

# Bronchopulmonary Dysplasia: The Resolving Cruces in neonatology

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**Abstract:** Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease of the preterm neonate which is typically causing extensive physiologic changes and results in improper lower respiratory tract development. It is one of the most common adverse neonatal outcomes due to prematurity. It has been approximately 40 years of discovery of this chronic disease of the newborns that affects their overall quality of life even in adulthood. Yet, it remains an invincible challenge in the preterm neonatal care victimizing about 1/4<sup>th</sup> of the preterm extremely low birth weight babies. This review aims at providing knowledge on the currently known definition, etiology, pathogenesis, clinical presentations, complications and various clinical interventions used for Bronchopulmonary dysplasia.

**Keywords:** Bronchopulmonary dysplasia, prematurity, respiratory tract, respiratory development, preterm neonates, lung injury.

## I. INTRODUCTION

Any baby born before 37 weeks of gestational age is considered preterm. Babies born at gestational age greater than 34 weeks are considered late preterms (LPTs), who are more stabilized in their cardiovascular-respiratory health status. Babies born between 28-32 weeks are categorized as very preterms (VPTs) and babies born less than 28 weeks gestational age are grouped as extremely preterms (EPTs). Preterm birth is associated with several acute and chronic clinical problems; the most commonly affected categories are the EPTs [1]-[5], [7]-[9]. One of the major clinical complications associated with prematurity is respiratory insufficiency due to underdeveloped or incomplete maturation of the respiratory system and the lungs. Bronchopulmonary dysplasia is an abnormal lung developmental pattern culminating in permanent alveolar tissue damage and reduced pulmonary functions. It's highly correlated with the prematurity where the development of lungs is still in progress. BPD is a devastating disease in neonates, especially the preterm neonates, as they tend to cause long term clinical and pathological effects in the patients causing a deliberate reduction in the quality of life of the affected. It is thus a major cause of concern clinically, socio-economically and globally [10].

### A. *Infant Respiratory Distress Syndrome: The Doorway to Bronchopulmonary Dysplasia*

Infant Respiratory Distress syndrome is also termed in different names like hyaline membrane disorders,

respiratory distress syndrome (RDS), neonatal respiratory distress syndrome (NRDS), etc.

It is defined as a respiratory disease of the neonate, especially the preterm neonate, in which the membrane composed of proteins and dead cells lines the alveoli thus making the gaseous exchange impossible or difficult. Hyaline is derived from the Greek word "hyalos" meaning a transparent stone like the crystal". The disease was named so due to the glassy appearance of the respiratory membrane in the patients.

Bronchopulmonary dysplasia is defined as a permanent irreversible respiratory injury that degrades a premature infant born <32 weeks gestational age into requirement of supplemental oxygen on/after 28 days of life, or 36 weeks of gestational age, whichever precedes the other. It is classified as mild, moderate and severe depending on the supplemental oxygen and respiratory support required at or after 36 weeks postmenstrual age [5]. If the infant is stable in room air, the BPD is considered mild. If there is a requirement of <30% oxygen, BPD is considered moderate and if the requirement of supplemental oxygen is >30%, the BPD is severe [5].

### B. *Major Etiological Factors Contributing to Bronchopulmonary Dysplasia*

Respiratory disease is predominantly caused by the deficiency of respiratory surfactant, a mixture of phospholipids and lipoproteins, which are secreted by the lungs, the type 2 alveolar epithelial cells. RDS is a common clinical concern in premature infants. Greater the degree of prematurity, the greater is the chance of developing the disease. BPD is predominantly caused by an improperly treated hyaline membrane disease that can deteriorate the developing lung tissues in an infant. It can also be caused by various other factors which include genetic predisposition, developmental problems due to antenatal infections, diseases with hyperoxic conditions and certain invasive respiratory support mechanisms in an immature respiratory system [5].

