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An update on pharmacologic approaches to Bronchopulmonary Dysplasia

Sailaja Ghanta, M.D.,
Division of Newborn Medicine, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Enders 9, Boston, MA 02115, Sailaja.ghanta@childrens.harvard.edu, Tel: (774) 249 8137, Fax: (617) 730-0260

Kristen Tropea Leeman, M.D., and
Division of Newborn Medicine, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Enders 9, Boston, MA 02115, Kristen.tropea@childrens.harvard.edu, Tel: (919) 475 9260, Fax: (617) 730 0222

Helen Christou, M.D.
Division of Newborn Medicine, Brigham and Women's Hospital, Boston Children's Hospital, Harvard Medical School, 75 Francis Street, Thorn 1005, Boston, MA 02115, hchristou@partners.org, Tel: (617) 515 8129, Fax: (617) 582 6026

Abstract

Bronchopulmonary dysplasia (BPD) is the most prevalent long-term morbidity in surviving extremely preterm infants and is linked to increased risk of reactive airways disease, pulmonary hypertension, post-neonatal mortality, and adverse neurodevelopmental outcomes. BPD affects approximately 20% of premature newborns, and up to 60% of premature infants born before 26 completed weeks of gestation. It is characterized by the need for assisted ventilation and/or supplemental oxygen at 36 weeks' postmenstrual age. Approaches to prevention and treatment of BPD have evolved with improved understanding of its pathogenesis. This review will focus on recent advancements and detail current research in pharmacotherapy for BPD. The evidence for both current and potential future experimental therapies will be reviewed in detail. As our understanding of the complex and multifactorial pathophysiology of BPD changes, research into these current and future approaches must continue to evolve.

INTRODUCTION

Mortality rates among very low birth weight (VLBW) infants have declined due to advances in perinatal care[1] but bronchopulmonary dysplasia (BPD) remains a major complication of prematurity resulting in significant mortality and morbidity[2]. Increased survival among VLBW infants contributes to the overall increase in the incidence of BPD. It is estimated that BPD affects up to 54% of infants born at <1000 grams[3]. The long term health consequences of BPD include respiratory disease that can persist into adulthood and increased susceptibility to respiratory infections, asthma, pulmonary hypertension, repeated hospitalizations, neurodevelopmental impairment and increased mortality[4, 5]. The etiology of BPD is multifactorial and includes exposure to mechanical ventilation, oxygen toxicity, infection, and inflammation. These contribute to impaired alveolar development and associated abnormal vascular growth and damage to the distal airways of the highly vulnerable premature lung[5, 6]. Multiple pharmacological and non-pharmacological approaches have been proposed for the prevention or treatment of preterm lung injury and BPD. While antenatal steroids, surfactant, protective ventilation strategies, targeted oxygen saturation goals, caffeine therapy, vitamin A therapy, and optimization of nutrition have helped to modestly improve BPD outcomes, they have also altered the course of BPD. This has led to the re-evaluation of previous therapies as our understanding of pathophysiology grows. Despite this, most current therapies continue to be supportive[2, 7]. While there have been many recent developments in pharmacotherapy for BPD, several therapies remain controversial due to unacceptable side effects and others need to be further optimized before they are widely used.

In this review, we present recent advances in pharmacologic approaches for the prevention and management of BPD, and discuss approaches with future potential. This review is based on published meta-analyses, randomized controlled trials (RCTs), systematic reviews, individual clinical studies and emerging work from animal models of disease. A list of current therapies discussed in this article for prevention and treatment of BPD is presented in Table 1. Table 2 lists the status of the experimental pharmacological agents discussed.

Methylxanthines

Caffeine—The CAP trial has provided unequivocal evidence for the beneficial effects of caffeine on BPD and has been extensively reviewed elsewhere[7-9]. Although the potential mechanism of the effect of caffeine on decreased incidence of BPD remains unknown, given the strength of the evidence, caffeine treatment for prevention of BPD is currently standard of care in most neonatal intensive care units.

