Bronchopulmonary dysplasia; what should we do to improve its outcomes?

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Running title: Bronchopulmonary dysplasia and its outcomes
Abstract
Bronchopulmonary dysplasia (BPD) is a chronic lung disease of preterm infants with multiple factors affected from prenatal to postnatal periods. Despite the great advances in neonatal care over almost 50 years, the rates of BPD are not decreased and may even have risen. Since more preterm infants even in periviable gestational age are survived nowadays, different stages of lung development have an effect on the pathogenesis of BPD. Hence the definition of BPD had been changed from ‘old’ BPD and ‘new’ BPD. In this review, the various definition of BPD, risk factors from prenatal to postnatal periods, management strategies according to different phases, and future directions for research files are discussed.

Key words: Bronchopulmonary dysplasia, Premature infant, Chronic lung disease, Lung injury, Inflammation
Introduction

Bronchopulmonary dysplasia (BPD) is a kind of chronic respiratory disease related to lung-injury in preterm infants\(^1\). It is known as a multifactorial disease with the most common morbidity in preterm infants. The very first description of BPD was evoked by Northway et al\(^2\) and it was originally described the clinical and radiological features of premature infants who had developed respiratory distress syndrome (RDS) with prolonged high inspired concentrations of oxygen ventilation\(^3\).

The incidence of BPD is still increasing or at least unchanged owing to an increasing survival rate of extremely preterm infants whilst the incidence is definitely decreased in preterm infants delivered at >28 weeks\(^4-6\). In Korea, it was reported as 28.9% in 2015\(^7\).

Since then with a tremendous development of various treatment modalities including antenatal steroids, early surfactant administration, strict fluid control, and less aggressive ventilation techniques, it is quite difficult to see so called ‘old (or classic)’ definition of BPD nowadays. The pathophysiology of BPD in the very preterm infants (VLBW) is thought to be a series of processes between lung injury and repair during lung development over the weeks to months and as such a concept of ‘new’ BPD had been come to the fore\(^3,8\). Afterwards, perhaps inevitably, various attempts were made to define diagnostic criteria almost over 50 years\(^9-11\). The definition of BPD was revised by the National Institute of Child Health and Human Development (NICHD) in 2000 that the definition should be separated between the infants with gestations of \(\leq 32\) weeks of postmenstrual age (PMA) and >32 weeks and proposing a severity of disease as well\(^13\).

BPD causes long-term complications in terms of respiratory, cardiovascular,
neurodevelopment from early childhood to adulthood and as a major public health problem in the end\textsuperscript{14}. Even though a wide variety of studies on the pathophysiology, prevention methods, and management modalities, there are still limitations about BPD treatment.

This review focuses on summarizing the different definition of BPD with recent studies about pathophysiology, current status of treatment, and will be discussed about recent newer therapies to improve outcomes of VLBWs.

**Changes in BPD Definition**

Since its first description in 1960s, BPD was referred to a group of moderately preterm infants with surfactant deficiency who survived with adverse outcome from prolonged ventilation with high oxygen supply. Hence, severe airway and parenchymal injury with alveolar cell hyperplasia, bronchiolar squamous metaplasia causing emphysema and septal fibrosis were typical radiologic and pathologic features of classic BPD\textsuperscript{8,14}.

Lung radiologic changes were also considered for the definition of BPD together with supplemental oxygen support in late 1970s\textsuperscript{8,11}. In one study, high resolution computed tomography (HRCT) showed linear and triangular opacities, air trapping and mosaic perfusion\textsuperscript{15}. Another study reported that preterm infants born at approximately 26 weeks in transient changes in lung development from canalicular to saccular stage had greater lung parenchymal changes\textsuperscript{16}.

With exogenous surfactant therapy in 1990s together with antenatal corticosteroids, preterm infants who might have died before could survive well even after discharged from neonatal
intensive care unit (NICU). By that time, Shennam et al\textsuperscript{10} suggested a simple definition of BPD for VLBWs as the use of oxygen supplementation at 36 weeks of PMA and this concept showed as a predictor of poor outcome at 2 years of age.

Owing to the advances in the field of neonatology, survival of extreme preterm infants who were born at the late canalicular-saccular stage of lung development has increased. Early surfactant administration with less invasive ventilation techniques in these groups made less oxygen requirement at the time of assessment and hence, it was difficult to categorize them as a classic BPD\textsuperscript{3,17}.

