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Neonatology

Pathogenesis & Management of Bronchopulmonary Dysplasia

Dr. Rabindran[1*], Dr. Shasidaran[2]
[1]Consultant, Neonatologist, Billroth Hospital, Chennai, India
[2]Senior Resident, Department of Radiology, S.R.M. Medical College and Research Centre, Chennai, India

Review Article

***Corresponding author**
Dr. Rabindran

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Abstract: Bronchopulmonary dysplasia is defined as oxygen dependency at 28 days of age or 36 weeks postmenstrual age. Pathophysiology of BPD is characterized by cytokine dysregulation, pulmonary edema, increased alveolar & capillary permeability, arrest in lung development & pulmonary interstitial thickening. Pathology in old BPD consists of alternating areas of atelectasis & overinflation, severe airway epithelial lesions, airway smooth muscle hyperplasia, extensive fibroproliferation, pulmonary hypertension & decreased internal surface area of alveoli. New BPD consists of fewer & larger simplified alveoli, negligible airway lesions, variable airway smooth muscle hyperplasia, variable interstitial fibroproliferation, fewer & dysmorphic capillaries & less severe arterial lesions. Risk factors for development of BPD include Prematurity, Mechanical ventilation with subsequent barotrauma / volutrauma, Oxygen toxicity, Genetic polymorphisms, Patent ductus arteriosus, fluid overload, Poor nutrition, Infection & inflammation & Surfactant deficiency. Abnormal vasculogenesis, hyperoxia, oxidant injury, nutritional imbalance, extracellular matrix alterations, nitric oxide, altered immune system, genetic factors, mechanical ventilation induced lung injury, PDA & fluid overload are some of the factors favouring occurrence of BPD. Management of BPD consists of judicious use of oxygen, steroids, caffeine, diuretics, gentle ventilation & antioxidant therapies.
Keywords: Bronchopulmonary dysplasia, New BPD, Steroids.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is characterized by airway injury, inflammation & parenchymal fibrosis among preterm infants who had received mechanical ventilation [1]. Previously oxygen supplementation at 28 days of age [2] or at 36 weeks postmenstrual age [3] were considered as definitions of BPD; however both were inaccurate in predicting long-term outcome [4]. In post-surfactant era, many preterms with BPD have mild initial respiratory course requiring minimal ventilatory support but subsequently deteriorate over time [5].

Pathology of BPD

Pathophysiology of BPD is characterized by 1) developmental dysregulation of proinflammatory cytokines; 2) cytokine-mediated lung inflammation; 3) pulmonary edema; 4) increased alveolar epithelial & capillary endothelial permeability; 5) volu-,baro, or oxy-trauma from mechanical ventilation & supplemental oxygen; 6) abnormal expression of local parenchymal & vascular growth factors leading to an arrest in lung development; 7) pulmonary interstitial thickening resulting in poor gas exchange.

Pathology in old BPD consists of alternating areas of atelectasis & overinflation, severe airway epithelial lesions, airway smooth muscle hyperplasia, extensive fibroproliferation, pulmonary hypertension & decreased internal surface area of alveoli. Comparatively, new BPD consists of fewer & larger simplified alveoli, negligible airway lesions, variable airway smooth muscle hyperplasia, variable interstitial fibroproliferation, fewer & dysmorphic capillaries & less severe arterial lesions [6, 7]. Decreased alveolarization & diminished, dysmorphic PECAM (platelet endothelial cell adhesion molecule) staining are consistent with an arrest at canalicular phase of lung development [6]. There is partial to complete arrest in alveolar-saccular development with decreased & diffuse alveolar septal fibrosis after receiving surfactant [7]. Risk factors for development of BPD include Prematurity, Mechanical ventilation with subsequent barotrauma/volutrauma, Oxygen toxicity, Genetic polymorphisms, Patent ductus arteriosus, fluid overload, Poor nutrition, Infection & inflammation & Surfactant deficiency. Factors in pathogenesis of BPD are mediated by hyperoxic lung injury, antioxidants, Nitric oxide (NO), pulmonary neuroendocrine system,

peptide growth factors, immune system & genetic polymorphisms.

