SYMPOSIUM : NEONATOLOGY – II
Evidence and Experience in Neonatal Medicine

Bronchopulmonary Dysplasia: An Update

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is a chronic lung disease associated with premature birth and characterized by early lung injury. Over the past 4 decades, there have been significant changes in its definition, pathology and radiological findings as well as management of BPD. Management of the acute phase and later stages of this lung disease continue to evolve. Use of non-invasive ventilatory techniques, recombinant human SOD and CC10 and inhaled NO are some novel approaches that are being studied. Adequate nutrition is vital to optimize lung growth and repair. The widely accepted practice of prophylaxis against viral infections has markedly decreased the rates of rehospitalization. Infants with BPD, however, continue to have significant pulmonary and neurodevelopmental sequelae. Unraveling the genetic contribution to BPD will potentially pave the way to improved preventive and therapeutic approaches. **[Indian J Pediatr 2007; 74 (1) : 73-77]**
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Key words : *BPD; Prematurity; Chronic lung disease*

The lack of a uniformly accepted definition of bronchopulmonary dysplasia (BPD) is related to the general disagreement amongst caregivers about the need for supplemental oxygen based on oxygen saturations on pulse oximetry. At a consensus meeting of National Institutes of Health in 2001, a new criteria for diagnosis and severity of BPD were proposed[1] which have been summarized in Table 1. During this meeting, it was also recommended that the original nomenclature of BPD be reinstated instead of "chronic lung disease of infancy" since BPD is distinct from the numerous other chronic lung diseases in pediatric and adult age groups.[1]

Incidence

The incidence of BPD is difficult to assess given the lack of universally accepted definition of BPD. The "classic" BPD described by Northway in 1967[2] has now been replaced by less severe forms of "new" BPD, which are infrequently found in patients >30 weeks of gestation and birth weights >1200 grams. In a recent study, where BPD was defined as oxygen need at 36 weeks post menstrual age, the incidence was 52% in infants with birth weights of 501-750g, 34% in infants with birth weights of 751-1000g, 15% in infants with birth weights of 1001-1200g, and 7% in infants with birth weights of 1201-1500g.[3]

Pathology

The pathology of the BPD lung from the pre-surfactant era was remarkable for presence of severe airway injury, inflammation and parenchymal fibrosis and marked heterogeneity in lung pathology with severe alveolar septal fibrosis in some areas and presence of normally inflated and/or hyperinflated lung in the adjacent sub-lobule or lobe.[4,5]

Pathological findings of the "new" BPD lung reveal more uniform inflation and less marked fibrosis and absence of both small and large airway epithelial metaplasia, smooth muscle hypertrophy and fibrosis, as compared to lungs of infants with "classic" BPD. Arrest of acinar development, resulting in decrease in alveolar number and a decrease in the arterial count with normal alveolar/arterial ratio was reported in the lungs of the patients with BPD regardless of whether the patients were treated with surfactant.[6] In addition to decreased alveolar number, various other abnormalities of distal microvasculature have been reported which include marked angiogenesis, proportionate to the growth of the air-exchanging lung parenchyma,[7] prominent corner vessels with variable capillary density in adjacent alveoli [8] or vessels that are more distant from the air surface.[7,9] All this data suggests that prenatal and postnatal alveolar and vascular development are closely linked.

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Table 1. Diagnostic Criteria for BPD.

	MILD Supplemental O_2 (for 28 days) and	MODERATE Supplemental O_2 (for 28 days) and	SEVERE Supplemental O_2 (for 28 days) and
< 32 weeks GA at birth	RA at 36 weeks corrected GA or at discharge	<0.3 FiO_2 at 36 weeks corrected GA or at discharge	≥ 0.3 FiO_2 +/- positive pressure support at 36 weeks corrected GA or at discharge
≥ 32 weeks GA at birth	RA by postnatal day 56 or at discharge	<0.3 FiO_2 by postnatal day 56 or at discharge	≥ 0.3 FiO_2 +/- positive pressure support by postnatal day 56 or at discharge