Pentoxifylline—Pentoxifylline is a methylxanthine derivative and phosphodiesterase inhibitor that has significant anti-inflammatory action. Newborn rats treated with pentoxifylline and exposed to hyperoxia showed improvements in survival, induction of lung antioxidant enzymes, reduction in fibrin deposition, and reversal of downregulation of vascular endothelial growth factor (VEGF)[10]. A randomized placebo-controlled study of 150 VLBW infants demonstrated a significant reduction in development of BPD among infants who received nebulized pentoxifylline, compared with those who received placebo[11]. Despite these positive findings, there is currently insufficient evidence to recommend its application outside of experimental studies.

Diuretics and Bronchodilators

Diuretics and bronchodilators are two common classes of drugs used in the symptomatic management of BPD. The evidence supporting their use has been reviewed elsewhere[12]. Although these medications target important components of the disease process, studies have shown that responses are variable and often transient[13, 14].

Corticosteroids

Given that inflammation is one of the main contributors to BPD pathogenesis, corticosteroid use makes physiologic sense mainly due to their anti-inflammatory properties. Both systemic and inhaled corticosteroids have been studied extensively in preterm neonates for prevention and treatment of BPD. These clinical trials can be classified as early (<8 days) and late (>7 days) depending on the timing of administration after birth[15-19].

Systemic corticosteroids—The Cochrane meta-analysis review of twenty-eight clinical trials of early systemic steroids revealed that they facilitated extubation and decreased the

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incidence of BPD. However, adverse effects such as hyperglycemia, gastrointestinal perforation, hypertension, infection, steroid-induced cardiomyopathy and long-term neurodevelopmental effects including cerebral palsy complicated the treatment[16]. Another Cochrane meta-analysis reviewed the use of steroids at >7 days in nineteen RCTs. They also noted that steroid treatment was associated with reductions in extubation faliure as well as BPD. The trends towards an increase in cerebral palsy or abnormal neurological examination in the steroid groups were partly offset by a trend towards decreased mortality. The combined rate of death or cerebral palsy was not significantly different between steroid and control groups[19]. Both the early and late steroid trials mainly used dexamethasone at high doses (>0.5-1 mg/kg/day). Given the available evidence, the European Association of Perinatal Medicine, the American Academy of Pediatrics and the Canadian Pediatric Society have advised against the early use of dexamethasone in the first week of life and have concluded that there is insufficient evidence to recommend routine use of systemic dexamethasone after seven days of life[20]. Later use of dexamethasone is currently undertaken with caution and 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 studies have attempted to evaluate the role of steroids other than dexamethasone. Hydrocortisone prophylaxis for early adrenal insufficiency to prevent BPD was examined[21] in a study of preterm infants weighing <1 kg and being mechanically ventilated. The infants were randomized to receive placebo or hydrocortisone, 1 mg/kg/day for 12 days and then 0.5 mg/kg/day for 3 days. No significant differences in survival rates between the two groups were found, but, 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 to the placebo group. At the time of this review, there are two ongoing clinical trials evaluating the use of hydrocortisone on survival without BPD. One of them (Premiloc) is a phase 3 trial to evaluate low doses of hydrocortisone in the first ten days of life for infants <28 weeks gestational age[22]. The second (SToP-BPD) is evaluating hydrocortisone given after one week of life over a 22 day tapering schedule to ventilator dependent neonates <30 weeks gestational age and <1250g BW[23]. These and additional trials are warranted in order to determine the role of low dose hydrocortisone therapy in the prevention of BPD. These studies must include long-term pulmonary and neurodevelopmental follow-up.

Inhaled corticosteroids—Inhaled steroids have also been evaluated in an effort to optimize the benefits of corticosteroids and minimize unacceptable systemic side effects. The trials did not demonstrate significant change on the BPD rate at 28 days or 36 weeks postmenstrual age (PMA) regardless of whether the therapy was given early (<7 days) or late (>7 days). In addition, inhaled steroids have been found to offer no advantage over systemic steroid therapy[24, 25]. Major concerns with inhaled corticosteroids included the type of steroids, dosage, the potential for systemic absorption, and uncertainty regarding drug delivery. At the time of this review, a multicenter randomized controlled clinical trial is underway in Europe (NEuroSIS) aiming to examine whether early administration of inhaled budesonide in preterm infants reduces the incidence of BPD. The study includes short term and long term outcomes[26]. There is also a phase 2 clinical trial underway evaluating inhaled beclomethasone in infants with the diagnosis of BPD to evaluate effect on exacerbations[27]. Inhaled corticosteroids continue to offer promise in the prevention and management of BPD, and larger randomized, placebo-controlled trials are needed to establish their efficacy and safety.