Vascular Hypothesis

During lung development, vascular growth is closely associated with alveolarization & any inhibition of vascular growth directly impairs alveolarization [8]. Vascular endothelial growth factor (VEGF) is involved in vasculogenesis & angiogenesis & hence impaired VEGF signaling leads to BPD [9]. Lower levels of VEGF were observed in tracheal aspirates during days 4 to 7 among infants who later developed BPD [10] & Anti-angiogenic factors such as endothelial-monocyte activating polypeptide II was increased [11].

Hyperoxia, antioxidants & nutrition

Oxygen alone can arrest septation of lungs in saccular stage of development [12]. Premature infants have low levels of antioxidants such as vitamins C & E, increasing their vulnerability to oxygen toxicity. Oxidative stress affects a complex array of genes involved in inflammation, coagulation, fibrinolysis, extracellular matrix turnover, signal transduction & alveolar enlargement [13]. Direct exposure to high concentrations of oxygen can damage the pulmonary epithelium, thereby causing BPD. Oxygen toxicity is mediated through reactive oxygen species. Hyperoxia augments transdifferentiation of pulmonary lipofibroblasts to myofibroblasts [14], increases apoptosis & expression of p21 & p53 [15], alters expression of cyclins & cyclin-dependent-kinase that control cell proliferation [16]. Antioxidants like N-acetyl cysteine & cysteine decrease further with onset of BPD [17]. Normal rise in vitamin C in bronchoalveolar lavage fluid noted during second week among preterms is delayed by 2 weeks in infants with BPD [18].

Extracellular matrix alterations

Extracellular remodeling occurs owing to changes in synthesis & deposition of extracellular matrix molecules such as collagen, elastin & fibronectin associated with degradation of extracellular matrix, modulated by various matrix metalloproteinases (MMPs) & tissue inhibitors of MMPs (TIMPs). Infants with BPD have lower plasma MMP-2 but higher MMP-9 & TIMP-1 levels [19]. There is increased collagen content [20] with abnormal scaffolding, thickened collagenous saccular walls, widened interstitium & arrest in septation [21]. Pulmonary basement membrane damage & defect in its modeling/remodeling are early hallmarks of BPD. Lower total level of MMP-2 in tracheal aspirates is an independent risk factor for BPD [22].

Nitric oxide and nitrotyrosines

Nitric oxide (NO) regulates pulmonary vascular, airway tone & inflammation. NO is a downstream regulator of VEGF & also contributes to oxidant stress via peroxynitrites. Plasma levels of 3-nitrotyrosine are increased during the first month in infants with BPD [23].

Neuroendocrine system & Peptide growth factors

Lung development & repair are modulated by various peptides like transcription factors (Nkx2, GATA), signaling molecules (transforming growth factor-beta, fibroblast growth factor, platelet-derived growth factor, bone morphogenetic factor-4) & extracellular matrix proteins [24]. Pulmonary neuroendocrine cells that secrete bombesin like peptides are increased in infants with BPD [25]. Parathyroid hormone–related protein deficiency is associated with BPD [26].

Immune system and inflammation

BPD is associated with maternal chorioamnionitis as intraamniotic endotoxin exposure can disrupt alveolar development, thereby reducing number of alveoli. Chorioamnionitis & postnatal infection amplify the inflammatory response of premature lung to mechanical ventilation [27]. Decreased production of anti-inflammatory cytokines, such as interleukin (IL)-10 & relative adrenal insufficiency contribute to the prolonged inflammatory state. Elevated cytokines like interleukin-6 & interleukin-8 may initiate the inflammatory cascade predisposing to BPD [28]. Chemokines such as MCPs (monocyte chemoattractant proteins) 1–3 & MIPs (macrophage inflammatory proteins) 1a & b are increased in tracheal aspirates of infants who develop BPD [29]. Prolonged neutrophil influx & increased cytokine activity in bronchoalveolar lavage fluid, colonization with specific microorganisms, such as Cytomegalovirus & Ureaplasma Urealyticum has been associated with an increased likelihood of BPD.

Genetic influence

Genetic predispositions to BPD have been identified in antioxidant defenses (eg, less efficient isoforms of glutathione-S-transferase-P1 [30]) & surfactant proteins [31]. Polymorphisms in intron 4 of the SP-B gene 55 & dominant mutations of SP-C56 are associated with BPD.