BPD: bronchopulmonary dysplasia; FiO_2: fraction of inspired oxygen; GA: gestational age; RA: room air

Pathogenesis

A proposed mechanism for the development of BPD has been shown in Fig. 1. An imbalance in the release of pro- and anti-inflammatory cytokines, occurring as a result of volu/baro trauma, hyperoxia, pulmonary edema, and/or sepsis, damages the immature lung. This is followed either by healing (resolution of injury) or repair of the lung (BPD).[10] Cytokine release and the responses of the immature lung are determined by allelic differences of the genes, creating a genetic susceptibility to BPD.[11]

Management

The principles of management, including pharmacotherapy, have been summarized in Table 2.

Outcomes in BPD

Pulmonary

Morbidity: There is significant pulmonary morbidity associated with BPD. Infants with BPD have higher rates of rehospitalizations, with up to 50% of very low birth weight (VLBW) infants with severe BPD needing re-hospitalization in the first year of life and 36% re-hospitalized the second year of life.[12] The commonest reasons for re-hospitalization in this population were reactive airway disease, pneumonia, respiratory syncytial virus (RSV) infection and worsening BPD. [12]

Radiological findings: Most studies show abnormal chest

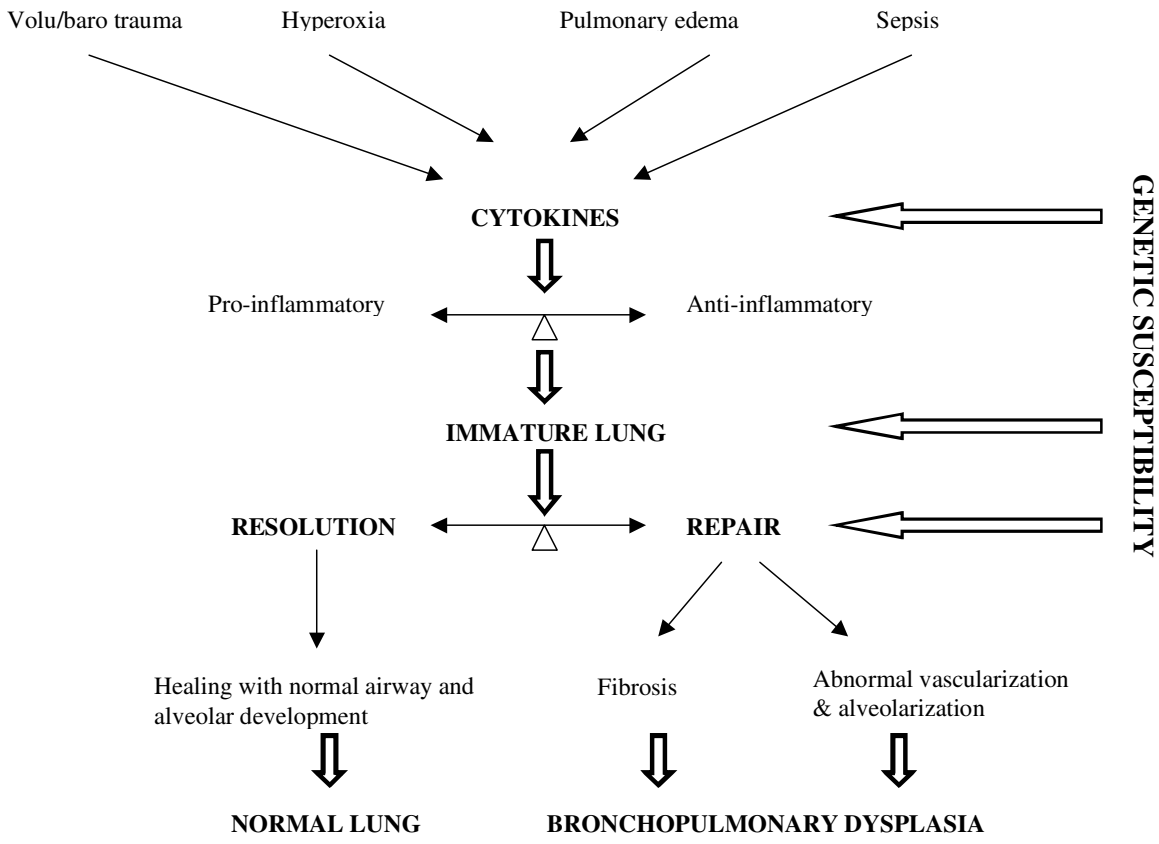

Fig. 1. Pathogenesis of BPD.

