Review Article

Bronchopulmonary dysplasia. Changing scenario over the decades

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Abstract

Bronchopulmonary dysplasia (BPD) is a common life threatening pulmonary morbidity in children. Its incidence remains high even after introduction of various newer modalities of treatments. Of late, there is a change in pattern in BPD because of survival of more and more tiny premature babies.

Key Words

Bronchopulmonary dysplasia (BPD), chronic lung disease, mechanical ventilation, oxygen therapy, surfactant

Introduction

Bronchopulmonary dysplasia poses a major threat to the tiny neonate who finally survives from various heroic life "saving" treatments from the NICU. In spite of various major breakthrough advances in the field of neonatology, the incidence of bronchopulmonary dysplasia (BPD) remains high. BPD is a major contributor of neonatal morbidity and mortality especially in premature babies where it is seen in approximately 25%of all cases[1]. This is mainly because of increase in the survival of extremely low birth weight babies as a result of the advances that has happened during the last decade, especially following the widespread use of mechanical ventilation, oxygen therapy and surfactant replacement. For many, BPD remains a lifelong burden[2].

History

Bronchopulmonary dysplasia (BPD) was first described by Northway et al in 1967 as severe chronic lung injury in premature infants who survived hyaline membrane disease after receiving mechanical ventilation and oxygen therapy. He described progressive stages, namely alveolar interstitial edema, atelectasis, fibrosis, emphysema and hyperplasia of bronchial epithelium based on the histological findings .Radiology of these infants showed areas of heterogeneity and coarse scattered opacities in the severely affected cases. As per his observation, BPD is a disease of preterm having gestational age 30 to 34 weeks with severe respiratory distress requiring mechanical ventilation and oxygen therapy[3].

As years passed, advances in the field of neonatology, including antenatal corticosteroid administration, surfactant therapy, and advanced ventilation techniques resulted in survival of more and more preterm babies having gestational age <26 weeks. The types of BPD

seen in these tiny neonates are different from Northway's description, clinically, radiologically and pathologically. These cases are renamed as "new" BPD in which development of alveoli and pulmonary vasculature is defective. They show more diffuse nature of the disease with fewer areas of hyper inflation and fibrosis [1, 3].

Incidence

The incidence of BPD varies widely as per various studies and ranges from 12% to 32% among premature infants born <32 weeks of gestation. The incidence is gradually increasing mainly because of the improvements in the survival of extremely low birth weight (ELBW) infants [1, 3].

Development of airways

Initial phase of lung development, the embryonic phase, is characterized by the formation of lung bud and initial branching of airways from the ventral foregut. Branching continues in the pesudoglandular phase (5-16weeks) and all bronchial divisions are complete by the end of 16th week of gestation. Canalicular phase (16-24 weeks) is characterized by completion of airways up to terminal bronchioles and by the formation of primitive gas exchange units. Saccular phase (24- 38 weeks) is characterized by the development of alveolocapillary membrane sufficient for effective gas exchange. Further maturation of alveoli, alveolar microvasculature and fine tuning of gas exchange continues till delivery (bulk alveolarization) and even after birth (late alveolarization). While insults happening during early stages of development affect alveolar formation and vascularization, adverse events occurring at any stage produce permanent damage to the developing lung[3].

Pathogenesis of BPD

The term BPD refers to pathologic findings of lungs in infants who were exposed to high oxygen concentration and mechanical ventilation. This condition is also called as chronic lung disease (CLD). Classically this condition is seen in survivors of respiratory distress syndrome secondary to hyaline membrane disease. BPD is characterized by prominent airway injury, epithelial metaplasia, smooth muscle hypertrophy, parenchymal fibrosis and areas of emphysema. Acute lung injury is caused by both barotrauma and volutrauma caused by mechanical ventilation[4]. Oxygen therapy gives additional insults to the already damaged airways. This injury results in release of inflammatory mediators that cause irreversible damage to airways and alveoli. Development of alveoli, airways and lung parenchyma are compromised, leading to emphysematous changes. Damaged mucociliary apparatus results in accumulation of epithelial cells, secretions and their debris inside the airways which may lead to collapse, hyperinflation or dilatation of airways. During the chronic phase of BPD, the interstitium finally become fibrotic with cellular hyperplasia. Increased retention of pulmonary fluid occurs because of ineffective clearance of interstitial fluid. Finally airways become hyperactive and develop increased muscularization. All these permanent changes in the airways eventually lead to decreased lung compliance and increased airway resistance[5].

Pathogenesis of "new BPD"

When the exposure occurs at early gestation (< 32 weeks), lung development is severely hampered. Cascade of events finally lead to alveolar arrest and disruption of microvasculature. The changes include decreased alveolar septa formation, fewer numbers of alveoli and reduced airway caliber and dysregulated micro vascular growth. Decreased alveolariation and abnormal vascular growth are the hallmarks of new BPD [3, 5].

In old BPD, lung development has already reached later stages like saccular and alveolar stage. Injury occurring during this period would not cause alveolar or vascular arrest, but result in severe inflammation and dysplastic changes in the airways, characterized by extensive alveolar fibrosis, airway abnormalities and pulmonary vascular remodeling.In new BPD, lungs are more uniformly inflated with minimal airway injury and less prominent fibrosis [3, 4, 5]

Causes of BPD "the changing scenario"

The causes of BPD are many and include maternal, fetal, perinatal and neonatal factors.

The most important factor in the pathogenesis of BPD is prematurity. Intrauterine growth restricted babies are having added disadvantage. There is a definite genetic predisposition. Family history of asthma and reactive airway disease increases the risk of BPD[5].

Exposure to high levels of supplemental oxygen or prolonged oxygen therapy is a strong risk factor for developing BPD.The damage is caused by more reactive oxygen radicles formed from molecular oxygen such as superoxide (O_2-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH-). Oxidant – antioxidant imbalance is a strong risk factor for BPD[6].

Over distension of lung during mechanical ventilation produce damage to the airways and capillary network. Both barotrauma (high peak inspiratory pressure) and volutrauma damage the preterm lung. Centers using mechanical ventilation more frequently are having high incidence of BPD. Increase in the use of nasal CPAP has reduced the incidence of BPD[2].

Patent ductus arteriosus with left to right shunt producing increased pulmonary flow, heart failure and pulmonary edema poses a great risk for developing BPD. Volume overload during intravenous fluid administration is also a risk factor[7].

Maternal infections leading to chorioamnionitis increases the risk of BPD. Similarly infection occurring in early weeks of birth, either by gram positive (group B Streptococci)or gramnegative (E-Coli, Klebsiella) or fungal infection are associated with BPD. Recently other organisms like Ureaplasma urealyticum, Cytomegalovirus and Adenovirus are implicated in the pathogenesis of BPD and the systemic inflammatory response developed against these organisms results in the production of inflammatory mediators responsible for the development of BPD[8].

Delayed initiation of enteral feed, inadequate parenteral nutrition, and catabolic state due to increased work of breathing also lead to BPD[3].

Antenatal steroids and BPD

Antenatal steroids administered to pregnant mothers at risk for premature delivery decreases the severity of many diseases in preterms including bronchopulmonary dysplasia, respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis. Betamethazone is the preferred drug and 2 doses, 12mg each, given by intramuscular route, 24 hours apart gives the desired effect. Even though the usefulness of antenatal steroids is established beyond doubt, its use is low especially in developed countries. Lack of use of antenatal steroids lead to higher morbidity of BPD among the survivors. The effects are not limited to newborn period but continue to infancy and childhood [3, 9].

Clinical presentation

Child will have tachypnea and in drawing of chest. Auscultation reveals crepitations. Distress is aggravated when we try to decrease the FIO2. Severity of BPD is classified based on oxygen requirement. ABG shows hypoxemia, hypercarbia and respiratory acidosis. Chest radiograph shows progressive changes. Initially findings are indistinguishable from respiratory distress syndrome showing diffuse reticulo granular pattern with air bronchograms. Haziness and density increases as the disease advance gradually progressing to hyperinflation and appearance of radiolucent areas. Advanced disease is characterized by areas of hyperinflation with large radiolucent areas with thick streaky densities in between. ECG shows features of right ventricular hypertrophy. Lung function tests reveal decreased forced expiratory flow rate, increased functional residual capacity, and increased residual volume[10].

Clinical grading of BPD

For definition and assessment of severity of BPD, following 4parameters are used. 1) Oxygen requirement 2) positive pressure 3) gestational age 4) duration of treatment. Definition and grading proposed by the National Institute of Child Health and Human Development (NICHD) and a physiological definition are in use. Main advantages of NICHD over previous definitions are that it better identified infants who are at high risk for poor pulmonary outcomes and neurodevelopment impairment[1].

Table NICHD. Severity based definition of BPD

Gestational age at birth	Mild BPD	Moderate BPD	Severe BPD
<32 weeks	Room air at 36 weeks post menstrual age or discharge	<30% oxygen at36 weeks post menstrual age or discharge	>30% oxygen and/or positive pressures at 36 weeks post menstrual age
<32 weeks	Room air at 56 days post natal age or discharge	<30% oxygen at 56 days post natal age or discharge	>30% oxygen and/or positive pressures at 56 days post natal age or discharge

The physiologic definition of BPD was developed by Walsh and colleagues. BPD is defined as a failure to maintain a saturation value greater than 90% when challengedwith 21% oxygen at 36 weeks' of post menstrual age[1].

Respiratory patterns and the risk of severity

Among premature infants, three distinct patterns of lung disease emerge in the first 2 weeks of life. In the first pattern baby develop mild distress, who progressively recovers. In the second pattern, neonate experiences significant pulmonary dysfunction from birth and requires prolonged respiratory support from birth. The third pattern is that of an initial improvement in lung disease in the first week of life, followed by deterioration that often requires mechanical ventilation and increased supplemental oxygen. This group is described as having pulmonary deterioration. Most of the patients who develop pulmonary deterioration develop BPD. The risk factors that leads to deterioration are sepsis, fluid overload, PDA, and prolonged surfactant deficiency. Deterioration is more common in extreme prematures and extreme low birth weight (ELBW) babies [1, 3, 10].

Treatment

Management of BPD has a 2 way approach. To minimize the ventilator support and to maintain an adequate functional residual capacity with the use of nasal CPAP.Oxygen saturation should be kept at minimum level; between 85-93%[11].

Mechanical ventilation

Barotraumas, volutrauma, and atelectasis have direct effects on lung damage and increase the risk of BPD. Patient triggered ventilation, high frequency ventilation and minimal ventilation with early weaning decrease the incidence of BPD. Early nasal CPAP, delivered with bubble CPAP system, with avoidance of mechanical ventilation are associated with lower risk of BPD[12].

Supplemental oxygen

Supplemental oxygen is given in such a way that SpO2 levels are between 85-93% in preterm with gestational age< 32 week, 87-95% with gestational age between 32-36weeks and 90-97%in babies older than 37 weeks[13].

Surfactant replacement

Surfactant replacement therapy has apparently increased the incidence of BPD in children < 28 weeks, since more and more tiny babies are surviving. But it has dramatically decreased the incidence of BPD in preterm babies older than 32 weeks of gestational age. Concept of late surfactant therapy has improved the survival with little morbidity[10].

Fluid management

Intravenous fluid administration is limited to minimum required, that is to maintain a urine output of 1-2 ml/kg/hour and sodium concentration between 140-145 mEq/L. After improvement in the condition, calorie dense nutrients are administered to prevent under nutrition [3, 10].

Drugs

Vitamin A

Vitamin A is essential for maintaining

epithelial lining of respiratory tracts. Since preterm infants don't have sufficient vitamin stores, they are at risk of Vitamin A deficiency and develop permanent damages in the respiratory epithelium .Vitamin A in the dose of 5000 IU intramuscularly; three times a week for the first 28days has reduced the incidence of BPD in ELBW babies [10].

Caffeine citrate

Caffeine citrate in the dose of 20 mg/kg loading dose followed by 5 mg/kg as daily maintenance dose started during the first week to babies with birth weight < 1250 gm has reduced the incidence of BPD and improved the neurodevelopmental outcome in these babies. Caffeine is discontinued at around 34 weeks, when the apneic episodes have resolved [3, 10].

Inhaled nitric oxide

Inhaled nitric oxide relaxes the airways and reduces pulmonary vascular tone and decrease lung inflammation thus minimizing BPD[14].

Diuretics

Diuretic are used to decrease retained pulmonary fluids. This results in decreased lung water content, with decreased interstitial and peribronchial fluids. Furosemide at a dose of 1 mg/kg/dose is given intravenously two times a day for few days. Chlorothiazide is used for continuing the treatment to minimize the toxicity of furosemide [15].

Postnatal corticosteroids

Various clinical trials with corticosteroid administration in the preterm babies failed to demonstrate any benefit regarding the development or progression of BPD. More over they can contribute to development of hypertension, hyperglycemia, cardiomyopathy or adrenal suppression in the neonate and can also affect his/her growth adversely. Various studies using inhaled steroids like budesonide also did not show any good result. Hence routine use of oral, parenteral or inhaled corticosteroids are not advocated for managing a baby with BPD in the new born period [16].

Antioxidant therapy

Antioxidant therapy using metallopor phyrins and recombinant superoxide dismutase (rhSOD) has shown promising results in some studies. But further trials are needed before recommending these drugs for treatment of BPD[3].

Outcome

BPD is one of the most common causes of mortality in preterm babies. Survivors are characterized by long term respiratory symptoms leading to reactive airway disorders and emphysema and they are characterized by having frequent severe lower respiratory tract infections requiring oxygen therapy, nebulizations and frequent hospitalizations. Among the non-respiratory manifestations, developmental delay ranks first probably due to associated intraventricular hemorrhage. They are prone for malnutrition and poor growth. Upper airway damage due to prolonged intubation, systemic hypertension, hearing and visual defects are other handicaps they are likely to have [3, 10].

Summary

BPD remains the commonest cause of chronic persistent or recurrent lung disease in children. Newer achievements in the treatment modalities only changed the clinical pattern but not the prevalence of the disease. We may hope that recent advances like caffeine, inhaled nitric oxide, anti -oxidants, and the less aggressive modes of therapies like minimum mechanical ventilation, early use of nasal CPAP, prolonged surfactant therapy will change the scenario in the near future [16].

References

1) Trembath A, Laughon M M, Predictors of bronchopulmonary dysplasia, Clin Perinatol 39 (2012) 585–601

2) Bates M L, Pillers D M, Palta M., Ventilatory control in infants, children, and adults with bronchopulmonary dysplasia, Respiratory Physiology & Neurobiology 189 (2013) 329– 337

3) Keller R L, Ballard R A., bronchopulmonary dysplasia in 658 in Avery's diseases of new born, 9th edn, Christine A. Gleason, Sherin U. Devaskar (editors). ElsevierSaunders; Philadelphia ; 2012;658-671

4) Bhat R., Management of bronchopulmonary dysplasia, Journal of Neonatology, vol 27,No1, January –March 2013:46-56

5) Vidyasagar D., Bronchopulmonary dysplasia: An emerging problem in India:Journal of Neonatology, vol 27,No1, January – March 2013:66-74

6) Fischer HS, Bührer C, Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis, Pediatrics - Nov 2013; 132(5); e1351-60

7) Ambalavanan N, Walsh M, Bobashev G, Das A, Levine B, Carlo WA, Higgins RD, Intercenter differences in bronchopulmonary dysplasia or death among very low birth weight infants. Pediatrics - Jan 2011; 127(1); e106-16

8) Prendergast M, May C, Broughton S, Pollina E, Milner AD, Chorioamnionitis, lung function and bronchopulmonary dysplasia in prematurely born infants. Arch. Dis. Child. Fetal Neonatal Ed. - Jul 2011; 96(4); F270-4

9) Vohr B.R., developmental Outcomes of Extremely Preterm Infants; Clin Perinatol 41 (2014) 241–255

10) Prasad R.B.; Bronchopulmonary dysplasia/ chronic lung disease In Manual of neonatal care; John P Cloherty(ed);7th edition;2011;417-428

11) Bhandari V., Noninvasive Respiratory Supportin the Preterm Infant; Clin Perinatol 39 (2012) 497–511

12) Pfister R.H., Soll R.F., Initial Respiratory Support ofPreterm InfantsThe Role of CPAP, the INSURE Method, andNoninvasive Ventilation; Clin Perinatol 39 (2012) 459–481

13) May C, Patel S, Kennedy C, Pollina E, Rafferty GF, Prediction of bronchopulmonary dysplasia. Arch. Dis. Child. Fetal Neonatal Ed. - Nov 2011; 96(6); F410-6

14) Vom Hove M, Prenzel F, Uhlig HH; Pulmonary outcome in former preterm, very low birth weight children with bronchopulmonary dysplasia: a case-control follow-up at school age. J. Pediatr. - Jan 2014; 164(1); 40-45.

15) Slaughter JL, Stenger MR, Reagan PB; Variation in the use of diuretic therapy for infants with bronchopulmonary dysplasia;Pediatrics - Apr 2013; 131(4); 716-23

16) Bose CL, Dammann CE, LaughonMM ; Bronchopulmonary dysplasia and inflammatory biomarkers in the premature neonate. Arch. Dis. Child. Fetal Neonatal Ed. - Nov 2008; 93(6); F455-61