Management of Severe Chronic Lung Disease of Prematurity

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Abstract

Advances in the medical care of Very Low Birth Weight (VLBW) infants have led to decreased mortality rates. Unfortunately, this has not been accompanied by a similar decline in the rate of Bronchopulmonary dysplasia (BPD). In fact, while severity of lung disease at many gestational ages has decreased, the improved survival of the most premature of infants has led to survival with significant respiratory morbidity. So while improvements in care have reduced the risk for severe lung disease in larger, more mature preterm infants, BPD continues to be a major cause of mortality and morbidity in extremely premature infants.

For the subset of infants with most severe BPD, who still require ventilator support at 36 weeks post-conception, management remains a significant challenge. No standardized protocols exist to optimally treat severe BPD.

Current available strategies include optimization of adequate gas exchange, including prolonged oxygen therapy or ventilator support, utilization of systemic steroid therapy, minimization of ongoing insults like aspiration, and treatment of other sequelae, including pulmonary hypertension.

Each of these treatment strategies carries significant toxicities of their own, but individualized evaluation of risk/benefit and appropriate use of such strategies may improve pulmonary outcomes.

Introduction

Improvements in neonatal intensive care have led to the improved survival of infants born at extremely low birth weight [1-4]. Unfortunately, the lungs of such infants are at an early stage of development [5], and so survival comes with potentially substantial morbidity [6,7].

Bronchopulmonary dysplasia (BPD) is the term used for lung disease of prematurity. Advances in neonatal care, like prenatal steroid therapy and surfactant therapy, have led to substantial changes in the clinical and pathological characteristics of BPD [8]. The definitions of BPD have also changed; the current definitions include (1) total duration of oxygen supplementation requirement for >28 days, (2) degree of prematurity (<32 weeks gestational age at birth), and (3) oxygen dependency at 36 weeks Postmenstrual Age (PMA) to characterize three degrees of severity [9]. Infants who meet the 1st two criteria for BPD, but do not require oxygen at 36 weeks PMA are defined with "mild" BPD. Infants who require <30% oxygen at 36 weeks PMA are defined with "moderate" BPD, and infants who require >30% and/or positive pressure at 36 weeks PMA are defined with "severe" BPD. Neither older nor newer definitions are very effective at describing pulmonary outcomes in the most severely affected infants; even the most recent definitions underestimate lung disease, as many premature infants born at early gestational ages are discharged home well after 36 weeks PMA.

The very small subset of infants with most severe BPD who still require significant support despite approaching 36 weeks PMA pose significant treatment challenges. This review will focus on current strategies require Home Oxygen Therapy (HOT) or a tracheostomy for long-term ventilation, but these infants represent the greatest challenge for neonatal intensive care units. Infants in this category of severity are at highest risk of long-term complications. The current management of infants with severe BPD should therefore be aimed at maintaining adequate oxygenation and gas exchange, limiting the risk of infection, and optimizing growth. Treatment regimens to achieve these goals can have significant toxicities. This review focuses on how to evaluate the current treatment options to optimize management for premature infants with the most severe BPD.

There are several major categories of treatments to consider for premature infants with the most severe BPD. These include: (1) Supplemental oxygen therapy (2) Ventilation (Invasive or non-invasive) (3) Anti-inflammatory therapy (4) Removal of ongoing exogenous injury (aspiration), and (5) Treatment of secondary harmful sequelae (pulmonary hypertension).

Supplemental Oxygen Therapy

The optimal target saturation to promote health while limiting toxicities remains unknown. Excessive oxygenation can lead to toxicities, including retinopathy and increased pulmonary exacerbations [10-13]. Mechanisms for direct oxygen toxicity to the lungs include proliferation of Alveolar Type II (ATII) cells and fibroblasts, alterations in the surfactant system, increases in inflammatory cells and cytokines, increased collagen deposition, and decreased alveolarization and microvascular density [14].

Alternatively, inadequate oxygenation contributes to pulmonary hypertension [15], decreased growth [16] and poor neurodevelopmental outcomes [17].

The conflicting evidence regarding optimal target oxygen saturations has contributed to wide variation in practice. The most recent data demonstrated that lower oxygen target saturations did not affect the combined outcome of severe retinopathy or death, but did increase mortality while substantially decreasing severe retinopathy among survivors [18].