TABLE 2. Management of BPD.

Intervention	Mechanism of Action	Comments
Oxygen Supplementation	To prevent oxygen toxicity (early phase). To prevent development of pulmonary hypertension and cor-pulmonale (later stage).	Maintain oxygen saturations between 88-92% (acute phase) and 90-95% (later stage). A wide variation in the acceptable oxygen saturation levels exists across centers.
Ventilatory strategies	Early phase: Short inspiratory times (0.24-0.4s),[35] rapid rates (40-60/min), low PIP (14-20 cm H_2O), moderate PEEP (4-6 cm H_2O), low tidal volume (3 - 6 mL/kg). Later stage: Adjust settings to maintain target blood gases.	Minimize time spent on endotracheal tube ventilation. If intubated, give "early" surfactant.[36] Extubate early to SNIPPV/NCPAP. Blood gas targets: pH 7.25-7.35 PaO_2 40-60 mm Hg (early phase) PaO_2 50-70 mm Hg (later stage) $PaCO_2$ 45-55 mm Hg (early phase) $PaCO_2$ 50-65 mm Hg (later stage). High frequency ventilation for "rescue", if conventional ventilation fails.
Methylxanthines	Central respiratory stimulant, decreases diaphragmatic fatigability, weak bronchodilator and diuretic.	Improves successful extubation rate. Decreases BPD.[37]
Vitamin A	Improving lung healing, decreasing susceptibility to infection, and increasing the number of alveoli.	If considering use, dose is 5000 IU administered intramuscularly 3 times per week for 4 weeks. 1 additional infant survived without BPD for every 14 to 15 infants who received vitamin A.[38]
Steroids	Decrease inflammation in the lungs.	Dexamethasone effective in weaning off mechanical ventilation when used "moderately early" and "delayed".[39, 40] Increased incidence of neurological sequelae with early use (<96 hours).[41] Inhaled steroids are used, especially in moderate to severe BPD, with no clear clinical benefit.
Diuretics	Decrease lung water and improve lung compliance.	Result in significant decrease in oxygen required, though duration of oxygen requirement is not significantly decreased. Furosemide: use daily or every other day in the acute phase Spironolactone and Thiazides: use for chronic therapy
Beta agonists	Bronchodilatation by decreasing airway resistance, improving dynamic compliance. Relieves hypoxic bronchoconstriction.	Nebulized albuterol is the most commonly used formulation. Transient relief. May increase large airway instability in infants with tracheomalacia and bronchomalacia.[42]
Anticholinergics	Bronchodilatation	Used in combination with beta agonists in infants with bronchospasm.
Nutrition	Promote lung and somatic growth	Optimal weight gain of 15-20 g/day
Immunization	Prophylaxis against RSV and influenza. Other immunizations should be as per chronological age rather than corrected gestation.	Decreases incidence of re-hospitalization and morbidity

PIP: peak inspiratory pressure; PEEP: positive end expiratory pressure; SNIPPV: synchronized nasal intermittent positive pressure ventilation; NCPAP: nasal continuous positive airway pressure

X-rays with subtle radiological abnormalities later in adolescence and adulthood.[13] Aquino *et al*[14] have reported a positive correlation between abnormal radiographic findings and pulmonary function.

