescued by estrogen administration.[172,174] These preclinical studies lead to the suggestion that estrogen and progesterone replacement therapy might be beneficial in preventing BPD. The only RCT to date looking at the effect of estradiol and progesterone replacement therapy on BPD, included 83 infants, less than 29 weeks' GA that received estrogen and progesterone replacement via a continuous infusion and did not demonstrate any significant difference between treatment and placebo groups.[175] Further studies are needed to assess if there is a role of this therapy in prevention of BPD.

Erythropoietin

Erythropoietin (EPO) has been proposed as a potential treatment for BPD due to its antioxidant, anti-inflammatory, and angiogenic effects.[176–178] However, studies in preclinical models of BPD had conflicting results. Although EPO ameliorates hyperoxia-induced lung injury in rodents,[178] a recent study suggested that high-dose EPO can exacerbate ventilator-induced lung injury in premature lambs.[179] An observational study showed decreased incidence of BPD in infants who received EPO for anemia of prematurity,[180] but in a recent meta-analysis of RCTs of early EPO for reduction of red blood cell transfusions in premature and low birth weight infants, the authors did not find any significant differences in the incidence of BPD as a secondary outcome.[181] Until more data become available from RCTs or preclinical models, EPO is not recommended as a routine treatment for prevention of BPD. Currently, a multicenter clinical trial is evaluating whether neonatal EPO treatment of ELGANs will decrease mortality and/or severe neurodevelopmental impairment.[182]

Cell Therapy

A relatively new and promising field in the treatment and prevention of BPD is the therapeutic use of stem cells. Although different stem cell types have been used effectively in preclinical models of BPD, current research focuses on mesenchymal stromal cells (MSCs) due to their multipotent properties, immunomodulatory effects, ease of isolation, and culture.[183] In preclinical models of BPD, MSC treatment has been shown to ameliorate hyperoxia-induced lung injury and vascular remodeling and improve survival.[184,185] The precise mechanisms underlying the effects of MSCs are incompletely understood. The initial theory of MSC engraftment to the lung tissue and replacement of damaged cells has not been proven, and experimental evidence supports that their mechanism of action is through paracrine effects.[186] Studies in experimental BPD showed that administration of conditioned media from MSCs is effective in preventing lung injury,[185,187,188] but a single active component of the MSC secretome responsible for this therapeutic effect has not yet been identified. Ongoing studies on MSC-derived extracellular vesicles or exosomes have shown similar effects with MSCs and conditioned media in ameliorating hyperoxia-induced lung injury.[189] In a recent phase I clinical trial, nine preterm infants with a mean GA of 25.3 ± 0.9 at high risk for BPD received one intratracheal dose of allogeneic human umbilical cord derived MSCs. The therapy was well tolerated with no serious adverse events or toxicity. Bronchopulmonary dysplasia severity and other perinatal adverse outcomes were found to be lower compared with matched controls.[40] A 2-year follow-up of these infants showed no adverse effects on respiratory, growth, and neurodevelopmental outcomes.[41] There are currently five ongoing clinical trials of MSCs for BPD prevention internationally, indicating that there is great promise in cell therapy and MSCs for the treatment and prevention of BPD.[42–48]

Conclusions

Improved understanding of the complex pathogenesis of BPD has led to the development of novel pharmacologic interventions for its prevention and treatment. Some therapies are biologically plausible but have not proven effective in clinical RCTs, while other therapies are effective even though the underlying mechanisms of protection remain unclear. There remains a need to further study biologically plausible therapies and to better understand both disease pathogenesis and mechanisms of action for any proposed pharmacologic intervention. Studies have to include longitudinal follow-up and full characterization of the safety profile for any proposed intervention.

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