C. Pathophysiology of Bronchopulmonary Dysplasia

In a normal healthy term baby (>36weeks gestation), sufficient amount of surfactant is produced by the lung cells. The surfactant production is initiated only after pulmonary maturation, that is, when the type 2 alveolar epithelial cells begin to differentiate and mature. This process may take a time period of upto 34 weeks of gestational age. It implies that as the baby is more preterm, the chance for respiratory distress due to surfactant deficiency is higher. When there is a deficiency for the surfactant in a neonate, the air-fluid interface of the film of the water lining the alveoli of the lung, which is the major gaseous exchange surface, exerts large forces that cause the alveoli to collapse, thus resulting in atelectasis. It results in a reduction of lung compliance and there is an increased workload to inflate the collapsed lungs. The collapsed lung together with improper gaseous exchange can cause increased oxygen demand leading to hypoxia, increased circulatory overload, increased cardiac output, metabolic acidosis and eventually cardiac failure, pulmonary failure along with other major organ damages.

The preterm infant is having an easily deformable rib-cage termed as compliant ribs that contributes to poor air entry despite the deep sternal retractions and breathing efforts to make an effective air exchange. It results in diffuse atelectasis or collapse of lungs. These damages may become irreversible and contribute to permanent lung injury. Permanent lung injury may include deformed alveoli, fibrosis, pulmonary cystitis, fibroids. They all cause a major damage to the air-diffusion tissues or the alveoli thus

imparting an irreversible, permanent, chronic condition called Broncho-pulmonary dysplasia (BPD)[6]. Bronchopulmonary dysplasia (BPD) is a major degraded form of hyaline membrane disorders primarily occurring with apnea of prematurity (AOP), progressing into respiratory distress syndrome (RDS) and degrading into BPD as a consequence of inadequate clinical therapy to RDS[7]. Clinically, bronchopulmonary dysplasia (BPD) is defined as the persistent or increased requirement of mechanical or ventilatory support and supplementary oxygen at or after 36 weeks post menstrual age (PMA) [2-4].

Factors that initiate BPD like the invasive respiratory procedures, antenatal infections etc, causes an impaired alveolarization and vascular deregulations. This in turn activates the inflammatory/immune responses of the body which on a chronic basis leads to permanent tissue structural and functional damage by the activity of inflammatory mediator like cytokines, interleukins etc. The development of lungs is arrested in BPD followed by alveolar tissue damage otherwise called alveolar simplification, impaired vascular development and abnormal pulmonary functionalities[2-4],[7-9]. The quality of life of the affected infants is compromised as they tend to have prolonged and recurrent hospitalizations leading to chronic alterations in their lung functionalities, neuro-developmental impairment [4].

Children with BPD do have airway hyper-responsiveness and irreversible emphysematous changes which exists into their adulthood [3-6].