The definition by NICHD\textsuperscript{13} is called as “New” BPD in which it defined separately for infants with gestations of >32 weeks of PMA and proposed a severity-based definition. Severity was categorized for preterm infants in need for supplemental oxygen for at least \(\geq 28\) days as mild BPD – room air at 36 weeks PMA or at discharge; moderate - supplemental oxygen <30\% at 36 weeks PMA or at discharge; severe - supplemental oxygen \(\geq 30\%\) and/or need for positive pressure at 36 weeks PMA or at discharge. A very recent subclassification of severe BPD is divided into two phenotypes: Type 1 is relatively less severe which includes infants using high flow nasal cannula or continuous positive airway pressure at 36 weeks PMA; Type 2, relatively more severe, as for those with mechanical ventilation\textsuperscript{18}. The differences between “old” and “new” BPD are summarized in Table 1.

From another point of view, BPD is divided into early, evolving and established BPD showing a step-by-step therapeutic approach: early phase refers to very early time from birth up to 1\textsuperscript{st} week of life; evolving as the period between 1\textsuperscript{st} weeks to 36 weeks PMA; established as occurred > 36 weeks PMA\textsuperscript{19}. 
The reason why there is no uniform definition of BPD is that it is based on a clinical aspect of treatment with oxygen only, and not considering radiology or laboratory test or histopathologic findings. It could result in some limitations of comparisons between many research works about BPD.

**Risk factors**

As known as a multifactorial disease, pathogenesis of BPD started from beginning of the lung development in prenatal period to postnatal period after birth and persisted even after NICU discharge. In addition, VLBWs have no ‘normal’ lung so to speak, they are very vulnerable to injury.

Inflammatory responses as an accumulation of neutrophils and macrophages into the injured lung together with growth factor elaboration and cytokines increased vascular permeability which resulted in the development of BPD\(^{20}\). Numerous inflammatory biomarkers in amniotic fluid as well as tracheal aspirate of neonates are studied to find early detectable marker for infants who would subsequently develop BPD\(^{19}\).

Chorioamnionitis, one of the common known factors for preterm delivery is an important major antenatal factor contributing the development of BPD\(^{21}\). Although clinical chorioamnionitis is sometimes does not correlate with histological chorioamnionitis or culture proven amniotic fluid infection, it represents a maternal and/or fetal inflammatory response\(^{22}\). Even though causes of chorioamnionitis are variant, infants delivered before 30 weeks’ gestation showed infected amniotic fluid with *Ureaplasma* and *Mycoplasma* and the most common isolated microorganism is *Ureaplasma*\(^{21,23}\). *Ureaplasma* colonization or
infection plays an important role in the pathogenesis of BPD, hence reducing colonization burden with prophylactic antibiotics or postnatal therapeutic treatment might be considered\textsuperscript{24}. Recent studies showed that genetic and/or environmental factors are considered to be a contributor for development BPD\textsuperscript{25,26}. A familiar tendency and heritability in twin studies have demonstrated a genetic susceptibility associated with BPD and many other studies focused on to find specific gene mutation associated with lung development, immunity, and oxidative stress with BPD\textsuperscript{27}.

Initial resuscitation technique just after delivery is an important factor as well since the preterm lung can be easily damaged by mechanical ventilation. Some studies showed that if initial resuscitation for preterm infants was started with large tidal volume, lung injury could occur and elevation of pro-inflammatory cytokines were shown with mechanical ventilation in surfactant-treated preterm lungs\textsuperscript{28,29}. To avoid such a secondary ventilator-associated lung injury, variable ventilation support methods together with early surfactant treatment is undoubtedly needed. The variable factors for initiation of ventilation such as tidal volume, end expiratory pressure, oxygen concentration, humidity, and temperature also affect the lung injury\textsuperscript{22,29}.

Other known factors affecting the development of BPD are intrauterine growth retardation, multiple births, patent ductus arteriosus, nosocomial infection or postnatal sepsis, and surgical necrotizing enterocolitis\textsuperscript{29}. These various factors sometimes independently or interacting with each other affected on different phases alone may result the severity of BPD in individual infants.
Prevention and treatments

Preventing and treating the development of BPD needs teamwork approach more than any other diseases from prenatal period with an obstetrician to postnatal period with many other experts including a respiratory therapist, a cardiologist, a gastroenterologist, a nutritionist, a rehabilitation physician, expert nurses in the neonatal field, and even a social worker apart from neonatologists.