Pulmonary Function: Most infants with BPD have decreased airway conductance and increased airway resistance which typically normalizes by 2-3 years of age.[15] Most children with history of BPD have significantly lower forced vital capacity (FVC), forced expiratory volume at 1 second ($FEV_{1)}$, forced expiratory flow at 25% of FVC (FEF_{25-75}), and increased residual volume/total lung capacity (RV/TLC) when compared to normal full term infants and preterm controls without BPD.[13]

Small airway abnormalities and airway hyperresponsiveness are most likely to persist long-term in patients with BPD.[10, 13] Tracheomalacia and bronchomalacia result from prolonged endotracheal intubation

and mechanical ventilation and are associated with increased airway compliance which predispose these infants to impaired airway clearance and acute episodes of cyanosis commonly referred to as "BPD spells". Other large airway problems commonly encountered are subglottic stenosis, airway granulomas and pseudopolyps and may require surgical intervention.

Mitchell *et al*[16] reported a decreased gas transfer and oxyhemoglobin saturations during exercise in school aged children (6-9 years) with past history of BPD when compared with full term controls and preterm children with no BPD, and attributed it to persistent lung structural abnormality or residual right ventricular dysfunction. Santuz *et al*[17] showed decrease in maximal exercise in capacity in BPD survivors aged 6-12 years when compared to healthy controls. Most studies, however, show no reduction in exercise capacity in children with BPD when compared to children with healthy term infants or preterm babies without lung disease.[10]

Neurodevelopmental

VLBW infants with BPD children have a greater fine and gross motor skill impairment as well as cognitive function and language delay as compared to VLBW infants without BPD.[18, 19]

Experimental Therapies

Use of early nasal continuous positive airway pressure (NCPAP)[20] or synchronized nasal intermittent positive pressure ventilation (SNIPPV)[21, 22] to minimize injury to the immature lung, has shown some benefit and large randomized clinical trials are currently underway.

Inhaled nitric oxide (iNO) may[23, 24] or may not[25, 26] be beneficial, and hence, more studies are needed to better identify the potential benefits to the target population that develop BPD.

Although the antioxidant recombinant Cu-Zn superoxide dismutase (SOD), did not show any difference in outcome,[27] infants <27 weeks of gestation that received SOD had decreased hospitalizations, emergency room visits and less frequent use of bronchodilator therapy at age 1 as compared to the infants that did not receive SOD,[28] suggesting that SOD may have interrupted an inflammatory cascade involving reactive oxygen reactive species and possibly conferring a long-term benefit.

Use of an anti-inflammatory protein, recombinant human Clara cell 10-kD protein (CC10) has shown some initial promise.[29]

Prevention

Prevention of BPD is obviously dependent on the prevention of premature labor and birth. Etiologies of preterm labor and premature rupture of membranes are currently being studied and a better understanding of these will likely impact on the incidence of preterm labor and hence, the number of infants at risk for development of BPD. The use of progesterone in prevention of premature labor has shown promise, although the prolongation of gestation as a result of use of progesterone, has yet to be shown to improve infant outcomes.[30] As far as prenatal lung maturation is concerned, antenatal steroids remain the single most effective intervention thus far.

Prevention, early diagnosis and treatment of sepsis, management of nutrition and fluid/electrolytes along with appropriate ventilatory management during the often stormy perinatal period remain of utmost importance to make an impact on the morbidity and mortality associated with BPD.[31-34] Lastly, twin studies have shown a strong genetic susceptibility to BPD, and thus, further unraveling of the genetic contribution to BPD will potentially pave the way for gene specific therapies.[11]

CONCLUSION

BPD is a chronic lung disease associated with premature birth and early lung injury. Understanding of the various mechanisms of development of this lung disease has progressed dramatically over the last 4 decades. These 4 decades have also seen a change in its definition, pathology and radiological findings as well as management of BPD. Management of the acute phase and later stages of this lung disease as well as other co-morbidities in preterm infants continue to play a role in the resolution of BPD. Adequate nutrition is vital to optimize lung growth and repair. The widely accepted practice of prophylaxis against viral infections has markedly decreased the rates of rehospitalization. Infants with BPD, however, continue to have significant pulmonary and neurodevelopmental sequelae.

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