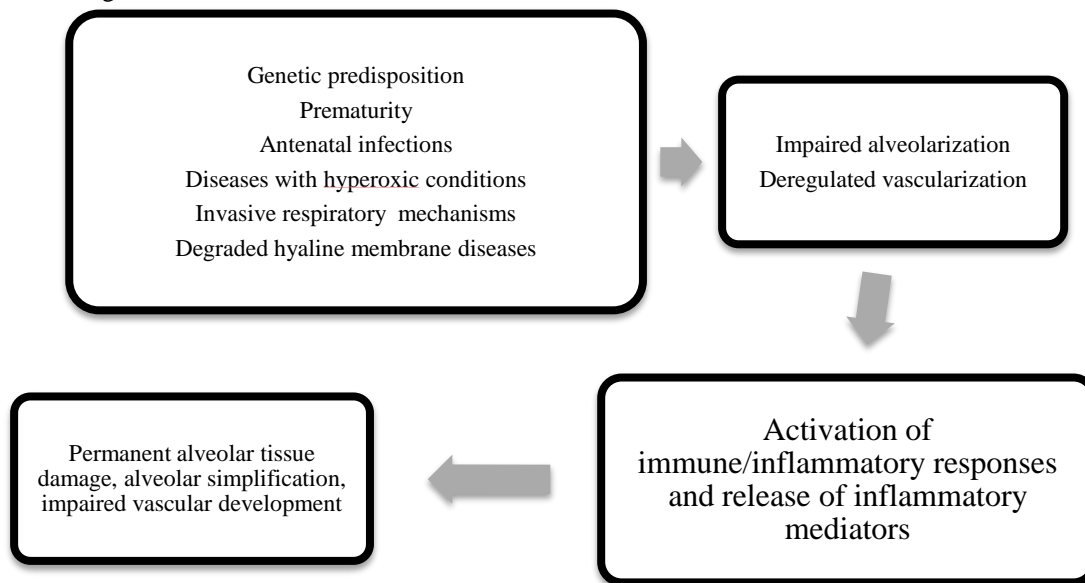


Figure 1: Pathogenesis of bronchopulmonary dysplasia showing the various stages of degradation of the disease into a permanent lung disease.

#### D. *The Signs and Symptoms of Bronchopulmonary Dysplasia*

The major clinical sign and symptoms of BPD vary as per the severity of the disease. Mild cases may not precipitate all among the clinical presentations of the disease while severe cases may fritter off with major or all of the symptoms [6-9]. Some of the classic infant signs and symptoms of bronchopulmonary dysplasia include rapid breathing/ increased respiratory rate, labored breathing with obvious retractions of lower chest while an inhalation, wheezing with grunting or naso-oropharyngeal sounds, intercostal retractions while each cycle of breathing, nasal flaring, sternal/sub-sternal pitting or deepening, difficulty in breast feeding/enteral feedings, requirement of continued supplemental oxygen therapy on/after 36weeks gestational age, repeated lung infections requiring medical intervention, recurrent apneic episodes/ degrading respiratory distress, peripheral cyanosis and an irritable infant having the normal sleep-activity pattern/routine of the neonate altered or disturbed due to the underlying breathing difficulty[6-9].

#### E. *Complications of Bronchopulmonary Dysplasia*

Since prematurity is closely associated with risks to develop bronchopulmonary dysplasia, the chronic complications of BPD is closely associated with the complications pertaining to prematurity per se [10]. Major long term complications associated to bronchopulmonary dysplasia include the following;

- 1) *Chronic Lower Respiratory Tract Functional Abnormalities:* More prominently seen in the younger infants, school-aged children, adolescents and young adults which depict that neonatal lung damage can persist into adulthood. The patient category had a larger residual volumes and lowered airway conductance. A significant reduction was found in the FEV1%, FVC for the children who suffered from the disease in their early neonatal period [8-10].
- 2) *Permanent Pulmonary Alveolar Damage:* BPD is associated with permanent anatomical and functional alterations or damage to the pulmonary system n entire with prominence given to the alveolar tissues. Prolonged requirements for supplemental oxygen in the neonatal period, invasive respiratory support mechanisms predicted subsequent structural and associated functional abnormalities in the high resolution CT scan of the patients [11-13].
- 3) *Recurrent Hospital Admissions:* BPD increases the hospitalization risk. Furthermore, it is the preterm infants who are at greater risk than the

term infants. The patients presented to the medical intervention with respiratory diseases or symptoms. The neonates who are discharged from the hospital with home oxygen therapy are at the highest risk for recurrent hospitalizations [10-13].