Antenatal care

The best way of preventing the development of BPD is preventing a preterm delivery as a matter of fact. Pharmacological interventions such as the administration of antibiotics, use of vaginal prostaglandin suppository, tocolytic agents such as magnesium sulphate and surgical interventions like cervical cerclage for cervical incompetence could possibly prevent preterm birth\(^{30,31}\).

Admiration of antenatal corticosteroid before delivery promotes maturation of surfactant and hence reducing the incidence of RDS although there is still controversy whether it reduces the incidence of BPD. Recent systemic review concluded that use of antenatal steroids was effective for accelerating fetal lung maturation in women at risk of preterm birth regardless of type of corticosteroid or single course or weekly repeat\(^{32}\).

At delivery room where a premature birth is imminent, team approach with on-site-tertiary neonatal facilities is definitely needed to improve mortality and long-term morbidity\(^3,33\). Initial stabilization at risk for RDS with CPAP, sustaining lung inflation, prudent titration of
supplemental oxygen during resuscitation to achieve targeted oxygen saturation are recommend with close observation with heart rate, chest wall movement, and pre-ductal saturations\textsuperscript{33,34}.

\textit{Postnatal care}

After delivery, therapeutic approach should be focused on two aspects: what ventilation technique could be applied and what pharmacologic treatment would be administrated in every different 3 phases.

Since preterm lungs are highly vulnerable to barotrauma and volutrauma, less invasive ventilation like avoiding endotracheal intubation is known as a promising treatment modality for reducing the development of BPD\textsuperscript{35}. Even when transferring preterm infants who require positive pressure ventilation from delivery room to NICU, it is recommend to use CPAP therapy with a T-piece resuscitator (Neopuff [Fisher and Paykel Healthcare, Auckland, New Zealand]), rather than using self-inflating bag to reduce development of BPD\textsuperscript{36}.

As mentioned above, avoiding unnecessary intubation is the best way to decrease the incidence of BPD from the respiratory care point of view. However, to prevent RDS most preterm infants need exogenous surfactant administration either prophylactic purpose or early rescue purpose. Hence, alternate routes of delivering surfactant through non-invasive or minimally invasive routes were introduced other than conventional endotracheal tube instillation\textsuperscript{17,37}. For instance, aerosolized surfactant by nebulizer was tried even though it was proven to be ineffective nowadays. Other methods were surfactant application via laryngeal mask airway, or surfactant administration directly to trachea via a thin catheter such as less
invasive surfactant administration (LISA) technique or minimally invasive surfactant therapy (MIST). Intubation and surfactant administration followed by immediate extubation (INSURE) technique could be an alternative way and a new modified strategy with alveolar recruitment maneuver before surfactant administration (IN-REC-SUR-E) could be another new method.

In early period before BPD is established, oxygen should be maintained between 91% and 95% to avoid oxygen toxicity. However, once BPD is established, oxygen supplementation is widely accepted with variation across centers even above 95% to prevent pulmonary hypertension and cor pulmonale.\(^{38}\)

Appropriate ventilation strategies are perhaps the most important thing to control the development of BPD. In early phase especially in the first week of life, one must try extubation and apply nasal CPAP or SNIPPV to minimize acute lung injury while maintaining low tidal volume (3-5 ml/kg), short inspiratory times (0.2-0.4 seconds), low PIP (14-20 cm H\(_2\)O), and moderate PEEP (4-6 cm H\(_2\)O).\(^{18,19}\) At evolving phase, i.e. after one postnatal week to 36 weeks’ PMA, the aim of respiratory care should be focused on optimizing adequate gas exchanges, reducing the work of breathing, healing of the injured airway.\(^{18}\) Avoiding intubation and maximizing non-invasive ventilation using CPAP, SIPPV, and HFNC are still effective strategies for decreasing lung injury.\(^{18,19}\) To achieve this goal, volume-targeted ventilation is known to have more advantages over pressure-supported ventilation and recent study recommended adjusting a tidal volume target of 7 ml/kg to reduce work of breathing.\(^{39}\)

When BPD is established, permissive hypercapnia is allowed to facilitate weaning and
optimizing adequate gas exchange, reducing the work of breathing, healing of the injured lungs as almost same as in the evolving phase. The special features of this phase is known as different combinations of lung regions with different airway resistance, compliance, and therefore with different time constants\textsuperscript{18}). Hence, at this point, larger tidal volume (10-12 ml/kg), longer inspiratory time (≥0.6 seconds), and resolving airways obstruction are needed to promote gas exchange\textsuperscript{18,19}).