It is likely that there may need to be different target saturations at different stages of development. For infants who are close to corrected...
term PMA, oxygen saturation targets should likely be >93%; for infants with documented pulmonary hypertension, this target should be increased to 95%.

**Appropriate Ventilation**

Adequate ventilation is necessary to maintain appropriate acid-base status to maintain healthy physiologic function, and in some cases, to maintain oxygenation. Although permissive hypercapnia is an appropriate strategy in the NICU to minimize ventilator toxicities in severe BPD, permissive hypercapnia cannot come at the expense of minimally acceptable pH and therefore longer-term ventilation may be necessary to maintain health.

There are limited options to deliver appropriate external ventilation—NIPPV, CPAP, or intubation with mechanical ventilation. Requirement for delivery of any of these modes when awake beyond a certain age is not developmentally appropriate, and in these cases, a tracheostomy with ventilator support becomes necessary.

Decisions to perform tracheostomy have significant implications for disposition. Most ventilators designed for infants cannot be used in infants less than 5 kilograms, so prolonged hospitalization in an acute-care or rehabilitation facility becomes necessary. The ability to safely care for infants on home ventilation requires a set of requisite skills and equipment, so even for many children who meet weight requirements, medical status precludes early discharge home.

Once a tracheostomy has been placed, permissive hypercapnea should still be the ventilatory strategy of choice.

Tracheostomies have potential complications, including stomal infection, frequent obstruction from secretions, granuloma formation, and bleeding. Improvements in technique and intensive care have contributed to relatively lower morbidity rates more recently [15].

Few studies have reported on the outcomes of infants with BPD who required a tracheostomy. Our center’s experience, and that of recent published studies, suggest that long-term outcomes can be very favorable [16].

**Corticosteroids**

Steroid therapy for BPD is now less common. Older studies had demonstrated that steroids improved rates of BPD when using any of the definitions of BPD. Positive effects on BPD rates were sustained, regardless of timing of use - early (<96 hours) as prophylaxis, moderately early (7-14 days) or later in the NICU course (>3 weeks), duration, or dosing [17-19]. Steroids have been shown to enhance surfactant production, decrease pulmonary edema, and decrease in inflammatory mediators.

Steroids are also known to have significant negative effects. Short-term toxicities include hyperglycemia, hypertension, and hypertrophic cardiomyopathy [20,21]. More significantly, steroids are known to have significant negative effects on pulmonary development, resulting in decreased alveolarization [22]. Perhaps most importantly, systemic steroid use in premature infants was noted to be associated with neurodevelopmental impairment, including increased risk of Cerebral Palsy (CP) [23-27].

As a result of these studies, early high-dose prophylactic use of steroids has been much more restrictive.

As a result of the toxicities of steroids, several strategies may be employed to consider their use:

1. Consider subcategories of infants for whom benefits of use outweigh risks of therapy
2. Attempt to find preparations that have efficacy with less toxicity

**Consideration of subcategories of infants for whom benefits of use outweigh risk**

A recent meta-analysis attempted to look at the relative risk/benefit of steroids in different populations of infants. It suggested that the relative risk of developing neurologic complications may be modified, depending on the risk of developing chronic lung disease [28]. Therefore, for individual patients, the actual risk of untreated inflammation needs to be weighed against the known risks of steroid treatment.

**Attempt to find preparations that have efficacy with less toxicity**

Inhaled steroids have the theoretical benefit of providing direct anti-inflammatory effects to the lungs while minimizing systemic toxicities. Unfortunately, along with the decrease in toxicities, the delivery of inhaled steroid in the NICU also does not reduce death or BPD rates, and does not have any impact on relevant short-term clinical respiratory outcomes [29,30]. Inhaled steroids are therefore not recommended at this time.

Dexamethasone had been the most commonly utilized steroid in the NICU. As a result, all of the studies that described neurodevelopmental toxicities involved dexamethasone. Several recent studies have attempted to look at other preparations of steroids to determine if the toxicities described with dexamethasone are due to non-steroid factors (preservative, etc.) or due to enhanced penetration to the brain. A study comparing prednisolone to dexamethasone in infant leukemic patient’s demonstrated equivalent efficacy with decreased neurotoxicity [31], and suggested that fluorination of dexamethasone might be a contributing factor.

While no studies have compared prednisolone to dexamethasone in a randomized trial in premature infants, some studies have suggested that prednisolone may be as efficacious with less toxicity [32,33].