- 4) *Pulmonary Hypertension:* Vascular deregulation accompanying BPD can culminate in pulmonary hypertension. Kim GB et al in their meta-analysis study reported that this complication occurred in 17% of the BPD cases regardless of its severity [11], [13]. The gold standard for the diagnosis of pulmonary hypertension is cardiac catheterization procedure but trans-thoracic echocardiography is the most frequently utilized technique for diagnosis as it is non-invasive and permits the assessment of heart function rapidly [11],[13]. Radio-diagnostic procedures like cardiac CT and magnetic resonance imaging are also used to study on the pulmonary vasculature characteristics. Vasodilators, prostaglandin analogues like epoprostenol, endothelin antagonists like oral bosentan, phosphodiesterase inhibitors like intravenous milrinone are used as per the clinical requirements of the patient who respond poor with previous therapies. Hypoxia and hypercarbia episodes are to be prevented or treated immediately along with adequate nutritional support, on absence of which may deteriorate the pulmonary hypertension [12].
- 5) *Recurrent Respiratory Infections:* The risk for respiratory infections is more in preterm infants than the term infants. An overlying respiratory disease like BPD increases the vulnerability. In children with BPD due to respiratory syncytial virus infection, reported that 59% of the children with BPD presented with the infection and 69% of them required medical intervention for cure [13], [14].  
The risk for developing other chronic respiratory illness like asthma, COPD, emphysema, pulmonary cystitis are higher in children who developed BPD in their neonatal period. But the BPD induced disease and the clinical disease without induction from BPD are both different. For example, patients with allergic asthma have an elevated eosinophilic inflammation and higher levels of exhaled nitric oxide while BPD induced asthma have a neutrophilic inflammation and lower nitric oxide levels [13], [15].

## F. Various Therapeutic Approaches

- 1) *Oxygen Supplementation:* Supra-physiological oxygen concentrations can lead to BPD and therefore strict control over the concentration and administration of supplemental oxygen is recommended in the preterm infants [13]. The oxygen saturation levels are assessed with the assistance of a pulse-oximeter. The SPO<sub>2</sub> levels should always be maintained above 85% as per the Neonatal Services and Clinical Guidelines (revised 2015). In the first few minutes of life, SPO<sub>2</sub> of 70-80% may be acceptable but after 5 minutes of life it should be rise to a level of 88-92% with a maximum limit of 96%.
- 2) *Ventilation:* As per the NSCG 2015, the intubation and mechanical respiratory support is to be used only under symptomatic deterioration of the infant and not under any prophylactic circumstances unless otherwise in cases of extreme prematurity, <26weeks. To avoid the risk associated with mechanical ventilation, non-invasive respiratory support systems like the nasal continuous positive airway pressure(NCPAP), non-invasive positive pressure ventilation(NIPPV), high flow nasal cannulas are used in the routine practices of neonatal intensive care unit [13], [14].
- 3) *Surfactant Therapy :* Surfactant therapy is capable of reducing the incidence or risk for developing bronchopulmonary dysplasia by reducing infant mortality rate and modifying characteristics of BPD. It also improved the success rates of respiratory support systems used such as the NCPAP, NIPPV which can be obviously understood by the early extubation rates or transition from invasive respiratory support to non-invasive support systems. Currently, modified animal derived surfactants are used for clinical purposes. Surfactants from bovine and porcine origin are the most commonly used. Addition of specific lipids to animal derived surfactants reduces their potential risk for developing health issues when administered to the patients but the processes involved in the pharmaceutical preparations of these modified surfactants are much more expensive [14]. Synthetic surfactants were attempted to be produced but due to the complex molecular structure of the natural surfactants, the production of one was much more delayed. Synthetic surfactants contain two peptide chains and a more complex phospholipid chain and which is able to stabilize the alveolar tissues [14].
- 4) *Clinical Caffeine Therapy:* The caffeine for apnea of prematurity (CAP) study conducted by Schmidt B et

al depicted that caffeine was able to significantly reduce the development and risk for BPD. Caffeine is clinically administered as caffeine citrate either intravenously or rarely as intramuscular [15]. It is administered with a loading dose of 15-20mg/kg/day followed by maintenance doses ranging from 5-10mg/kg/day. Caffeine is well tolerated than any other methyl xanthine being previously used in neonates. It has a comparatively safer therapeutic dose range with lower adverse effects in the patients. Caffeine is proven to be useful in the treatment of apnea, neonatal respiratory distress syndromes and therefore it can be prophylactically used for the prevention of bronchopulmonary dysplasia [15].

