Chronic Neonatal Lung Disease

• Bronchopulmonary dysplasia (BPD) first described in 1967 by Northway
  • Defined as $O_2$ dependence at 28 days post birth
  • Now termed ‘old BPD’
• Post-surfactant era – ‘new BPD’
  • arrest at the canalicular phase of lung development
• Definition changed in 1988 to $O_2$ dependence at 36 wks
• Incidence of BPD
  • 68% of infants <29wks and <1500g
  • varies with gestational age
Pathology

Old BPD
• Alternating areas of atelectasis and hyperinflation
• Severe airway epithelial lesions
  • (hyperplasia and squamous metaplasia)
• Decreased internal surface area and alveoli
• Airway smooth muscle hyperplasia
• Extensive fibroproliferation
• Prominent vascular hypertensive lesions

New BPD
• Decreased, large and simplified alveoli
  • (alveolar hypoplasia, decreased acinar complexity)
• Negligible airway epithelial lesions
• Variable airway smooth muscle hyperplasia
• Variable interstitial fibroproliferation
• Decreased, dysmorphic capillaries
• Less severe arterial/arteriolar vascular lesions
• Less septal fibrosis that appears more diffuse
**BPD - definition**

- Defined by $O_2$ use\(^1\):
  - Changed again in 2000
  - $\geq 28$ days supplemental oxygen use

- Classified into:
  - Mild: breathing room air at 36w cga ($<32w$) or 56d ($\geq32w$) or discharge
  - Moderate: supplemental $O_2 <30\%$ FiO\(_2\) at 36w cga ($<32w$) or 56d ($\geq32w$)
  - Severe: $\geq30\%$ FiO\(_2\) or ventilation at 36w cga ($<32w$) or 56d ($\geq32w$)

\(^1\)Jobe. Am J Respir Crit Care Med 2001:163
Aetiology

- a heterogeneous group of lung disorders in infants
- results from complex interplay between
  - impairments in premature lung such as surfactant deficiency,
  - perinatal insults such as infection,
  - damage resulting from supportive care of the infant due to barotrauma or volutrauma from mechanical ventilation and oxygen toxicity from supplemental oxygen
Aetiology

Chronic inflammation in the infant lung

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Recurring cycles of lung damage and repair

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Impaired alveolarisation and vascularisation in the developing lungs

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Significant effects on lung mechanics, gas exchange, and pulmonary vasculature
Aetiology-Prenatal Factors

• Prenatal, result in impaired lung growth:
  • Maternal smoking
  • Chorioamnionitis
    • may amplify the inflammatory response of the premature lung to mechanical ventilation
    • Other studies have shown protective effect of chorioamnionitis
  • Ureaplasma colonisation
    • Meta-analysis found signif association
  • Pre-eclampsia

• Genetic
  • Studies of siblings and twins suggest a high concordance of BPD with shared genetic inheritance
  • Potential modifier genes could include
    • asthma-related genes
    • genes that encode the surfactant proteins
    • genes that encode for inflammatory cytokines: Tumour necrosis factor (TNF)-α
    • genes that encode for growth factors

• Epigenetic factors
Aetiology-Postnatal Factors

- Oxygen toxicity
  - mediated through reactive oxygen species
  - antioxidant defences lower in infants
    - glutathione peroxidase and catalase
    - N-acetyl cysteine (NAC), a precursor of cysteine, is rate-limiting precursor for glutathione synthesis
  - Vitamin A needed for normal lung growth and ongoing integrity of respiratory tract epithelial cells
Aetiology-Postnatal Factors

- Mechanical Ventilation
  - Barotrauma and volutrauma
  - Injury most likely during initial resus
- Infection
  - Bacterial sepsis assoc with higher rates of BPD
Aetiology-Postnatal Factors

- Patent ductus arteriosus (PDA)
  - Association between PDA and BPD
  - Compounded if infection also present
  - Indomethacin prophylaxis isn’t protective
  - PDA ligation ↑ BPD risk
- Association may be due to other factors
  - High fluid intake in first few days of life
  - Adrenal insufficiency
Treatment of NCLD - Prevention

• Antenatal prevention:
  • Prevention of premature birth e.g. progesterone
  • Antenatal steroids to induce lung maturation
  • Maternal antibiotics for chorioamnionitis
Treatment of NCLD - Prevention

• Postnatal prevention:
  • Ventilation strategies
    • Permissive hypercarbia; no proven benefit but trend to reduced rates BPD
    • Gentle ventilation; benefit from volume-targeted
    • nCPAP; +early prophylactic surfactant reduces BPD rates
    • Nasal intermittent positive pressure ventilation; reduces BPD
  • $\text{SaO}_2$ 90-95% to prevent $\text{O}_2$ toxicity
  • Inhaled nitric oxide (iNO): routine use not recommended-no proven benefit in humans
Treatment of NCLD - Prevention