Mechanical ventilation

Premature lungs are susceptible to injury due to presence of immature alveoli that are surfactant deficient, atelectatic, fluid filled & supported by a highly compliant chest wall. Ventilator induced lung injury can be divided into high ventilator pressures (barotrauma), high tidal volume delivery (volutrauma) & repeated opening & closing during ventilation of closed atelectatic alveoli (atelectrauma) [32]. Multiple proinflammatory & chemotactic factors (macrophage inflammatory protein-1, interleukin-6, interleukin 1-beta, & interleukin-8) are found in the air spaces of ventilated preterm infants from day 1 of life in air spaces of infants who subsequently developed BPD [33].

PDA & fluid overload

Due to increased pulmonary blood flow & subsequent increase in interstitial lung fluid, PDA causes increased pressure, oxygen requirements & also increases duration of ventilation. PDA is associated with elevation of myeloperoxidase in alveolar lavage fluid suggesting damage to pulmonary endothelium & subsequent adhesion & migration of neutrophils to lung tissue [33].

Management of BPD

As the pathogenesis of BPD is multifactorial, the management consists of addressing the primary pathology. Generally preventive strategies of BPD occurrence like judicious oxygen weaning, early extubation, prompt use of antibiotics & treatment of PDA with proper fluid balance is better than treating an established BPD.

Antenatal & postnatal steroids

Antenatal glucocorticoids accelerate lung maturation, increase surfactant production & lung compliance, reduce vascular permeability & increase lung water clearance [34]. They help in lung septation & maturation of alveolar-capillary membrane leading to better gas exchange. Postnatal administration of dexamethasone is associated with earlier extubation & decreased BPD. Early postnatal dexamethasone treatment begun within 14 days of life significantly reduces risk of BPD at 28 days postnatal age & 36 weeks postmenstrual age [35]. Inhaled steroids are also shown useful in prevention & treatment of BPD [36].

Caffeine therapy

Caffeine use is associated with lower incidence of BPD. Methylxanthines act by non-specific inhibition of adenosine receptors A1 & A2.

Diuretics

BPD initially presents with an exudative phase during which pulmonary edema develops due to proinflammatory cytokine-induced increased alveolarcapillary membrane permeability. They improve lung mechanics by reducing alveolar & interstitial oedema [37]. Through drug-induced increases in local prostaglandin production, furosemide causes pulmonary vasodilation & via selective inhibition of upregulated pulmonary Na-2Cl-K cotransporter it also favors transpulmonary fluid absorption [38]. Furosemide inhibits noncholinergic & nonadrenergic contraction of bronchial smooth muscle, resulting in bronchodilation & decreases airway resistance. It decreases release of inflammatory mediators, including leukotrienes & histamine from lung tissue [39] & IL-6 by blood mononuclear cells [40].

Ventilatory strategies: Volume targeted modes of ventilation

Volume targeted modes have advantages over traditional pressure limited methods as they reduce incidence of BPD [41]. Ventilatory strategies include minimizing ventilatory support by early use of nasal CPAP, tolerating higher $PaCO_2$, using low tidal volume. Early initiation of nasal CPAP reduces need for intubation & mechanical ventilation thereby reducing BPD [42]. Nasal intermittent positive pressure ventilation (NIPPV) improves tidal & minute volumes & decreases occurrence of BPD [43].

Nutrition

Nutrition helps in normal lung development & repair. Under-nutrition & protein deficiency increase the vulnerability of oxidant induced lung damage & impair lung growth & DNA synthesis. Vitamin A, Inositol, selenium, sulphur containing amino acids & Vitamin E protect against BPD [44]. Daily calorie intake should be increased to 120 to 150 Kcal/kg. Human Milk Fortifier, fat supplementation, multivitamin supplements help in increasing nutritional intake.

Antioxidant therapy

Preliminary studies in premature infants have shown that prophylactic use of both single & multiple intratracheal doses of recombinant human CuZn superoxide dismutase mitigate inflammatory changes & severe lung injury from oxygen & mechanical ventilation. Administration of antioxidants like vitamin C & E antenatally might reduce BPD not only by increasing anti-oxidant defences, but also by reducing preterm delivery as they reduce occurrence of maternal preeclampsia.

CONCLUSION

BPD is one of the dreadful complications among preterm newborns.With advancement of medical care & increased survival of extreme preterms there is increase in the incidence of BPD. Understanding the pathology of BPD & prompt management is mandatory for improving survival of such preterms.

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