Postnatal steroid whether to use or not to use, time, duration, type (dexamethasone or hydrocortisone) is still in dispute since the results of long-term adverse effects on neurodevelopmental outcomes are diverse\textsuperscript{40,41}). Recent Cochrane reviews concluded that the use of early (<8 days) systemic corticosteroids and late (≥7 days) inhalation reduced the outcome of BPD\textsuperscript{42,43}). While routine clinical use of dexamethasone in the first week of life is not recommended, when weaning off mechanical ventilation, it is effective to use the low-dose dexamethasone (0.89 mg/kg over 10 days) first introduced in ‘the dexamethasone: a randomized trial study (DART) study\textsuperscript{44}). Another multicenter randomized double blind placebo controlled study, the PREMILOC study proposed the positive effect of increasing survival rate of extremely preterm infants without BPD with early low-dose prophylactic hydrocortisone apply\textsuperscript{45}). However, a very recent STOP-BPD study, by the Europe investigating group reported that early low-dose hydrocortisone (cumulative dose 72.5 mg/kg) initiated between 7 and 14 days after birth showed no favorable outcomes of BPD at 36 weeks’ PMA and hence it did not recommend\textsuperscript{41}). When using a systemic corticosteroid, one must consider the benefit versus its potential short-term adverse effects like hyperglycemia, systemic hypertension, nosocomial infection, and possible intestinal perforation.
With the idea that it would be less toxic, inhaled corticosteroids are actively studied in addition to systematic use. Early inhaled budesonide study with total of 863 preterm infants less than 28 weeks administrated within 24 hours after birth showed lower incidence rate of BPD than placebo group, but the mortality was higher. A meta-analysis study of inhaled corticosteroid including beclomethasone, budesonide, fluticasone, flunisolide, and dexamethasone concluded the possible potential effect, budesonide in particular of reducing the risk for BPD but not with mortality and morbidities.

Another trial of combination of intratracheal corticosteroid-surfactant mixture by Yeh et al demonstrated a significantly lower incidence of BPD compared to surfactant only treated group and a meta-analysis study also concluded the decreased risk of BPD with intratracheal budesonide-surfactant mixture administration.

Nutritional support is also very important part of preventing BPD since preterm infants with BPD need 15% to 25% higher energy requirement than infants without BPD and thus, high-calorie intake of 140 -150 kcal/kg/d is needed to overcome lung injury from oxygen free radicals, to promote lung growth and linear growth. This could be achieved with mother’s breast milk or calorically dense formular feeding.

Other medications such as diuretics, caffeine, vitamin A, macrolide antibiotics for Ureaplasma colonized respiratory tract, nutrition also are known to help decreasing the incidence of BPD (Table 2).

Some new pharmacological studies are going on about use of recombinant Clara cell 10-kilodalton protein, recombinant superoxide dismutase, leukotriene receptor antagonist, inositol, and tocopherol.
Conclusion

In a systemic review of 31 international guidelines for perinatal care demonstrated that near 70% of institutions recommend to give comfort care at 22 weeks’ of GA and active resuscitation at 25 week’s GA\textsuperscript{54}. In addition, trend of survival rate of more extremely preterm infants is increasing especially born at 23 and 24 weeks and survival rates without major morbidity are increased for infants 25-28 weeks except BPD although there is a difference in survival of those periviable live births between countries\textsuperscript{6,55}. All those great improvements discussed above about BPD had been achieved over almost 50 years; however, additional researches are needed in the field of definition, deliver room intervention, NICU protocol for evolving BPD, and follow-up managements\textsuperscript{56}. Apart from all those general cares and practices, some special attention is needed for caring those infants with severe BPD.

Conflict of interest

The author declares no conflicts of interest
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Table 1. The differences between “old” versus “new” bronchopulmonary dysplasia

