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## Bronchopulmonary Dysplasia

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### 1. Introduction

Bronchopulmonary dysplasia (BPD) continues to be the most common and most important complication in preterm infants with RDS. The incidence varies from 20 to 60 % in preterm infants whose weight are < 1500 gram. The presence of BPD is often associated with significant mortality and short term and long term morbidity, including growth failure and neurodevelopment delay.

The exact mechanism and pathogenesis of BPD is not completely understood. However, epidemiology study suggests a changing prevalence and clinical features in recent years. The traditional descriptions of BPD (so call classic or old BPD) are essentially related to lung injuries following mechanical ventilation while the recent description of BPD (new BPD) is probably related more to prematurity of the lungs. The relation between these two types of BPD is not clear. Recent studies indicated that inflammation may play an important role for both the classic and new BPD. Once lung injuries have established, managements are essentially supportive, therefore every effort should be focus on prevention. Proper respiratory care is the most essential in preventing lung injury. Other medications, either to improve the pulmonary function or to reduce the lung inflammation, have been tried with various successes. There is no magic bullet to cure the disease.

### 2. Definition

The original definition of bronchopulmonary dysplasia by Northway was base on radiological and pathological characteristics in prematurely born infants with respiratory distress syndrome (RDS) who were treated with mechanical ventilation and oxygen supplementation. Subsequently, the definition of BPD was changed to respiratory sequelae in infants requiring oxygen supplementation more than 28 days after birth since BPD may occur in tiny premature infants who have not previously had RDS. This definition was not

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without debate, because it includes a wide range of infants, i.e. from those ultimately appear to have no residual problems to those with severe BPD. A more practical definition was used: respiratory sequelae in infants who reach term age but are oxygen or mechanical ventilation dependent. The introduction of antenatal steroid prophylaxis, postnatal surfactant treatment caused revolutionary care of premature infants. Nowadays, more extreme low birth weight infants with birth weight < 1000gm and gestation age 23-28 weeks survived, they experienced a mild initial respiratory course, but required a low concentration of oxygen for a long time. In 2001, the United States National Institute of Child Health and Human Development (NICHD) conducted a workshop. A new definition, which categorizes the severity of BPD, was proposed.

### **2.1 Classic bronchopulmonary dysplasia ( Classic BPD )**

As described above, the classic BPD was defined as a chronic lung disease occurs in premature infants who had respiratory distress after birth, require oxygen supplementation or mechanical ventilator support at 28 postnatal days or 36 weeks postmenstrual age (PMA). Four stages I, II, III and IV are classified base on radiological findings and associated pathologic changes. Stage I and II describe acute and subacute course of respiratory distress syndrome. Stage III and IV often represent changes associated with chronic lung disease.

Stage I (2-3 days) is a period of acute RDS. The radiologic picture is similar to RDS.

Stage II (4-10 days) is a period of regeneration. The chest radiograph shows complete opacity of the lung obscuring the heart and lung borders.

Stage III (10-20 days) is a period of transition to chronic disease. The early radiographic changes are replaced by areas of coarse, irregular shaped densities and areas of cyst lesions. Areas of density are caused by interstitial edema or atelectasis due to obstruction of small bronchioles with luminal debris. The cysts represent foci of emphysema.

Stage IV (beyond 1 month) is a period of chronic disease. Chest radiograph shows large cysts and marked fibrosis and edema with areas of consolidation and areas of overinflation.

This definition becomes less relevant in current practice, since the improvement care of RDS, and survival of very tiny babies, classic BPD is uncommonly seen now, instead a new form of BPD (new BPD) is much increased.

### **2.2 New bronchopulmonary dysplasia ( New BPD )**

BPD is now defined clinically as a chronic lung disease occurring in premature infants who need for supplemental O<sub>2</sub> for at least 28 days after birth, and its severity is graded according to the oxygen concentration and positive pressure of respiratory support at near term. For gestation age 32 weeks or more, the time of determination varies between 28 days to 56 days before discharge. For gestation age less than 32 week, the time of determination is 36 weeks postmenstrual age 36 weeks. A physiologic test such as pulse oximetry saturation is recommended to confirm the requirement of oxygen supplementation at the time of assessment (Table 1). Again, this definition is made clinically and the incidence of BPD can be various from hospital to hospital.

## **3. Epidemiology**

The incidence of BPD varies among different institutions. This is due to differences in neonatal risk factors among different populations, patient care management and the discrepancies in the definition of BPD. Incidence figures must be interpreted with caution.

Gestation age	< 32 weeks	> 32 weeks
Time point of assessment	36 wk PMA or discharge to home, whichever comes first	28 d to 56 d postnatal age or discharge to home, whichever comes first
<b>Treatment with oxygen &gt; 21% for at least 28 d plus</b>		
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 PMA or discharge, whichever comes first	Need for < 30% oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need for $\geq$ 30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need for $\geq$ 30% oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first

Adapt from Jobe A, Bancalari E. Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med* 2001; 163: 1723-1729.

Table 1. Definition of New Bronchopulmonary Dysplasia: Diagnostic Criteria

For example, better prenatal and postnatal care increase survival of the very tiny infants, more infants who previously would have died now survive and remain oxygen/ventilator dependent at 28 days of age, the overall rate of BPD may increase, but the severity is much less. The denominator may also be different, some reports used all live births of premature infants as denominator; while others used only survived infants.

Parker et al reported the incidence of BPD increased from 10.6% in 1976 through 1980, to 21.7% (1981 through 1985), and to 32.9% (1986 through 1990) in very low birth weight neonates (1500 g or less) admitted to a regional newborn care center in USA, while there was concurrent decline of neonatal death during the same periods (26.4%, 18.3%, and 15.9%, respectively). The diagnosis of BPD was given if neonates were treated supplemental oxygen for at least 28 days as a surrogate for oxygen treatment on postnatal day 28.

In 2007, a report from NICHD Neonatal Research Network database of USA shows the survival rate and the incidence of BPD (defined by supplemental O<sub>2</sub> at 36 weeks PMA) in infants with birth weight of 501-1500g almost unchanged between 1997 and 2002. The survival increases slightly (from 84 to 85%) and the incidence of BPD decreases by 1% (from 23 to 22%). Tiny infants have highest rate and severity of BPD: 6% in 1250-1500g; 14% in 1001-1240g; 33% in 750-1000g and 46% in 501 to 750g.

Since the release of a consensus statement by the American Academy of Pediatrics and the Canadian Pediatric Society in 2002, the use of postnatal corticosteroid has decreased. There was concern that the decreased use of postnatal steroid might increase the risk of BPD. A recent report from America which includes 77520 premature infants born at  $\leq$ 32 weeks gestation in California, the overall rate of BPD increased over the decade: 20% in 1997-1999, 24% in 2000-2003 and 25.4% in 2004-2006. The rate of severe BPD also increased significantly: 3.6% 1997-1999, 5.1% in 2000-2003, and 9.5% in 2004-2006.

## 4. Pathology of bronchopulmonary dysplasia

The characteristic changes of classic BPD are airway injury and inflammation, airway epithelial cell metaplasia, and parenchymal fibrosis. In contrast, the characteristic morphology of “new” BPD is disruption of lung development (Figure 1).

### 4.1 Classic bronchopulmonary dysplasia

Four stages are classified according to the severity and anatomic component involved.

Stage I alveolar and interstitial edema with hyaline membranes, atelectasis, and necrosis of bronchial mucosa are present.

Stage II atelectasis becomes more evident, alternating with areas of emphysema. There is widespread necrosis and repair of bronchial mucosa. Cellular debris fills the airways.

Stage III extensive bronchial and bronchiolar metaplasia and hyperplasia evolve. Areas of emphysema are surrounded by areas of atelectasis, accompanied by massive interstitial edema with thickening of the basement membranes.

Stage IV massive fibrosis of the lung with destruction of alveoli and airways are present. In addition, there is hypertrophy of bronchial smooth muscle and metaplasia of airway mucosa. Finally, there is actual loss of pulmonary arterioles and capillaries and medial muscular hypertrophy of remaining vessels.

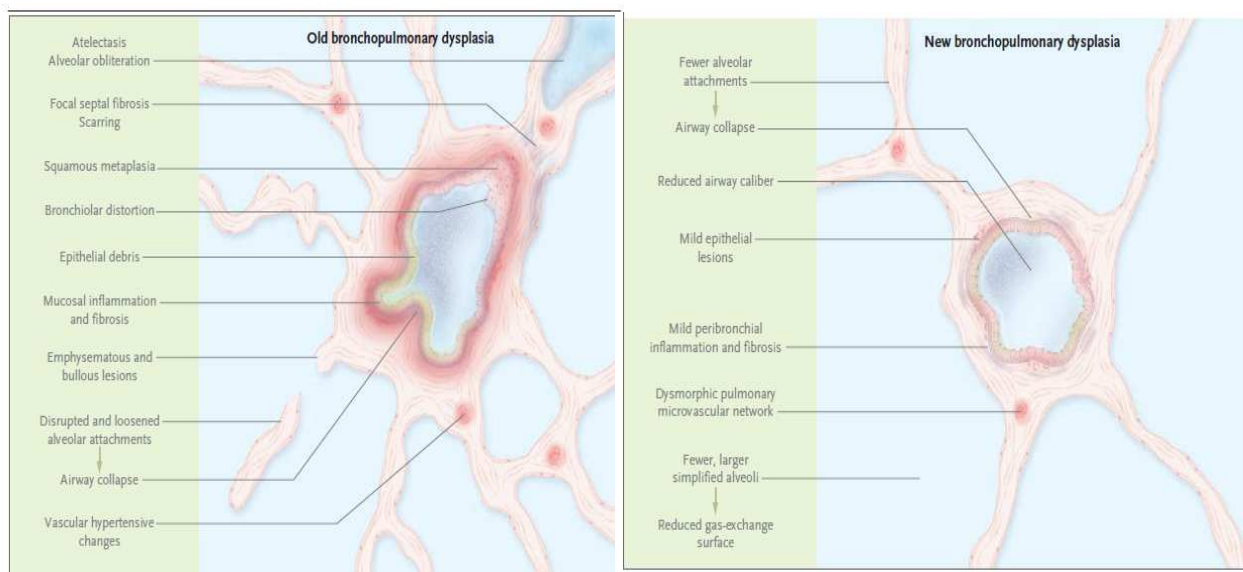


Fig. 1. Airway and Parenchymal Damage in Old and New BPD. „Old“ and „new“ BPD are two different morphologic outcomes of variable combinations of factors capable of injuring lungs of differing maturity. In old BPD, intense inflammation and disruption of normal pulmonary structures lead to a nonhomogeneous airway and parenchymal disease. In contrast, the main feature of new BPD is diffusely reduced alveolar development, which is associated with a clinically significant loss of surface area for gas exchange, with airway injury, inflammation, and fibrosis that are usually milder than in old BPD.

(From Baraldi E., Filippone M. Chronic Lung Disease after Premature Birth. *N Engl J M.* 2007, 357(8);1951)



#### 4.2 New bronchopulmonary dysplasia

Hislop et al. reported that mechanical ventilation of low birth weight infants leads to fewer alveoli. Husain et al. reported that extremely premature infants (gestation age ranged 24 to 32 weeks) dying of BPD had partial to complete arrest in acinar development whether infants received surfactant treatment or not. The alveolar structures are larger, simplified, and fewer in numbers. The amount of alveolar septal fibrosis is substantially less and tends to be more diffuse in surfactant-treated infants than in infants who did not have surfactant treatment. Coalson studied the autopsy lung specimens from infants who had received both prenatal steroids and surfactant treatment and have found the following findings: enlarged air spaces with minimal alveolization, dysmorphic capillary configuration and variable alveolar wall cellularity and fibrosis. Airway and vascular lesions, when present, tend to be present in infants, who over time develop more severe disease.

### 5. Pathogenesis

The pathogenesis of BPD is multifactorial. The original concepts of risk factors include: (1) prematurity; (2) respiratory distress; (3) mechanical ventilation; (4) oxygen supplementation. These factors still play an important role in the development of new BPD. However, infection and inflammation, pulmonary edema as result of and patent ductus arteriosus (PDA) or fluid overloading, nutritional deficiencies and genetic factors may also contribute to lung injury. Classic BPD is heavily influenced by injury inflammation and fibrosis; while new primarily is an arrest of development, disorder or delayed modeling and remodeling. ( Figure 2 )

#### 5.1 Prematurity

Bronchopulmonary dysplasia occurs most commonly in premature infants. Extreme low birth weight infants have a deficiency of surfactant and immature lung parenchyma, compliant chest wall , inadequate respiratory drive and immature antioxidant enzyme system. Most of these infants need supplemental oxygen and assisted ventilation after birth to achieve adequate gas exchange. The functional and structural immaturity increases the risk of lung injury and disruption of normal alveolar development from antenatal and postnatal insults.

Infants born at 23-28 weeks gestation are just beginning to alveolarize the distal saccule of the lung in parallel with the development of the alveolar capillary bed. Alveolar development can be delayed with hypoxia, hyperoxia, inflammations, glucocorticoids, and poor nutrition.

Patent ductus arteriosus (PDA) is present in most ELBW infants. PDA shunt increases pulmonary blood flow, and may result in pulmonary edema. Lung compliance is reduced and lung resistance is increased, creating a need for more vigorous and protracted ventilator support.

#### 5.2 Oxygen toxicity

Inspiration of high oxygen concentration is a major factor in the pathogenesis of BPD, though the precise concentration and duration of oxygen that is toxic to the immature lung has not been established. Any concentration in excess of room air might increase the risk of lung damage when administered over a period of time. Early pulmonary change caused by oxygen toxicity consists of atelectasis, edema, alveolar hemorrhage, inflammation, fibrin

deposition, and thickening of alveolar membrane. Continuous high oxygen exposure causes influx of polymorphonuclear leukocytes containing proteolytic enzymes which causes inflammatory reaction and cytotoxic damage.

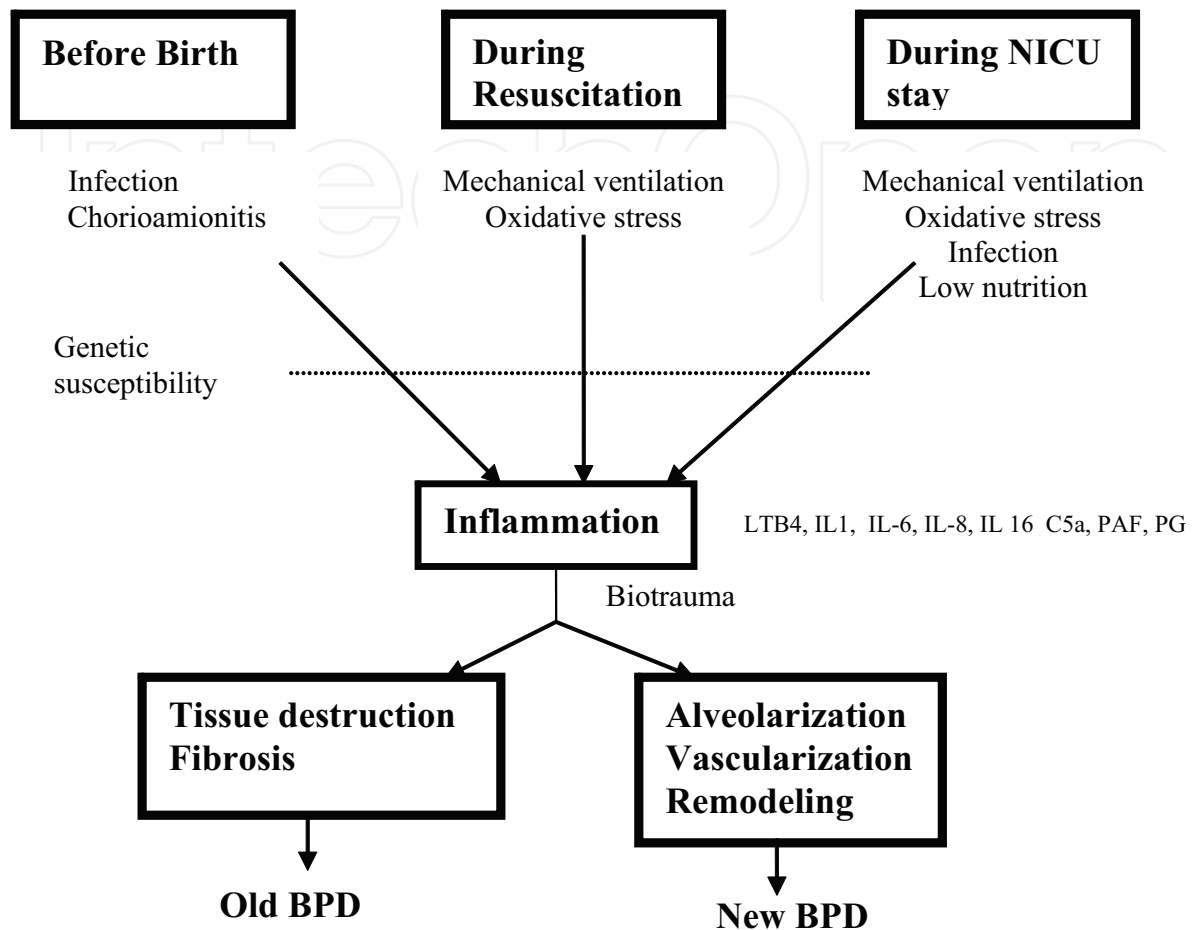


Fig. 2. Pathogenesis of Bronchopulmonary Dysplasia

The fetal lung is exposed to relatively low oxygen tension around 20 to 30 mmHg. Immediately after birth, the arterial oxygen tension climbs to 100 mmHg. The sudden increase of oxygen tension cause substantial oxidative stress. The principle mechanism involves the univalent reduction of molecular oxygen and formation of free oxygen radicals such as superoxide free radical ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), hydroxyl free radical ( $OH$ ) and singlet oxygen ( $^1O_2$ ). These oxygen free radicals are highly reactive molecules that can cause oxidative damage to lung tissue and trigger the inflammatory reaction. Premature infants have inadequate antioxidant defense system because their antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GP) are not mature and nutrients deficiencies (vitamin E, vitamin C, beta-carotene, uric acid) are common, thus they are vulnerable to develop lung injury from oxygen toxicity.

### 5.3 Mechanical ventilation-barotrauma and volutrauma

Barotrauma is the lung injury caused by the pressure used to inflate the lung. The inspiratory pressures needed to inflate the surfactant-deficiency premature lungs often fivefold greater than the physiologic pressure of the normal lung. The alveoli are not

homogenous inflated; some units remain collapsed and require higher pressure to reopen, whereas others become over distended. The resistance of collapsed alveoli to inflate leads to over distension of distal bronchioles during peak inflation and damage of bronchiolar epithelium. These over distension of airways and irregular aeration of alveoli lead to inflammation and release of cytokine.

Barotrauma produces alveolar shear stress, disruption of alveolarization, pulmonary air leak, and release of damaging cytokine and other biologically substances. High ventilator pressure has long been considered as a major cause of BPD, but tissue damage is now more attributed to over-distension of the lung from high tidal volume ventilation (volutrauma). In an animal experiment, Dreyfuss et al. demonstrated the most severe lung injury was seen with high tidal volume with high or low pressure. There were no abnormalities with low volume at high pressure. In clinical settings, however, high pressure usually delivers high volume, which in turn stretches alveolar wall and capillaries.

#### **5.4 Inflammation**

Inflammation plays the central role in the development of BPD. Inflammatory reaction may be triggered by factors including infection before or after birth, oxygen free radicals, barotraumas or volutrauma from mechanical ventilation, and pulmonary edema. Neutrophils and macrophages are recruited in the airway and pulmonary tissues. The activated neutrophils adhere to the endothelium of the pulmonary vascular system and thus initiate a sequence of pathogenetic events. Infants who subsequently develop BPD are found to have high concentration of proinflammatory and chemotactic factors in the tracheobronchial aspirate such as leukotrine B<sub>4</sub>, interleukin-1 $\beta$ , interleukin-8, soluble ICAM-1, anaphylatoxin C5a, platelet aggregation factor and prostaglandin. Pulmonary inflammation affects normal alveolization and angiogenesis, these may further lead to remodeling of developing lung resulting in BPD. Leukotrienes may remain elevated in BPD infants even at 6 months of age and cause bronchoconstrictoin, vasoconstriction, edema, neutrophils chemotaxis and mucus production.

#### **5.5 Prenatal and postnatal infection**

##### **5.5.1 Chorioamnionitis**

Premature infants who were exposed to maternal chorioamnionitis and required mechanical ventilation after birth have higher incidence of BPD. Proinflammatory mediators IL-1, IL-6 and IL-8 were detected in the early tracheal aspirates from these infants, suggesting lung inflammation occurred before birth. *Ureaplasma urealyticum* is the most common organism associated with chorioamnionitis. Several studies have suggested an association between *Ureaplasma urealyticum* tracheal colonization and the development of severe respiratory failure and BPD in very low birth weight infants, but results have not been consistent.

##### **5.5.2 Postnatal infection**

Very low birth weight infants with early onset systemic infection or local pneumonia usually present with respiratory signs including cyanosis and apnea which required oxygen therapy or ventilator support. Intubated infants are prone to develop nosocomial infection with deteriorating gas exchange, and are at great risk for development of BPD. The presence of a systemic infection in premature infants was noted to increase the risk of late ductal reopening and failure to respond to medical treatment with indomethacin. Infants with



infection and those with PDA had higher levels of 6-ketoprostaglandin F1- $\alpha$  than did control subjects. Levels of tumor necrosis factor- $\alpha$  were also elevated in infants with infection and in those with late PDA. The risk of BPD is enhanced if there is active PDA present at the time of infection.

### **5.6 Pulmonary edema, patent ductus arteriosus and fluid overloading**

Increases pulmonary blood flow from left-to-right shunt blood flow crossing patent ductus arteriosus may result increasing interstitial fluid and pulmonary edema. Pulmonary compliance is reduced and resistance is increased, creating a need for prolonged ventilator support with higher oxygen concentration and ventilation pressure. Clinical evidence suggests that infants with RDS who receive great fluid intake or who do not show a diuretic phase during the first few days of life have a high incidence of BPD. This may be because high fluid intake increases the incidence of PDA. Elevated concentration of myeloperoxidase was noted in the tracheal fluid of infants with PDA, suggesting the increased pulmonary blood flow may result in damage of the pulmonary endothelium and adhesion and migration of polymorphonuclear cells into the lung tissue.

### **5.7 Nutrition, Vitamin A**

Premature infants are undernutrition for days and weeks after birth due to critically ill state, intolerance of enteral feeding and fluid restriction. Sick infants have high caloric demand for growth, increased work of breathing and metabolism. Inadequate nutrition may amplify the lung injury of mechanical ventilation, oxygen toxicity and hinder the repair and recovery course. Vitamin C scavenges free oxygen radicals, as well as it interacts with vitamin E. Vitamin A is important in regulating early lung development and alveolar formation. Vitamin A deficiency may promote chronic lung disease by impairing lung healing, increasing the loss of cilia and squamous-cell metaplasia, increasing susceptibility to infection, and decreasing the number of alveoli.

### **5.8 Genetics**

Studies in VLBW twins demonstrated that BPD status in one twin was a highly significant predictor of BPD in the other twin, irrespective of birth order, Apgar scores and other factors. Monozygotic twins had more BPD and a long duration of hospitalization. Lung development is regulated by a variety of genes that balance between pro- and anti-inflammation, oxygen toxicity, cell injury and death, tissue repair, and infection. Specific genes that are known to be involved in these biologic pathways have been evaluated for their potential contribution to BPD. Approximately half of the initial genetic-association studies have not been replicated.

## **6. Clinical course**

Most infants who develop BPD usually have various degree of respiratory insufficiency resulting from RDS, pneumonia or poor respiratory effort after birth. Oxygen therapy or mechanical support is needed to maintain adequate gas exchange. Their pulmonary condition may show improvement in the first few days but deteriorate later. The pulmonary resistance increases gradually and blood gas shows carbon dioxide retention. Infants require more concentrated oxygen and more ventilator support. The deterioration may be triggered

by (1) systemic or local infection; (2) the presence of pulmonary edema associated with PDA, fluid overload or congestive heart failure; (3) severe airway obstruction caused by bronchospasm or tracheobronchomalasia. BPD is often anticipated when mechanical ventilation and oxygen supplementation extend beyond 10 to 14 days.

Some infants who have mild or moderate BPD show a slow but steady improvement and wean from support after 28 days old. On the other hand, some deteriorate and ultimately require months of oxygen supply and ventilator support. Respiratory acidosis with high PCO<sub>2</sub> greater than 55 mmHg associated with compensated metabolic alkalosis is common. Hypoxemia and hypercarbia result from ventilation-perfusion mismatch and alveolar hypoventilation.

The oxygen requirement decrease gradually as the disease process improves, but it can increase during feeding, physical activity or episode of infection. Intubated infants are easily agitated either because of discomfort or airway obstruction; they are also prone to get nosocomial infection. Growth failure with poor weight gain is common due to insufficient enteral intake and increase work of breathing. Some infants with severe BPD develop pulmonary hypertension, right ventricular hypertrophy and eventually die of right-side heart failure (cor pulmonale).

Radiologic manifestation of mild BPD usually appears normal or mild haziness lung field. Moderate to severe BPD may show hyperinflation, lobar or segmental atelectasis, gas trapping with pulmonary interstitial emphysema (PIE) and increased lung streaking. Fibrosis band and enlarged cyst usually occurs in severe BPD.

Supplemental oxygen and /or ventilator dependent Recurrent respiratory infection Lung atelectasis Gastrointestinal reflux Aspiration pneumonia Apnea Hypertension Wheezing and bronchospasm Signs of inappropriate ADH Signs of pulmonary hypertension and cor-pulmonale Poor postnatal growth Increase incidence of sudden infant death Increase fetal hemoglobin Neurodevelopmental delay
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Table 2. Clinical features associated with BPD

## 7. Prevention of bronchopulmonary dysplasia

As stated above, the pathogenesis of BPD has been linked to immature lung tissue, barotraumas and volutrauma resulting from mechanical ventilation, oxygen injury, and proinflammatory factors. Reduction of the incidence and severity of BPD may be possible through reduction of the causes of BPD. Among many strategies studied in the past, antenatal corticosteroids treatment, postnatal surfactant therapy, and gentle ventilation have been proved to be the most effective methods to target the development of BPD and decrease its severity.

## **7.1 Pharmacologic agents**

### **7.1.1 Antenatal corticosteroid**

Antenatal corticosteroid (ANC) was noted to be the most successful agent in reducing respiratory syndrome and increasing survival in premature infants by Liggins and Howie in 1972. It was not widely used until 1994 when the Consensus Development Conference Statement of National Institute of Health was published. Now women are at risk of preterm birth between 24 and 34 weeks' gestation are routinely given a course of corticosteroid before delivery. A single course of antenatal corticosteroids treatment is associated with an overall reduction of neonatal death, RDS, intraventricular hemorrhage, necrotizing enteritis, respiratory support, intensive care admissions and systemic infections in the first 48 hours of life. Long term follow up study demonstrates improvement of neurodevelopmental outcomes. Steroids accelerate structural maturation and surfactant synthesis of the lung, thus decrease the severity of RDS and BPD. The overall incidence of BPD in the population is not decreased due to increased survival of tiny babies.

Antenatal corticosteroid is most effective if given more than 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids. Treatment for less than 24 hours is still associated with better outcome, ANC should be given unless immediately delivery is anticipated or there is evidence corticosteroid will have an adverse effect on the mother. Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis and infection.

Betamethasone is the steroid of choice, when available, to be given in a course of two doses of 12mg administered intramuscularly 24 hours apart. An alternative regimen would be four doses of 6mg dexamethasone intramuscularly every 12 hours. Betamethasone is associated with a greater reduction in the risk of death than dexamethasone; it also decreases risk of periventricular leukomalacia which was not found with dexamethasone treatment. Weekly repeat course of ANC reduce the occurrence and severity of RDS, but the short benefits are upset with a reduction in weight and head circumference. Weekly repeat course of ANC are not recommended. Prenatal steroid may decrease airway septation and aveolarization in animal, it is not clear if prenatal steroid itself or the associated increased survival of tiny infant would contribute to the recently high incidence of new BPD.

### **7.1.2 Postnatal surfactant therapy**

The surfactant deficiency lung of premature infants is highly susceptible to lung injury and significant inflammatory reaction. The function of surfactant is to recruit alveoli and prevent atelectasis. Surfactant replacement reduces initial inspired oxygen and ventilation requirements as well as the incidence of respiratory distress syndrome, death, pneumothorax, pulmonary interstitial emphysema and the combined outcome of death or BPD. Combined use of prenatal steroid and postnatal surfactant therapy has proved to have an additive effect in improving lung function. As results of these treatments, the severe classic BPD is rarely seen today.

### **7.1.3 Methylxanthines**

Apnea of prematurity occurs in at least 85 percent of infants who are less than 34 weeks gestation. Widely used treatments include application of continuous positive airway pressure and the prescription of methylxanthines. In fact, methylxanthines – caffeine, theophylline and aminophylline are one of the most common drugs used in premature infants. They inhibit

sleepiness-inducing adenosine and improve respiratory drive, reduce the frequency of apnea and the need for mechanical ventilation. Methylxanthines also inhibit TNF- $\alpha$  and leukotriene synthesis, thereby reducing inflammation and innate immunity.

Toxicity with theophylline is more common than with caffeine. Side effects are usually associated with plasma level over 20ug/ml. Serum levels less than 10ug/ml is not beneficial as an aid to wean the ventilator. Because of the narrow range of therapeutic levels of theophylline, caffeine is the drug of choice in the treatment of apnea of prematurity. Davis et al demonstrated an improvement in minute ventilation, an increase in tidal volume, a decrease in lung resistance and improved lung compliance 1 hour following 10 mg/kg of caffeine. In a randomized study by Schmidt et al, infant who received caffeine were less likely to use oxygen at 36 weeks postmenstrual age, and more likely to have ventilator discontinued earlier.

#### **7.1.4 Postnatal corticosteroid**

Because inflammation plays a central role in the pathogenesis of BPD, systemic corticosteroids especially dexamethasone have long been used for prevention and treatment of BPD. Lung inflammation is down-regulated by dexamethasone therapy. Dexamethasone is a potent, long acting steroid with almost exclusive glucocorticoid effect. Compared to hydrocortisone, dexamethasone is 25-50 times more potent. The half-life is 36-54 hours. Dexamethasone has been extensively studied in neonatal medicine and has shown to improve pulmonary function, facilitate extubation and decrease the incidence of BPD. However; many associated adverse side effects prevent the routine use of dexamethasone. The short term side effects include hyperglycemia, hypertension, hypertrophic cardiomyopathy, growth failure, GI bleeding and perforation. The risk of GI perforation increases with concomitant indomethacin treatment. There is also a concern of the chronic suppression of the hypothalamic-pituitary-adrenal axis, and long term neurodevelopmental delay.

Striking evidence from multiple studies of the adverse effects of dexamethasone and its long-term neurological effects on preterm infants prompted the American Academy of Pediatrics and the Canadian Pediatric Society to strongly discourage the use of corticosteroids to prevent or treat BPD in 2002. Since the release of this consensus statement, the use of corticosteroids has decreased significantly, the incidence and severity of BPD increased significantly during this decade. To each gestation age, the time-related increase in BPD is inversely related to the decrease of dexamethasone use. The decline in use of dexamethasone associated with a concomitant increase in the use hydrocortisone. However, the use of hydrocortisone did not have any impact on the rate and severity of BPD.

#### **7.2 Gentle ventilation**

Mechanical ventilation both causes and treats BPD. When used, lowest ventilator setting to obtain adequate ventilation must be applied to minimize the barotrauma-volutrama and oxygen toxicity.

##### **7.2.1 Tidal volume, inspiratory pressure and target range of oxygen saturation**

In premature infants with lung disease, functional residual volume is reduced and some parts of alveoli are collapsed. The ideal tidal volume would be that open these collapsed area without over-distend the other areas. In general, initial PIP is set 16-20 cmH<sub>2</sub>O in order to achieve a tidal volume of 4-6 ml/Kg in ELBW with respiratory failure. Peak inspiratory

pressure >20 mmHg is rarely needed. Peak end expiratory pressure is usually set at 4 cmH<sub>2</sub>O, and short inspiratory time 0.3-0.4 seconds are used.

Oxygen saturation monitored by pulse oximetry offers the most reliable estimate of arterial oxygenation and easy to use. The ranges of oxygen saturation should be targeted between 91 to 95%. Oxygen therapy is very toxic for preterm babies, and maintaining even slightly high oxygen saturation contributes to retinopathy of prematurity and increases the duration of oxygen treatment. The STOP-ROP (Supplemental Therapeutic Oxygen for prethreshold Retinopathy of Prematurity) research group showed that newborn babies who had received oxygen supplementation to maintain saturation at 96-99% presented more pneumonia and a greater incidence of chronic lung disease than did those whose saturation was maintained at 89-94%. The results of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) demonstrated that lower target range of oxygenation at 85 to 89% did not significantly decrease the combined risk of death or BPD, but it resulted in an increase in mortality.

### 7.2.2 Permissive hypercarbia

Higher levels of PCO<sub>2</sub> 45-65 mmHg with pH above 7.20 now are accepted, thus allowing gentle ventilation to minimize lung injury. Early studies suggest that BPD occur more often among newborn infants with PaCO<sub>2</sub> below 40mmHg. A randomized, controlled study of NICH Neonatal network demonstrated that mechanical ventilated extremely low birth weight infants who were assigned to minimal ventilation (PCO<sub>2</sub> target >52 mm Hg) required less ventilator support at 36 weeks compared with infants with routine ventilation (PCO<sub>2</sub> target <48 mm Hg) (1% vs. 16% respectively, p<0.01). Unfortunately, after enrollment of 220 patients, the trial was halted because of unanticipated non-respiratory adverse events related to dexamethasone therapy. The relative risk for death or BPD at 36 weeks in both groups is no difference.

### 7.2.3 Nasal continuous positive pressure (nCPAP)

Nasal continuous positive pressure supports the breathing through a number of mechanisms: (1). splinting the airway thereby preventing airway obstruction, (2). dilating the airways and reducing resistance to airflow and so diminishing work of breathing, (3) aiding lung expansion and so reducing ventilation perfusion mismatch and improving oxygenation. Nasal CPAP used after extubation can prevent the instability associated with possible respiratory failure and reintubation.

Nasal CPAP, rather than intubation and ventilation, might be started shortly after birth for infants born at 25 to 28 weeks' gestation. In the randomized, controlled Continuous Positive Airway Pressure or Intubation at Birth (COIN) trial, there were fewer days of ventilation in the CPAP group, and a few CPAP infants received oxygen therapy at 28 days, but not at 36 PMA weeks. The early CPAP group did not significantly reduce the rate of death or BPD. Pneumothorax occurs in 6% of the CPAP infants and 3 % in the intubated group. Report from SUPPORT study, infants born 24-28 weeks of gestation, were randomly assigned to intubation and surfactant treatment, or to CPAP treatment initiated in the delivery room. There is no significant difference of death or BPD at 36 weeks. Infants who received CPAP treatment, as compared with infants who received intubation and surfactant treatment, less frequently required intubation or postnatal corticosteroids for BPD, and required fewer days of mechanical ventilation.



The value of early CPAP as a replacement of intubation and ventilation apparently to be established. Surfactant treatment is most effective if given shortly after birth. Tiny infants with respiratory distress receive nCPAP alone after birth may miss the benefit of prophylactic surfactant therapy. In our practice, we intubate these infants soon after birth, give a dose of surfactant treatment, then extubated and change to CPAP support if infants can tolerate, to avoid mechanical ventilation.

## 8. Management of BPD

Despite of the recent advances of neonatal medicine, little progress has been made in treatment of BPD. Cornerstones of treatment are pulmonary support to maintain optimal oxygen saturation and prevent complications and nutritional support to promote growth. Most patients with mild to moderate BPD gradually improve as healing occurs and lung growth continues. Infants with severe BPD especial who are ventilator dependent are more likely to have acute episodes of pulmonary decompensation secondary due to nosocomial infection, severe airway constriction, pulmonary air leak, increased pulmonary edema and the development of tracheobronchomalacia or cor pulmonale. Physical examination, radiographic survey, laboratory tests and echocardiogram are important in differential diagnosis and guide for specific treatment.

### Respiratory support

Infants with established BPD who are ventilator dependent, gentle ventilation are preferred to avoid further lung injury. Oxygen saturation should be kept within 90-95%. Inappropriate low oxygen tension may induce pulmonary vasoconstriction and /or bronchospasm with resultant increase frequency of apnea and hypoxia. Higher PCO<sub>2</sub> (55 to 65 mmHg) is accepted if pH is in normal range. Weaning these from mechanical ventilation is difficult and must be accomplished gradually. Caffeine or theophylline are usually used during the weaning phase to stimulate respiratory drive. Nasal CPAP may be applied to infants after extubation.

Infants with BPD who are not on oxygen therapy may experience oxygen desaturation with feeding or physical activity, additional oxygen supply might be need.

### Pharmacologic agents

Most medications used for treatment of BPD are targeted on one of the following pathophysiologic mechanisms of BPD: (1) bronchopulmonary constriction and airway hyperreactivity, (2) pulmonary edema, (3) airway inflammation, and (4) chronic lung injury and repair.

### Bronchodilators

Infants with BPD have increased airway resistance due to peribronchial smooth muscle hypertrophy and airway hyperactivity. Acute bronchospasm in response to hypoxia event could lead to sudden deteriorating pulmonary status. Bronchodilators have been shown to reduce airway resistance, improve lung compliance and increase tidal volume in infants with BPD during acute episodes of bronchospasm. However, their effects are usually short-lived, and many drugs have significant cardiovascular side effects. Inhaled  $\beta$ -2 agonists such as albuterol or levalbuterol have shown to reverse acute episodes of bronchoconstriction and cause few cardiovascular side effects. An initial trial dose can be administered through a meter-dose inhaler with a spacer device or as a nebulized solution. If patients show improvement of gas exchange, the  $\beta$ -2 agonists can be given up to 48hours duration.

Chronic use of  $\beta$ -2 agonists is not recommended since there is no long term benefit in treatment or prevention of BPD in preterm infants. Ipratropium bromide is another anticholinergic preparation that dilates airway.

Methylxanthines are competitive nonselective phosphodiesterase inhibitors, prevent breakdown of cyclic AMP and cyclic GMP. This leads to raise intracellular c-AMP and c-GMP. They also inhibit TNF- $\alpha$  and leukotriene synthesis, thereby reducing inflammation and innate immunity. Methylxanthines are nonselective adenosine receptor antagonists. Adenosine can cause broncho-constriction and potentiate immunologically induced mediator release from lung mast cells. Inhibition of this action will cause bronchodilatation. Theobromine, a metabolic product of caffeine and theophylline, causes vasodilatation and increases urine volume. But methylxanthines are weak bronchodilators with mild diuretic effect, and are infrequently used in the treatment for acute bronchospasm.

### **Corticosteroid**

As discussed above, systemic corticosteroids improve lung function and reduce the need of mechanical ventilation, but because the concern of long term adverse neurological outcome, now this treatment is reserved for infants with severe BPD who cannot be weaned from ventilator support. Dexamethsone with lower dose and shorter duration are usually used to facilitate extubation. A recent pilot study by Yeh et al , has shown that intratracheal instillation of budesonide by using surfactant as vehicle can effectively deliver budesonide to the lung and suppress the lung inflammation and improves pulmonary outcome without significant short term and long term side effects. More studies are needed before it can be recommended.

### **Nutrition and fluid supply**

Adequate nutrition is difficult to achieve in infants with BPD because of high caloric demand, poor tolerance of enteral feeding and restriction of fluid intake. Impaired growth is common in these infants. Malnutrition can delay somatic growth and the development of new alveoli, making successful weaning from ventilator less likely. Infants with poor nutrition are also susceptible to infection. Also, there are special nutrients and vitamins that are frequently deficient in these infants and their lack may increase the risk of lung injury.

Many infants with BPD experience increased energy needs. The reasons for this are not entirely clear; increased work of breathing, catecholamine release due to stress, increased energy requirements for feeding, and the effects of medications probably all play a role. It is not unusual for infants with BPD to require 130 or even 160 Kcal/kg/day to support adequate growth. It may be difficult to provide adequate calories for these infants. They may have ongoing fluid restrictions due to concerns about pulmonary edema. They may experience fatigue with feeding or delayed gastric emptying. Increasing the caloric density of formula or breast milk with a balanced proportion of carbohydrate and fat may be helpful. A high carbohydrate load increases production of CO<sub>2</sub> which may be a concern in infants with respiratory compromise. Excess carbohydrate may also lead to osmotic diarrhea. Excess dietary fat may delay gastric emptying and exacerbate gastroesophageal reflux.

### **Diuretics**

Infants with chronic lung disease tend to retain interstitial fluid which results in increased respiratory distress, increase in oxygen requirement, increase in ventilator settings, hypoxemia and hypercarbia. Diuretics mobilize fluid, improve lung compliance and decrease resistance.

### Furosemide

Furosemide is the most commonly used diuretic. It is a potent and rapid acting loop diuretic. It can be used orally and intravenously. The main benefit of the intravenous route is a quick response.

Mechanism of Action: At the ascending loop of Henle, furosemide inhibits active reabsorption of chloride resulting in lower sodium and water reabsorption. It also acts against antidiuretic hormones, and increases urine aldosterone excretion. Furosemide decreases left ventricular filling pressure by increasing venous capacitance. Furosemide helps in chronic lung disease by both diuretic and vasculature effects.

Adverse effects: Main adverse effects of chronic furosemide therapy are hypercalciuria, nephrocalcinosis and hypochloremia. Electrolytes should be monitored carefully. Ototoxicity is related to plasma concentration and is usually reversible after cessation of therapy. Other side effects include: osteopenia, cholelithiasis, displacement of bilirubin and hyperparathyroidism.

According to Cochrane review in preterm infants < 3 weeks of age with BPD, intravenous furosemide administration has either inconsistent effects or no detectable effect. In infants less than 3 weeks of age with BPD, a single intravenous dose of 1 mg/kg of furosemide transiently improves pulmonary mechanics. Chronic enteral or intravenous furosemide administration improves both oxygenation and pulmonary mechanics. The Cochrane review concluded that there is little evidence to support any benefit of furosemide administration with respect to ventilatory support, length of hospital stay, survival or long-term outcome. Accordingly, routine or sustained uses of systemic loop diuretics in infants with BPD cannot be recommended.

Inhaled furosemide has been shown to transiently improve pulmonary function. No long-term outcomes have been studied. More trials are needed before this delivery method can be recommended for routine use.

### Thiazide Diuretics

Thiazides work by inhibiting sodium reabsorption in the distal tubule. In contrast to furosemide, thiazides decrease calcium excretion.

### Potassium Sparing Diuretic

Spirolactone is a competitive antagonist of aldosterone. It is a weak diuretic and is usually given in combination with thiazides. There are very few randomized control trials. By Cochrane reviewer's opinion, in infants less than 3 weeks of age with BPD, chronic administration of thiazide and spironolactone improves lung compliance at four weeks of treatment and reduces need for furosemide. Only one study showed long-term benefits such as decreased rates of death and artificial ventilation.

Diuretics				
Drug	Site of Action	Route	Onset	Dose
Furosemide	Loop diuretic	IV PO	15-30 min 30-60 min	1 mg/kg/dose 1-3 mg/kg/dose
Hydrochlorothiazide	Distal tubule	PO	1-2 hrs	2-4 mg/kg/day
Spirolactone	Aldosterone antagonist	PO	3-5 days	1.5-3 mg/kg/day

Table 3.

### Inhaled Nitric Oxide (INO)

INO decreases pulmonary vascular resistance and improves oxygenation. It is proposed that INO will improve oxygenation, improve ventilation and will decrease respiratory support. Side effects include methemoglobinemia and direct pulmonary injury if excessive INO is used

Studies on INO were done with different doses, started at different ages, different durations of treatment, and in infants whose characteristics were different among the studies. INO was approved by FDA to term and near-term infants. AAP Committee on Fetus and Newborn recommended that centers that provide INO therapy should provide comprehensive long-term medical and neurodevelopment follow-up and should establish prospective data collection for treatment time, course, toxic effects, treatment failure, use of alternative therapies, and outcomes.

A systematic review which included 11 studies failed to show a significant benefit of INO on BPD. Cochrane database for systematic review by Keith J Barrington in 2006 concluded: INO as rescue therapy for the very ill ventilated preterm infant does not appear to be effective, and may increase the risk of severe IVH. Later use of INO to prevent BPD also does not appear to be effective. Early routine use of INO in mildly sick preterm infants may decrease serious brain injury, and may improve survival without BPD. Further studies are needed.

### Antioxidants

Free radical and oxidant stress cause damage to DNA, cell membrane, protein and lipids. Free radicals are produced by many mechanisms such as mitochondrial electron transport chain, prostaglandin metabolism, ischemia-reperfusion, hypoxia, neutrophil and macrophage activations, and endothelial cell hypoxanthine-xanthine oxidation. There is a balance between free radical production and clearing by the antioxidant system. The antioxidant defense system includes enzymatic components such as Co-Zn superoxide dismutase (SOD) glutathione peroxidase, and a non-enzymatic components such as glutathione, selenium, zinc, vitamin E and vitamin C. Preterm infants have an immature antioxidant defense system, and are highly exposed to oxidant stress, therefore prone to get tissue damage. Many antioxidant agents have been tried to treat or prevent BPD in newborn. These include:

**Vitamin E:** Tocopherol is a fat-soluble, anti-oxidant and it decreases reactive oxygen species. The American Academy of Pediatrics Committee on Nutrition has recommended daily supplementation of 5-25 IU of vitamin E in preterm infants. Supplementing very low birth weight infants with vitamin E as an anti-oxidant agent has been proposed for preventing or limiting retinopathy of prematurity, intracranial hemorrhage, and chronic lung disease. In clinical trials, vitamin E supplementation did not affect the incidence of BPD. Vitamin E supplementation significantly increased the risk for necrotizing enterocolitis and sepsis.

**Superoxide dismutase:** Intra-tracheal administration of CuZn SOD in preterm infants did not reduce BPD. It decreased the need for asthma medications, emergency department visits and hospitalizations during the one year follow-up. Rosenfeld et al showed that radiologic evidence, clinical signs of BPD and days of CPAP were less in patients treated with SOD, and no side effects were observed. Cochrane database concluded that there is insufficient evidence that superoxide dismutase is efficient in preventing chronic lung disease of prematurity, but it is well-tolerated, and has no serious adverse effects.



**N acetyl cysteine (NAC):** NAC is a precursor of cysteine, which is essential in Glutathione synthesis. Glutathione is a non- enzymatic antioxidant. NAC treatment in preterm infants did not prevent BPD or death, and did not improve lung function at discharge from the hospital .

**Allopurinol:** Allopurinol is inhibitor of xanthine oxidase, an enzyme which generates superoxide radicals. It did not decrease BPD in preterm infants of 24-32 weeks' gestation.

**Metaltonin:** Metaltonin is a hormone that is found in all biological organisms, and is a potent free radical scavenger. Melatonin treatment reduced the proinflammatory cytokines (IL-6, IL-8 and tumor necrosis factor (TNF)-alpha), and improved the clinical out- come in mechanically ventilated newborns with respiratory distress.

**Vitamin A:** Vitamin A is very important for the health of epithelial tissues. It reduces ciliary loss, and is associated with increased alveoli. In animals studies, vitamin A deficiency has been associated with necrotizing tracheobronchiolitis and squamous metaplasia the changes akin to BPD. Very low birth weight infants are known to have low vitamin levels.

There have been several studies looking at vitamin A in the prevention of BPD. The largest study by Tyson et al showed significant decrease (from 62% to 55%) in combined outcome of death or chronic lung disease.

Meta-analysis also revealed similar results.

A follow-up study did not show any untoward outcome at 18 to 22 months of age. Many units routinely use vitamin A for prevention of BPD. Five thousand IU of Vitamin A has to be given by tri-weekly intramuscular injections for four weeks. In one study it was given by oral route but was not effective in preventing BPD. Intravenous emulsion preparation needs to be studied by randomized control trials.

**Cimetidine:** In animal studies, lung injury as result of induction of cytochrome P450 by oxygen exposure may result in the release of free radical oxidants and arachidonic acid metabolites, that can be reduced by cimetidine. In study by Cotton et al of infants weighing less than 1250 grams who were mechanically ventilated and required oxygen, Cimetidine had no significant effect on the severity of respiratory insufficiency at 10 day postnatal age, and did not affect the tracheal aspirate levels of inflammatory markers or arachidonic acid metabolites.

**Azithromycin:** A macrolid antibiotic, azithromycin, acts act as a free radical scavenger, inhibits cytokines, and inhibits neutrophil chemotaxis. In a study by Ballard HO et al on extremely premature infants requiring mechanical ventilation, azithromycin did not affect mortality, incidence of BPD and days on ventilator.

**Alpha-1 protease inhibitor (A1PI):** Matrix Metalloproteinase is a member of a family of extracellular enzymes that are essential in proteolysis activity against extra cellular matrix proteins such as collagen, elastic lamina and fibronectin. These enzymes are produced by variety of cells such as fibro- blasts, osteoblasts, macrophages, monocytes and neutrophils. These enzymes are essential in growth, tissue remodeling, angiogenesis and wound healing. If the balance between activation and inhibition of this enzymes is disturbed, many pathological conditions can occur such as bronchopulmonary dysplasia. In a study by Stiskal JA et al, the incidence of CLD in survivors was lower in infants treated with intravenous A1PI as compared with a placebo group, but the difference was not statistically significant. The incidence of pulmonary hemorrhage was lower in the treated group.

**Thyroxine,** did not reduce the incidence of BPD. Estradiol and progesterone hormonal replacements were studied in 83 infants, but did not show decrease in incidence of BPD.



## 9. Conclusion

BPD is disease of multi-etiology. A large number of extremely preterm infants who survive are developing BPD, but the severity of the lung damage is considerably less than that observed in the classic form of BPD. Because most of these infants have only mild initial respiratory distress and, therefore, do not receive aggressive ventilation, other factors must be involved in the pathogenesis of this new, milder type of BPD. Clinical and epidemiological data strongly suggest that infections, either prenatal or postnatal, and the presence of PDA are major factors in the development of BPD. For this reason, efforts to prevent BPD in extremely low-birth weight infants should include an aggressive approach in the prevention and effective treatment of infections and PDA. BPD has long term adverse pulmonary and neurodevelopment outcome. Steroids usage for treatment of BPD also has been shown to have adverse neurodevelopment. Available data are sometime conflicting and inconclusive; clinicians must use their own clinical judgment to balance the adverse effects of BPD with the potential adverse effects of steroids for each individual patient.. Very low birth weight infants who remain on mechanical ventilation after 1 to 2 weeks of age are at very high risk of developing BPD . When considering corticosteroid therapy for such an infant, clinicians might conclude that the risks of a short course of glucocorticoid therapy is warranted . This individualized decision should be made in conjunction with the infant's parents. Other treatment and management are largely been supportive and most of them have no long term benefits. A recent pilot study from Yeh et al indicated that intratracheal instillation of budesonide using surfactant as vehicle can effectively deliver budesonide into the lungs and can significantly suppress lung inflammation, improve pulmonary outcome and without immediate and long term adverse effect.. More studies are needed to prove this. Until that time, proper respiratory care and avoidance of NICU infection are the most important steps leading to lower incidence of BPD.

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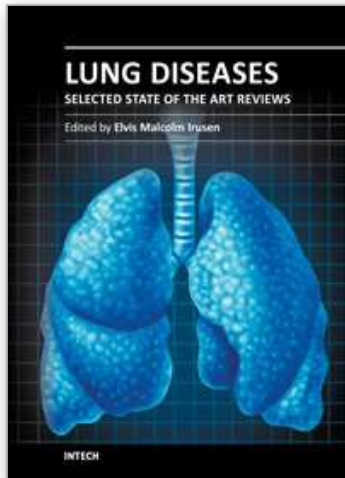
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