• Postnatal prevention:
  • Corticosteroids: aid extubation, but significant side effects
  • Other drugs with evidence for benefit
    • Vitamin A; reduces BPD/death in extremely low birth-weight infants
    • Inositol (B vitamin cofactor); significant reduction in BPD in 2 trials
    • Recombinant human Clara cell 10-kilodalton protein (CC10), an anti-inflammatory protein has shown some initial promise
    • Recombinant Cu-Zn superoxide dismutase, an antioxidant, improved outcome in one study in babies < 27 wks
  • Caffeine; mechanism unknown
Treatment of NCLD - Prevention

• Postnatal prevention-therapies with no proven benefit
  • *N*-acetyl cysteine
  • Macrolides
  • Vitamin E
  • Selenium
  • Cromolyn
Treatment of NCLD

• Oxygen
• Nutrition
• Avoidance of ETS exposure
• Bronchodilators: no RCT proving benefit
• Inhaled corticosteroids: no RCT showing benefit
• Diuretics:
  • Loop diuretics e.g. frusemide no benefit in infants <3 wks old, and transient improvement in lung mechanics after single dose in older infants
  • Distal diuretics eg thiazides plus spironolactone: Cochrane review of chronic therapy given to infants >3 weeks old showed improved lung compliance but not long term outcome
• Immunisation
  • Routine immunisations
  • Prophylaxis against RSV and influenza decreases incidence of rehospitalization and morbidity
  • Parental influenza and pertussis
• Treatment of PAH
  • Sidenafil, bosentan
  • No RCTs showing benefit
Outcomes

- Many studies from pre-surfactant era
Morbidity

• 50% of preterm infants with BPD are re-hospitalised within first 2 years
• Respiratory symptoms persist beyond the first 2 years of life into the preschool years, adolescence, and early adulthood
• Symptoms similar to asthma – cough. SOB, wheeze
• Increased incidence of ‘asthma’
  • Different pathophysiology from asthma
  • No evidence to support conventional asthma treatment
Lung Function in BPD

• Increased airway reactivity
• 56% abnormal baseline spirometry at age 11yrs\textsuperscript{1}
• Variable reports of exercise test results

\textsuperscript{1}Fawke. Am J Respir Crit Care Med 2010; 182
Pulmonary Hypertension (PAH)

- 25% to 43% of BPD patients develop PAH
  - Fatal in 14% to 38% of those
- Develops due to disruption of the pulmonary circulation structure and a rise in pulmonary vascular resistance due to alveolar injury and inadvertent periods of hypoxia.
- Associated with worse survival rates
- More common in SGA
- Echocardiography does not accurately estimate systolic PAP consistently
- Improves with age, usually in first year
- Long term effects unknown
Quiz
A boy born at 28 weeks’ estimated gestational age (EGA) who requires FiO2 of 28% at 36 weeks of age is diagnosed with moderate (BPD). His nursery course was relatively uncomplicated. Given that he received state-of-the-art treatment both before and after birth, in 2014 the pathologic basis of his lung disease would primarily involve:

- A. diffuse cystic changes
- B. fibrosis of bronchiolar walls
- C. ongoing inflammation
- D. reduced numbers of alveoli
- E. smooth muscle hypertrophy
Question 2

A boy born at 28 weeks’ EGA is diagnosed subsequently with moderate BPD. Which of the following contributed most to the development of his BPD?

• A. early onset bacterial sepsis.
• B. indomethacin prophylaxis.
• C. low tidal volume ventilation.
• D. maternal chorioamnionitis.
• E. prolonged exposure to 30% FIO\textsubscript{2}
Question 3

Aside from averting premature birth, the most effective and safest way to prevent BPD in ELBW infants is the postnatal administration of

• A. azithromycin.
• B. cromolyn.
• C. oral glucocorticosteroids.
• D. selenium.
• E. vitamin A.
Question 4

A 5-month-old girl with moderate BPD still requires an FiO2 of 28%. Her long-term health is most likely to be promoted by

- A. augmented caloric intake.
- B. increased fluid intake.
- C. inhaled bronchodilators.
- D. inhaled glucocorticosteroids.
- E. loop diuretics.
The life span of a patient with severe BPD is most likely to be determined by

- A. alveolar development.
- B. degenerative grey matter disease.
- C. malnutrition.
- D. obstructive airway disease.
- E. pulmonary arterial hypertension.