Intra-tracheal corticosteroids—In order to overcome the difficulties of consistently delivering inhaled steroids to the lungs, new drug delivery methods are being studied. A prospective, randomized pilot study of 116 premature infants <1500g BW compared the effects of surfactant or a combination of surfactant and budesonide mixture on BPD. The combined outcome of death or BPD was lower in the surfactant and budesonide combination group[28]. There is currently an ongoing phase 2 and phase 4 clinical trial continuing to assess the effect of budesonide given with surfactant on the outcome of BPD[29, 30]. Further data from larger trials including long term neurodevelopmental outcomes is necessary before this approach can be recommended.

Macrolide Antibiotics

Azithromycin, erythromycin and other macrolide antibiotics are potent immunomodulatory and anti-inflammatory agents that can suppress the formation of pro-inflammatory cytokines in the lung[31]. Their antimicrobial properties are effective against *Ureaplasma urealyticum*, an organism closely associated with development of BPD in preterm infants[32, 33]. Use of erythromycin in intubated infants in clinical trials did not reduce BPD[34]. Azithromycin is a newer-generation macrolide that has fewer side effects and increased anti-inflammatory properties compared with erythromycin. It has been shown to reduce interleukin-6 (IL-6) and IL-8 production by tracheal cells obtained from prematurely born infants[31]. However, in a RCT, the incidence of BPD was not significantly reduced by azithromycin treatment[35]. In another randomized placebo-controlled trial of clarithromycin, the incidence of BPD was significantly lower in the clarithromycin group compared to the placebo group in premature infants with a BW between 750 to 1250g, who received treatment for ten days[36]. However these results are not generalizable as the proportions of infants receiving prenatal steroids and postnatal surfactant were relatively low in this study. At the time of this review, there is an ongoing randomized clinical trial evaluating the effect of clarithromycin on BPD[37] and routine use of the macrolides for the prevention of BPD is not recommended.

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Recombinant Human Clara Cell 10-Kilodalton Protein (rhCC10)

Clara cell secretory protein (CCSP), also known as Clara cell 10-kD protein (CC10) is an endogenous immune-modulating and anti-inflammatory agent. It is secreted by bronchiolar epithelial cells and is the most abundant protein in the mucosal fluids in normal healthy lungs but may be deficient in the premature infant[38]. Recombinant human CC10 (rhCC10) is protective in animal models of lung injury by improving pulmonary compliance and oxygenation, decreasing inflammation and up-regulating surfactant protein and VEGF expression[39, 40]. A randomized, controlled pilot study of 22 ventilated preterm infants with respiratory distress syndrome showed that intra-tracheal rhCC10 was well tolerated and significantly reduced the amount of inflammatory markers in the tracheal aspirates. There was no difference seen in the rate of BPD in those infants given rhCC10 as compared to control infants[41]. The properties of rhCC10 make it a promising agent in the treatment and prevention of BPD; however, evidence from randomized, controlled trials is needed to determine dosing and efficacy.

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Leukotriene Receptor Antagonist

Montelukast is a leukotriene receptor antagonist that blocks leukotrienes from causing smooth muscle contraction, cytokine production, and an inflammatory response. Montelukast and other leukotriene inhibitors have been beneficial in asthma. Because of shared pathogenetic mechanisms between asthma and BPD, it is plausible that montelukast may be effective in preventing BPD[42]. Montelukast is currently being evaluated in VLBW neonates in a phase 1 and phase 2 clinical trial to evaluate its effect on development of BPD[43, 44].