<table>
<thead>
<tr>
<th>Infants at risk</th>
<th>Old (or Classic) BPD</th>
<th>New BPD</th>
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<tbody>
<tr>
<td>Clinical</td>
<td></td>
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<tr>
<td>characteristics</td>
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<td></td>
<td>Pre-surfactant era</td>
<td>Post-surfactant era</td>
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<td></td>
<td>Prolonged invasive ventilation with high inspired oxygen</td>
<td>Gentle or non-invasive ventilation</td>
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<td></td>
<td>Severe airway injury</td>
<td>Interfere with lung development</td>
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<tr>
<td>Pathological</td>
<td>Interstitial and alveolar edema</td>
<td>Arrested acinar development</td>
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<tr>
<td>aspects</td>
<td>Intense airway inflammation</td>
<td>Less prominent inflammation</td>
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<tr>
<td></td>
<td>Lung parenchymal fibrosis</td>
<td>Less fibrosis</td>
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<tr>
<td></td>
<td>Metaplasia of the respiratory epithelium</td>
<td>Alveolar hypoplasia with fewer and larger alveoli</td>
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<tr>
<td></td>
<td>Pulmonary artery smooth muscle hypertrophy</td>
<td>Abnormal and fewer vascular arteries growth</td>
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<tr>
<td>Radiologic</td>
<td>Cystic emphysema</td>
<td>Diffuse haziness</td>
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<tr>
<td>findings</td>
<td>Over-inflated lung filed</td>
<td>Decreased lung field</td>
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<td></td>
<td>Alveolar septal fibrosis</td>
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Abbreviation: BPD, bronchopulmonary dysplasia
Table 2. Treatment recommendations according to the BPD stages (modified from Abman et al\textsuperscript{18}, Bhandari and Bhandari\textsuperscript{19})

<table>
<thead>
<tr>
<th></th>
<th>Early phase (≤7 days after birth)</th>
<th>Evolving phase (&gt;1 week to 36 weeks’ PMA)</th>
<th>Established phase (&gt;36 weeks’ PMA)</th>
<th>After NICU discharge</th>
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</thead>
<tbody>
<tr>
<td><strong>Oxygen supplementation</strong></td>
<td>Usually FiO\textsubscript{2} to target SpO\textsubscript{2} (91% - 95%), though wide variation exist between NICUs</td>
<td>Same as for early phase</td>
<td>Adjust FiO\textsubscript{2} to higher SpO\textsubscript{2} (usually ~95%) in order to prevent pulmonary HT and cor pulmonale</td>
<td>Consider discharge on up to at least 1 L/min via nasal cannula</td>
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<tr>
<td><strong>Ventilator strategy</strong></td>
<td>Try to apply non-invasive ventilation extubate early to SNIPPV/nCPAP</td>
<td>Avoid invasive ventilation; maximize non-invasive ventilation (SNIPPV/nCPAP/HHFNC)</td>
<td>Same as early and evolving phases</td>
<td>Discharge with monitor if needed</td>
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<td></td>
<td>Short inspiratory times (0.2-0.4 seconds), Low tidal volumes (3-6 ml/kg), Rapid rates (40-60 /min)</td>
<td>Low PIP (14-20 cm H\textsubscript{2}O), Moderate PEEP (4-6 cm H\textsubscript{2}O),</td>
<td>Longer inspiratory times (≥0.6 seconds)</td>
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<td><strong>Blood gas targets</strong></td>
<td>pH 7.25–7.35; PaO\textsubscript{2} 40–60 mm Hg; PaCO\textsubscript{2} 45–55 mm Hg</td>
<td>pH 7.25–7.35; PaO\textsubscript{2} 50–70 mm Hg; PaCO\textsubscript{2} 50–60 mm Hg</td>
<td>pH 7.25–7.35; PaO\textsubscript{2} 50–70 mm Hg; PaCO\textsubscript{2} 50–65 mm Hg</td>
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<tr>
<td><strong>Medications</strong></td>
<td>Methylxanthines</td>
<td>Steroids; dexamethasone (IV) for weaning off mechanical ventilation</td>
<td>Steroids; dexamethasone or hydrocortisone (IV), prednisolone (PO), inhaled corticosteroids</td>
<td>Steroids; prednisolone (PO), inhaled corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Bronchodilators</td>
<td>Diuretics; furosemide and/or spironolactone, and/or thiazides</td>
<td>Bronchodilators</td>
<td>Diuretics</td>
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<td></td>
<td>Pulmonary hypertensive agents</td>
<td>Anti-reflux agents</td>
<td>Pulmonary hypertensive agents</td>
<td>Bronchodilators</td>
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<td>Anti-reflux agents</td>
<td>Immunization for prophylaxis against RSV and influenza</td>
<td>Anti-reflux agents</td>
<td>Pulmonary hypertensive agents</td>
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<td>Immunization for prophylaxis against RSV and influenza</td>
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Abbreviations: PMA, postmenstrual age; NICU, neonatal intensive care unit; HT, hypertension; SNIPPV, synchronized nasal intermittent positive pressure ventilation; nCPAP, nasal continuous positive airway pressure; HHFNC, humidified high flow nasal cannula; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure