Bronchopulmonary Dysplasia

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EDUCATION COORDINATOR
Bronchopulmonary Dysplasia

- Definition
- Incidence
- Pathogenesis
- Pathophysiology
- Respiratory management
- Future therapies
Definition

- Classic BPD as described by Northway in 1967
- “New” BPD

Classic BPD

- First described by Northway in 1967
- He noticed the chronic lung changes the babies who survived mechanical ventilation for treatment of RDS

- Divided into four stages
  - Stages 1 and 2 occur in 1st ten days of life and are indistinguishable from RDS
  - Stages 3 and 4 transition into chronic stages of lung disease

- Required component:
  - Respiratory support beyond one month of age
  - Ventilation or oxygen therapy
Chest X-ray

- Cyst formation
- Fibrotic changes
- Hyperexpansion
- Alternating areas of atelectasis
New BPD

- Bancalari further refined the definition to include
- Ventilation for the first three days of life
- Respiratory symptoms at 28 days of life
  - tachypnea
  - auscultatory rales
  - retractions
- Need for supplemental oxygen to maintain a partial pressure of oxygen at 50 mmHg
- Most important definition is the need for supplemental oxygen at 28 days of life and appropriate radiographic findings

BPD X-ray
Incidence

- Depends on birth weight and is inversely related

- <1000 g: 40-85%
- 1000-1500 g: 10-30%
- >1500 g: 3-5%
Pathogenesis

Intrauterine lung development → Extraterine lung development → BPD

Canalicular stage

Saccular stage

Preterm delivery at 26 weeks GA → Alveolar stage

Term: 20 24 28 32 36 40
Pathogenesis

- At 26 weeks saccules function as “alveoli”
- Vascular proliferation finishes at 26 weeks
- Alveolar hypoplasia
- Alveoli appear around 30 weeks
- Fetal lung must continue to develop
Pathogenesis of BPD

- Infection/Cytokines
- Initiation of Ventilation
- Glucocorticoids
- Nutrition

- Stress
- Intrauterine Lung Development
- Antenatal Glucocorticoids

- Postnatal Lung Development
- Lung Injury; Inhibition of Lung Development

- Inflammation
- Overdistention
- Infection

- Oxygen
No single factor has been identified as the cause of BPD

- Barotrauma/Volutrauma
- Oxygen/antioxidants
- Inflammation
- Infection
- Nutrition
- Genetics
Barotrauma/Volutrauma

- Positive pressure ventilation provokes complex inflammatory cascade
- Cytokine release
- Surfactant deficiency
  - Increased surface tension
- Pulmonary interstitial emphysema (PIE)/Pneumothorax
- Strongly associated with the development of BPD
Oxygen/antioxidants

- Balance between oxygen free radicals and antioxidant defense

- Free radicals are toxic to living cells

- During oxidative metabolism free radicals are formed

- Hypoxia and inflammation increases free radical formation
Inadequate concentrations of antioxidants at birth

Damage caused by free radicals include:
- lipid peroxidation
- mitochondria injury
- protein nitration
- unraveling of nucleic acids

Chronic hyperoxia induces inflammation and lung injury

Epithelial and endothelial cells extremely susceptible to oxidant injury leading to edema and cell dysfunction
Antioxidants versus GA
<table>
<thead>
<tr>
<th>Radical</th>
<th>Symbol</th>
<th>Antioxidant</th>
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<tbody>
<tr>
<td>Superoxide anion</td>
<td>O$_2^-$</td>
<td>Superoxide dismutase, uric acid, vitamin E</td>
</tr>
<tr>
<td>Singlet oxygen</td>
<td>$^1$O$_2$</td>
<td>β-carotene, uric acid, vitamin E</td>
</tr>
<tr>
<td>Hydrogen peroxide</td>
<td>H$_2$O$_2$</td>
<td>Catalase, glutathione peroxidase, glutathione</td>
</tr>
<tr>
<td>Hydroxyl radical</td>
<td>OH$^-$</td>
<td>Vitamins C and E</td>
</tr>
<tr>
<td>Peroxide radical</td>
<td>LOO$^-$</td>
<td>Vitamins C and E</td>
</tr>
<tr>
<td>Hydroperoxyl radical</td>
<td>LOOH</td>
<td>Glutathione transferase, glutathione peroxidase</td>
</tr>
</tbody>
</table>

Reference: Avery's Neonatology

- Multicenter trial in 2000 published in Pediatrics

- Study question- ‘Determine if high FIO2 would prevent the development of severe ROP”

- Results-
  - Minimal effect on eyes
  - 55% increase of BPD and pulmonary infections
Inflammation

- **Causes**-
  - Oxygen free radicals
  - Pulmonary barotrauma
  - Infectious agents

- **Mechanism**
  - Activation of leukocytes and neutrophils to site of injury

- **Inflammatory mediators**
  - Cytokines
  - Tumor necrosis factor-alpha
  - Interleukin1-beta
  - Interleukin 8
  - Transforming growth factor- beta
Infection

- Studies show that infection leads to inflammation

- Types of common infection
  - Intrauterine infection
  - Chorioamnionitis
  - Funisitis

- Strong correlation between the presence of BPD and the development of late-onset sepsis

- Severity of BPD increased LOS and mortality
Nutrition

- Adequate calories and essential nutrients for growth may be lacking
- Immunologic and antioxidant defenses may be inadequate due to poor nutrition
- Increased metabolic needs and rapid growth requirements
- Antioxidant enzymes (e.g., copper, zinc, selenium)
- Vitamin deficiency - vitamin E and C
multicenter trial of vitamin A supplementation in premature infants at risk for developing BPD

- Demonstrated that large doses of intramuscular vitamin A three times per week
  - 7% reduction in the incidence of BPD

- Findings- Vitamin A deficiency is an important contributor to lung injury.
Genetics

- Strong family history for asthma

- Family history of airway hyperactivity

- Genetic research for BPD will potentially pave the way to improved preventive and therapeutic approaches
Respiratory Management

- Mechanical Ventilation
- Oxygen
- High frequency ventilation
- Continuous positive airway pressure
- Permissive hypercapnea
- Inhaled nitric oxide
- Bronchodilators
- Corticosteroids
Mechanical Ventilation

- **Prolonged ventilatory support**
- **Early Phase**
  - Short inspiratory times .24-.4 seconds
  - Rapid rates 40-60
  - Low PIP 14-20 cmH20
  - PEEP 4-6
  - VT- 3-6 mL/kg
  - FIO2@ < 50%
  - Blood gases
    - PaO2 40-60 mmHg
    - PaCO2 45-55 mmHg
Mechanical Ventilation

- Mean airway pressure maximized to reduce atelectasis
- Adequate humidity and temperature of 36.5 – 37.0
- Methylxanthines before extubation or NCPAP just after extubation may facilitate successful extubation
- HFOV as rescue if conventional ventilation fails
- Permissive hypercapnea (pH 7.28-7.35)
Oxygen

- Chronic hypoxia
- Vasoconstriction
- Pulmonary hypertension
- Oxygen is a pulmonary vasodilator- stimulating the production of endogenous NO
- PaO2 should be maintained between 50 and 70 mm Hg in infants with BPD
- Maintain oxygen saturations at 88% to 92%
- If oxygen-dependent infants can maintain an SaO2 of more than or equal to 90% for at least 40 minutes in room air they can be successfully weaned from supplemental oxygen
HFOV


- Meta-analysis

- Randomized 1771 preterm or low birth weight infants with respiratory failure to HFOV versus conventional ventilation

- Reduction in BPD at 36 weeks postmenstrual age (PMA) of borderline significance (random effects model RR = 0.70; 95% CI = 0.46-1.06)

- Randomized clinical trial
- 500 infants born at 601-1200g
- HFOV versus conventional ventilation before 4 hours of age
- Reduced the need for supplemental oxygen need at 36 weeks PMA from 56% to 47%

First to consider the possibility that the use of CPAP, a gentler less invasive form of respiratory support, might reduce pulmonary injury and subsequent BPD

After controlling for known confounding factors, the NICU with the highest use of CPAP had the lowest rate of BPD

Evidence-based approach is lacking
Continuous Positive Airway pressure


- Observational study of 171 infants born at 401-1000g

- Bubble CPAP used as the initial mode

- 10% trend toward improvement in the composite outcome of death or oxygen requirement at 36 weeks PMA

CPAP was used in an extremely preterm baboon model of BPD

125 days gestation (term baboon gestation is 185 days)
Preterm baboon infants were given two doses of surfactant, daily caffeine, and were extubated to CPAP at 24 hours of age versus conventional ventilation.

Evaluations at 28 days of the CPAP-treated animals showed:

- minimal evidence of pulmonary injury
- minimal fibrosis or inflammation
- pulmonary compliance similar to 156-day full term baboon infants
Permissive hypercapnea

- Provide adequate oxygenation and ventilation without associated lung injury

- “Gentle ventilation”

- Minimize barotrauma and volutrauma

- New data from the lamb model of BPD suggest that the benefits of permissive hypercapnea might extend beyond the reduction in pressure-induced pulmonary injury
Permissive hypercapnea

- Strand M, Ikegami M, Jobe AH.
- Effects of high PCO2 on ventilated preterm lamb lungs.
Preterm lambs subjected to identical peak inspiratory pressures, tidal volumes, and inspired oxygen.

Supplemental exogenous carbon dioxide to reach targeted PaCO2 levels ~100 mm Hg (control PaCO2s ~40-50 mm Hg).

Results.............

Decreased pulmonary inflammation
  - Decreased WBC
  - Decreased hydrogen peroxide (free radical)
  - Decreased IL-1 and IL-8 (inflammatory cytokines)

Suggesting a beneficial effect of higher PaCO2 independent of minimal ventilation-related reduction in barotrauma.
Permissive hypercapnea

- Randomized factorial design trial
- Primary outcome of death or BPD at 36 weeks PMA
- 220 infants
Carlo et al.

- 501-1000g requiring MV < 12 hours of age for a total of 10 days
- Used conventional ventilation
- FIO₂ >= .30 and dexamethasone
- (PaCO₂ < 48 mm Hg) OR (PaCO₂ > 52 mm Hg)
- Relative risk for death or BPD at 36 weeks PMA was 0.93 (95% CI = 0.77-1.12)
- Ventilator support was significantly reduced at 36 weeks in the hypercapnea group (1% vs 16%; P < 0.01)
Inhaled nitric oxide

- Randomized clinical trial of 207 infants
- Significant reduction in the composite outcome of death or BPD at 36 weeks PMA
- iNO treated (49% vs 64%).
Schreiber et al.

- Magnitude of this effect was greater among infants whose respiratory illness was less severe (oxygenation index <6.94)
- Mortality rates among control subjects in the study population were higher than have been observed at some centers, raising questions regarding whether the study results are generalizable to broader populations
- Take a prudent approach to iNO therapy among preterm infants
Bronchodilators

- β₂-agonist is the agent of choice in the treatment of reversible bronchospasm in infants with BPD
- Ipratropium bromide is a related muscarinic antagonist
- Methylxanthines (e.g., caffeine, theophylline)
Corticosteroids

- Potent anti-inflammatory properties
- Dexamethasone
- Down-regulation of the inflammatory cascade
- Improvements in pulmonary function in infants with severe BPD
- Excessive doses and prolonged use of corticosteroids result in:
  - Impair head growth
  - Neurodevelopmental outcome
  - Poor lung structure
  - Decreased long-term survival
NEWS FROM THE NURSERY
Future therapies

- Inositol
- Low-dose corticosteroid treatment
- Cytokine targeted therapies
Inositol is an essential nutrient

307 subjects enrolled in three relatively small clinical trials suggest that intravenous inositol supplementation from 5 to 20 days is associated with reduced mortality and oxygen dependence at 36 weeks PMA.

Larger multicenter clinical trials are needed to verify and assess the generalizability of these findings.

Reference upon demand.
**Low-dose corticosteroid treatment**

- Antenatal maternal treatment with betamethasone reduces surfactant deficiency and other complications of prematurity.

- Watterberg *et al.* were first to report cortisol deficiency among preterm infants at highest risk of BPD, and, in a pilot clinical trial, discovered that early low-dose hydrocortisone treatment was associated with a reduction in BPD among the treated infants.

- Postnatal dexamethasone- complications of treatment (e.g., hypertension, hyperglycemia, growth failure, intestinal perforation) and long-term neurodevelopmental disabilities.

- Further research needed.

- Reference upon demand.
Cytokine targeted therapies

- Cytokine therapies aimed at blocking harmful and up-regulating beneficial humoral factors

- Vozzelli et al. who tested antimacrophage chemokine (anti-MCP-1) treatment in a newborn rat model of lung injury

- Examination of the animals at one week showed reduced pulmonary macrophages and neutrophils in bronchoalveolar lavage fluid among the anti-MCP-1 treated group.

- References upon demand
References

The End