The pharmacological actions of caffeine include stimulation of the respiratory center in the medulla oblongata, increase in mean respiratory rate, increased tidal volume, improved pulmonary blood flow, increased carbon-dioxide sensitivity and increased diaphragmatic contractility. It also has cardiovascular effects that tend to contribute to the enhanced pulmonary effects of caffeine. Caffeine stimulates the myocardium and increases the heart rate, cardiac output is increased, stroke volume is increased, all of the effects which cause an increase in the mean arterial blood pressure [15].

- 5) *Glucocorticosteroid Therapy:* Early extubation and reduced incidence of BPD is seen with ventilated infants administered with glucocorticosteroids within the first 2 weeks of life. But, no effect was found in children who were administered with these drugs at >3weeks of life. Hydrocortisone in hemisuccinate form in a dose of 1mg/kg/day in 2 divided doses for 7days followed by 0.5mg/kg/day for 3days is recommended. Optimal results were also observed with low dose dexamethasone in a dose of <0.2mg/kg/day in ventilated infants. Shinwell ES et al conducted a meta-analysis suggesting that inhaled steroids such as beclomethasone, budesonide, fluticasone, dexamethasone are capable of reducing the incidence of BPD development at 36 weeks of post-menstrual age(RR=0.77, 95%; CI0.65-0.91) [16]. Despite these benefits, glucocorticoid therapy in preterm infants remains a controversy due to its adverse effects associated with the vulnerable category of population- the preterms. Glucocorticosteroid therapy is found to have adverse effects such as hyperglycemia, hypertension, hypertrophic cardiomyopathy, severe retinopathy of prematurity and cerebral palsy. The chronic effect of corticosteroids on neurodevelopment is not yet clearly studies and therefore requires further studies to be done to establish the doses and its dosage regimen for inhaled steroids [16].

- 6) *Vitamin A Therapy*: Vitamin A is inevitable for the development and maturation of respiratory system. Clinical administration of vitamin A is essential in preterm infants since they lack optimal concentrations of vitamin A in their body to support and maintain the respiratory growth and development. Since it promotes the developmental process of the respiratory system, it is predictable that vitamin A reduces the risk of BPD development [17]. Vitamin A does not reduce the infant mortality, duration of mechanical ventilation and hospitalization risk associated with prematurity. It also does not account for any neurodevelopmental benefits. However, vitamin A is administered to preterm infants in a dose of 5000U intramuscular in 3 divided doses in a week for a total of 12 such doses. The administration is very painful and is associated with an increased potential for developing sepsis [17].
- 7) *Nitric Oxide Therapy*: Neonates with acute hypoxemic respiratory failure and chronic pulmonary hypertension may be benefitted from the administration of inhalational nitric oxide. Nitric oxide is not effective in preventing the development of bronchopulmonary dysplasia in preterm infants. Sokol G M et al in their study found out that there were no advantages for administration of nitric oxide early after birth or in later days of life. Therefore it is not recommended by experts and clinicians. However nitric oxide combined with vitamin A reduced the incidence of BPD and BPD associated mortality in very low birth weight preterm infants (750-999g) along with neurodevelopmental advantages such as increased neurocognitive outcomes at year one of life in the very low birth weight categories [18].

## II. CONCLUSION

Bronchopulmonary dysplasia is a major concern in the department of neonatology. It is undoubtedly one of the major factors contributing to neonatal death. Since the disease is closely associated with prematurity of the infant born, it can be very devastating leading to chronic respiratory problems and infantile death within the first year of life. Therefore the disease has to be deeply understood, learnt and researched upon to find more promising results. With the limited knowledge on pathogenesis, causes, prevention and risk factors for the disease, certain clinical therapies were developed. Some of the clinical interventions such as the surfactant therapy, caffeine therapy, and vitamin A are successful in the prevention of bronchopulmonary dysplasia while others like nitric oxide therapy had no effect. Some even had potentially deleterious effect like that of corticosteroids therapy which is still on debate. It is therefore highly demanded that further studies should be conducted in

the context of preventing, treating the disease thereby solving a major clinical, socio-economic global mishap.

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