In our practice, the first-line systemic steroid choice is prednisolone (2 mg/kg/day) for 3-5 days, followed by a taper to avoid rebound inflammation or adrenal insufficiency.

In summary, postnatal corticosteroids should not be utilized in the routine management of BPD due to concern regarding neurotoxicity. However, in infants with severe BPD who continue to require mechanical ventilation beyond 36 weeks gestation, a short course of steroids should be considered, with full disclosure of risks and benefits to the parents.

**Minimization of Reflux/Acciditation**

Gastroesophageal Reflux (GER) is a known complication in infants with BPD. GERD can complicate respiratory status in infants with BPD due to association with frequent aspiration, pneumonia, apnea, and failure to thrive [34-39]. Gastro-esophageal reflux in preterm infants may result in recurrent pulmonary insult due to aspiration of gastric contents, and intractable obstructive apnea. Fundoplication is effective in controlling reflux when medical management has failed [40,41]. While a direct cause-effect relationship cannot be established, it is clear that in a subset of infants, treatment of GER can improve respiratory status.

Post-pyloric feeds may prevent reflux/aspiration until the lower esophageal sphincter matures, the intra-abdominal esophagus

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lengthens, and BPD resolves. Nasojejunal (NJ) feeding can be attempted to determine if improvement can be achieved. For infants with gastrostomy tube, conversion to a gastro-jejunal tube (G-J) should be considered.

Complications of jejunal feeding include the need for continuous feeds, and difficulties of maintaining placement of the tube in appropriate position. Specific additional challenges with gastro-jejunal tubes include increased frequency of blockage, and risk of intussusception.

Empiric trial of post-pyloric feeds may be warranted in infants with severe BPD. Improvement should be noted within 3–4 weeks. If post-pyloric feeds are continued, re-challenge with straight gastric feeds should be considered when the respiratory status shows consistent improvement.

**Treatment of Secondary Sequelae (Pulmonary Hypertension)**

Pulmonary arterial hypertension is an increasingly recognized complication of severe BPD [42]. For many patients with BPD, PH may be mild and can resolve with catch-up growth. However, in subsets of infants, the presence of PH can contribute significantly to increased morbidity and mortality [43–46]. Risk factors for the development of PH in BPD remain incompletely understood, and it is likely a multifactorial process. Infants that are born small for Gestational Age (SGA) are at higher risk for developing PH compared to non-SGA infants [42–45], and severity of lung disease likely also contributes. The relative contributions of the alveolar maldevelopment in BPD, and the role of pre-eclampsia and oligohydramnios are also controversial, but are likely contributors to PH.

Diagnosis of PH in BPD is often made by echocardiogram, although when clinical suspicion is high, cardiac catheterization may be necessary, as ECHO can sometimes underestimate pulmonary pressures [47,48]. Evaluation by echo should be considered in all preterm children with severe BPD who require supplemental oxygen and/or need positive pressure ventilation close to 36 weeks PMA. Cardiac catheterization should also be considered when acute responsiveness to pulmonary vasodilators would be beneficial.

For most patients with severe BPD and PH, treatment can be restricted to growth and patience. For patients with severe PH, evidence of right ventricular dysfunction, or refractory pulmonary disease, treatment with pulmonary vasodilatation may be required. An empiric trial of inhaled nitric oxide (iNO) may provide short-term evidence for the potential efficacy of treatment, but is expensive, and can be difficult to wean. Sildenafil has been used in preterm infants with BPD and PH [49–53].

In our center, we proceed with cardiac catheterization before starting Sildenafil. More recently, the FDA recently issued a warning against the use of sildenafil for pediatric PAH between 1 and 17 years of age due to an apparent increase in mortality during long-term therapy [54].

This will likely further limit the use of this therapy in patients with BPD. As with all of the therapies described in this review, the individual risk-benefit for individual patients should be carefully weighed. Certainly for cases of mild PH, sildenafil should not be utilized.

**Conclusion**

Improvements in NICU care are leading to improved outcomes for most patients with BPD. However, the subset of infants with severe BPD remains a challenge. Oxygen supplementation, more aggressive ventilation, corticosteroid therapy, minimization of gastro esophageal reflux/aspiration, and treatment of secondary complications like pulmonary hypertension may benefit such patients and result in improved longer-term pulmonary outcomes for these patients.

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