Vitamin A

There is currently sufficient evidence to support the use of Vitamin A for the prevention of BPD. The current evidence solely supports the intramuscular delivery of high dose vitamin A to extremely low BW (ELBW) infants[45]. Neurodevelopmental outcomes at 18 to 22 months were not different in the two experimental groups, and interestingly there was also no difference in respiratory outcome at 18 to 22 months[46]. Although current evidence supports the use of high dose intramuscular vitamin A supplementation for the prevention of BPD in premature infants <1000 grams BW, there are no long-term benefits in pulmonary or neurodevelopmental outcomes.

Surfactant

There has been new focus on surfactant in regards to the mode and timing of administration, as well as the type of surfactant given. Animal-derived surfactant is currently the surfactant of choice in comparison to synthetic protein-free and protein-containing surfactant. However, the United States Food and Drug Administration (FDA) approved the protein-containing synthetic surfactant lucinactant for commercial use in March 2012. It contains a 21-residue synthetic peptide that mimics the function of surfactant protein B[47]. Synthetic surfactant may eliminate the risks of inflammation and immunogenicity associated with animal derived surfactant[48]. One study measured markers of inflammation in human airway epithelial cells exposed to hyperoxia and treated with lucinactant or beractant. Lucinactant-treated cells demonstrated greater cell viability and secreted less IL-6[49]. A Cochrane meta-analysis reviewed two studies comparing protein-containing synthetic surfactant to animal-derived surfactant preparations in infants <32 weeks gestational age with BW between 600 and 1250g[50-52]. The findings support similar efficacy between the protein containing synthetic surfactants and animal surfactant in preventing death or BPD. Therefore, there is currently insufficient evidence to support the use of protein containing synthetic surfactants over animal derived surfactants.

With regards to the mode of delivery of surfactant, several new devices are being explored. A multi-center pilot study of 17 premature neonates <32 weeks gestation was carried out with a new device that involves the inhalation of aerosolized synthetic protein-containing surfactant through a vibrating membrane nebulizer. The procedure was well tolerated[53]. A small prospective observational study found that tracheal lavage with surfactant solution is safe in the short-term and effective in reducing oxygen requirement in ventilated infants <28 weeks gestation who deteriorate between postnatal days 7 and 28[54]. Further studies are required to compare the efficacy of these techniques with that of conventional intra-tracheal administration before their use can be recommended.

There continues to be ongoing research into late surfactant replacement therapy. A pilot trial administered 2 or 3 booster doses of surfactant to a total of 87 infants who were ventilated at 7 to 10 days[55]. These doses were safe and transiently improved respiratory status as well as composition and function of endogenous surfactant. However, there was no significant difference in the proportion of survivors without BPD with an increased number of late doses. A RCT of later surfactant treatment in mechanically ventilated preterm infants between 600 and 900g BW with a synthetic protein-containing surfactant also found trends towards decreased rates of mortality or BPD at 36 weeks' PMA, but no significant difference[56]. There is a current ongoing clinical trial powered to identify an improvement in the rate of BPD at 36 weeks' PMA in extremely low gestational age newborns randomized to receive either inhaled nitric oxide (iNO) alone or iNO with a regimen of late surfactant[57].

Inositol

Inositol enhances synthesis and secretion of surfactant phospholipids, thereby improving pulmonary function. A Cochrane meta-analysis that included all infants who received inositol treatment showed a significant reduction in death or BPD compared to untreated controls. However, when BPD was analyzed independently, no significant reduction was seen, although there was a trend towards a decrease in incidence[58]. Currently two phase 2 studies have been initiated with the support of the National Institute of Child Health and Human development to form the basis for a potential future large RCT of inositol[59, 60]. Inositol is not currently recommended for prevention of BPD but further trials may be warranted in the surfactant era to confirm positive preliminary findings and to study the long-term effects.

Antioxidants

Superoxide Dismutase (SOD)—Animal and human studies demonstrated an imbalance between free radical formation and antioxidant enzymes in the newborn period. This imbalance is thought to contribute to BPD pathogenesis. A RCT of recombinant human CuZnSOD demonstrated its safety but failed to detect a difference in the primary outcome of BPD. The long term pulmonary follow-up showed significant decrease in several indicators of lung disease in the treatment group over the first year of life including reduction in need for asthma medications, fewer emergency department visits, and fewer hospitalizations in infants born before 27 weeks gestation[61]. It thus appears that the role of SOD in the management of BPD may warrant further study in order to address its effect on other neonatal morbidities as well as the effects of dosage, mode of delivery, frequency and type of preparation of SOD.

N acetyl-cysteine (NAC)—NAC is a glutathione precursor with antioxidant properties. In a multicenter double blind placebo-controlled trial intravenous NAC was not found to be effective in decreasing the incidence or severity of BPD[62] or in improving lung function[63].

Tocopherol (Vitamin E) and Ascorbic Acid (Vitamin C)—Vitamins E and C act as scavengers of reactive oxygen species produced during high oxygen exposure and can prevent lipid peroxidation. Current evidence does not support use of vitamin E supplementation alone or in combination with vitamin C to prevent BPD[64, 65].

Lutein and Zeaxanthin Supplementation—Carotenoids (lutein, β-carotene, zeaxanthin, lycopene) are important antioxidant factors found in human milk[66]. A multicenter, double-blind RCT with 229 infants of <33 weeks gestation found a decreasing trend, but no significant difference in rates of BPD in infants randomized to a daily dose of lutein and zeaxanthin compared to placebo[67]. Additional studies of carotenoid supplementation are possibly warranted to examine effect and to determine optimal dosing.

Although the mechanisms are 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 reactive oxygen species.

Pulmonary Vasodilators

Pulmonary hypertension is increasingly recognized as a complication of premature birth and BPD. BPD-associated pulmonary hypertension is estimated to occur in 30-45% of infants with moderate to severe BPD[68, 69] and can contribute to the severity and persistence of BPD symptoms and impose additional morbidity and mortality[70]. Several agents are currently being evaluated separately and in combination therapy to target the pulmonary hypertension associated with BPD.

Inhaled Nitric Oxide (iNO)—iNO is a selective pulmonary vasodilator that decreases pulmonary vascular resistance without affecting systemic vascular tone. Animal studies have shown that iNO reduces lung inflammation, improves surfactant function and promotes lung and alveolar growth, suggesting that iNO may be beneficial to prevent or treat BPD[71]. Fourteen randomized, controlled clinical trials of variable design and study population have been conducted to test the ability of iNO to reduce mortality or the incidence of BPD in preterm infants. These trials have yielded inconsistent results with some finding benefit and others finding no difference in rates of BPD in infants treated with iNO[72]. A NIH consensus development conference concluded that current evidence from the RCTs of iNO does not support use of iNO in the care of premature infants of <34 weeks gestation. This applies to early-routine, early-rescue, or later rescue regimens [73]. Additional trials to define the optimal dose, timing and duration of iNO therapy in prevention on BPD in both ventilated and non-ventilated neonates are warranted and are ongoing at the time of this review[57, 74, 75].

Sildenafil—Sildenafil is a selective cyclic guanosine monophosphate (cGMP) specific phosphodiesterase inhibitor that results in increased cGMP levels and ultimately increased pulmonary vasodilation. It has been shown to improve alveolar growth, preserve lung angiogenesis and decrease right ventricular hypertrophy in animal models of BPD[76, 77]. It is also an attractive therapeutic option for infants with pulmonary hypertension caused by BPD because it can be given orally, and over longer periods of time with apparent low toxicity. Several case series of infants with pulmonary hypertension and BPD have shown short-term improvements in pulmonary hemodynamics and gas exchange in those treated with oral sildenafil[78, 79]. These early studies suggest that sildenafil is well tolerated in infants with pulmonary hypertension and BPD and leads the way to future RCTs evaluating sildenafil in pulmonary hypertension associated with BPD.

Dietary interventions

DHA—Docosahexaenoic acid (DHA) is an n-3 long-chain polyunsaturated fatty acid found in fish and fish oils that has immunomodulatory and anti-inflammatory properties[80]. In a multicenter, RCT, 657 preterm infants of <33 weeks' gestation consumed expressed breast milk from mothers taking either a high-DHA diet or a standard-DHA diet. The study was designed to examine neurodevelopmental outcomes, but rates of BPD were also compared. There was a significant reduction in BPD in the high DHA group in all infants with a BW of <1250g and in boys. However, the authors' could not exclude the possibility that these findings were due to chance because of the absence of significant interactions between treatment and infant gender or BW[81]. Further studies, specifically designed to examine the effect of DHA on BPD are warranted before a high-DHA diet can be recommended.

Citrulline—Endogenous NO is produced from the metabolism of L-arginine to L-citrulline. L-citrulline is regenerated during NO synthesis from L-arginine. Animal studies have shown that exposure to hyperoxia decreases plasma levels of L-citrulline and that L-citrulline supplementation restored plasma levels, preserved alveolar and vascular growth in the setting of hyperoxic exposure, and decreased pathologic pulmonary vascular remodeling and right ventricular hypertrophy[82]. The safety, bioavailability, and efficacy of L-citrulline with regards to BPD and pulmonary hypertension need to be studied in neonates before this therapy can be recommended.

Estradiol and Progesterone

Estrogen and progesterone are important in lung growth. Ovariectomy in a female rat model reduced the gas exchange surface area by impaired formation of alveoli and this was rescued by estrogen administration[83]. In addition, treatment of pig fetuses with estrogen and progesterone receptor antagonists significantly impaired alveolar formation[84]. In a randomized placebo-controlled study, 83 infants <29 weeks gestational age and <1000g BW were given continuous infusions of estradiol and progesterone for at least 2 weeks. There was no difference between the estradiol/progesterone and the placebo group in the primary outcome of BPD or death[85]. This therapy may warrant testing in larger studies.

Erythropoietin (EPO)

Treatment with EPO has the potential to mobilize endothelial progenitor cells in animal models and has been shown to partially reverse the histological features of BPD in rodents[86]. In a retrospective study, neonates with BW between 500 to 1,500g and gestational age <32 weeks who received EPO for anemia of prematurity were compared to those who did not receive EPO, for incidence of BPD. The incidence of BPD was lower in the group that received EPO after adjusting for significant risk factors[87]. Previous RCTs of EPO for anemia of prematurity have failed to demonstrate any significant difference in rates of BPD as a secondary outcome[88]. There is a randomized, multicenter, ongoing clinical trial of prophylactic EPO given to infants <32 weeks gestation in the first three hours of life to assess effect on cerebral outcome. BPD will be a secondary outcome[89]. At this time, based on the lack of data from RCTs powered to find a difference in BPD, EPO cannot be recommended to prevent BPD.

Cell therapy

The potential therapeutic utility of stem cells is a growing and promising field for novel treatment of various diseases including BPD. Intrinsic properties of mesenchymal stem cells such as their capacity to respond, migrate, and repair damaged tissue make them an attractive candidate for prevention and repair of neonatal lung injury. In animal models, bone marrow-derived mesenchymal stem cells (BMSCs) ameliorated injury in neonatal rodent models of BPD[90-92] by preventing lung injury and lung inflammation. This protection was observed despite a very low level of BMSC engraftment in the lungs. In fact, even more profound improvement in alveolar simplification and vascular injury was seen after delivery of BMSC-conditioned media indicating that a paracrine mechanism is likely involved[90]. A possible mechanism of action could be stimulation of endogenous lung stem/ progenitor cells by MSC-secreted factors[93]. Further studies in animal models of BPD are needed to address whether BMSCs can provide protection by a paracrine immunomodulatory response leading to release of specific growth factors and anti-inflammatory molecules. There is a current open label, single center, phase 1 clinical study to evaluate the safety and efficacy of umbilical cord-derived mesenchymal stem cell treatment in premature infants with BPD[94] .The results of this study and long term follow-up are pending at the time of this review.

Induced pluripotent stem cells (iPS) were first reported in 2006 after fibroblasts treated with pluripotent transcription factors were capable of forming clonal cells with pluripotency[95]. iPS cell technology has the potential of producing disease-specific stem cells. Recent work producing disease-specific lung progenitor cells from human cystic fibrosis iPSCs[96] is a promising first step to further exploration of the potential of this technology for neonatal chronic lung disease.

Preliminary animal and *in vitro* studies are currently exploring the possibility of use of other cell therapy options including embryonic stem cells, amniotic fluid stem cells, placental stem cells, and endogenous lung stem cells[97]. The research and field of cell therapy for prevention or treatment of BPD is growing[98]. No definitive human studies or results have yet to show benefits, but preclinical studies are ongoing and suggest great promise for future potential therapies for BPD.

CONCLUSION

Several pharmacologic therapies have been evaluated in well-conducted clinical trials and meta-analyses. Although for some of these therapies definitive evidence of efficacy is lacking there are several ongoing areas of research that show potential. Our current understanding of the complex and multifactorial pathophysiology of BPD suggests that targeting individual pathways is unlikely to have a significant impact on outcome. We need to continue to seek insights into the basic mechanisms of neonatal lung development, injury and repair in order to identify novel targets for intervention. In addition, ongoing research focused on genetic determinants of BPD may lead to targeted therapeutic approaches based on host factors and specific patient genetic and epigenetic makeup[99]. Finally, development of prediction tools for BPD based on perinatal and postnatal risk factors may prove very useful in stratifying patients by risk category in future RCTs of new interventions[100]. In clinical practice, minimization of ventilator-induced lung injury, oxygen toxicity and infection as well as continued optimization of nutrition should also continue to be pursued. As we evaluate novel approaches, it is essential to focus not only on short-term outcomes and safety profiles but also on long-term pulmonary and neurodevelopmental outcomes.

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Table 1

Pharmacological agents in clinical use to prevent/treat BPD

Class of drugs	Recommended Dose and duration of treatment	Comments
Caffeine	Caffeine citrate Loading dose: 20-25 mg/kg IV/PO Maintenance: 5 to 10 mg/kg/d IV/PO Discontinue at least 5-7 days prior to discharge	Recommended for treatment of apnea of prematurity and prevention of BPD
Vitamin A	5000 IU intramuscularly 3 times per week in infants <1000 grams for 4 weeks	1 additional infant survived without BPD for every 14 - 15 infants who received vitamin A
Systemic corticosteroids	Variable doses and duration (early, late)	Not recommended for early use; consider later use for infants with rapidly deteriorating respiratory status; 2 ongoing trials to evaluate usage of hydrocortisone to prevent BPD
Diuretics	Furosemide: 1mg/kg IV or 2mg/kg po Hydrochlorothiazide: 20-40mg/kg/day po Spironolactone: 2-4mg/kg/day po Duration guided by clinical response and adverse reactions	Loop: use sparingly in early evolving BPD Thiazides/spironolactone: consider for judicious chronic use
Bronchodilators	Guided by clinical response and adverse reactions	Limit use to infants with bronchospasm and acute clinical response

Table 2

Experimental novel pharmacological agents for prevention/treatment of BPD

Class of therapy	Status	Comments
Macrolide antibiotics	Phase 3 trial in progress evaluating the effect of clarithromycin on BPD	Routine use not recommended
Leukotriene receptor antagonist (*Montelukast*)	Phase 1 and phase 2 clinical trials in progress	Has not yet been evaluated in BPD, but mechanism of action suggests potential effect on BPD
Inositol	Two phase 2 trials in progress	Preliminary studies of inositol-treated infants showed a reduction in death or BPD, however no difference in BPD analyzed alone; majority of studies done prior to widespread surfactant use
Intra-tracheal corticosteroids	Phase 2 and phase 4 trials in progress assessing budesonide given with surfactant	Pilot study showed reduction of BPD or death in infants treated with surfactant and budesonide as compared to surfactant alone
Late surfactant	Phase 3 trial in progress evaluating effect on BPD on infants receiving late surfactant and iNO	Late surfactant therapy found to be safe and transiently improved respiratory status and function of endogenous surfactant; no effect on BPD seen in pilot studies
DHA	Ongoing clinical trials	Has shown promise based on animal models and a RCT that was not powered to find a difference in BPD
Cell therapy	Phase 1 trial open to study umbilical cord-derived MSC treatment in BPD	Preclinical studies suggest potential for impact on BPD