Bronchopulmonary Dysplasia Infant Chronic Lung Disease

Department of Cardiopulmonary Sciences
RSTH 421: Neonatal Pediatric Respiratory Care
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BPD OBJECTIVES:

- Identify and define a definition of B.P.D.

Describe the incidence and risk factors for the development of B.P.D.

Describe the etiology, pathogenesis, and pathophysiology of B.P.D.

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BPD OBJECTIVES:

Describe the x-ray findings of B.P.D.

Identify and describe the clinical findings in B.P.D.

Discuss the treatment, interventions, management, and prognosis for B.P.D.

Given a clinical scenario recognize and suggest appropriate treatment for the BPD infant

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Bronchopulmonary Dysplasia

- Also known as Chronic Lung Disease (CLD) results primarily from the effects of positive pressure ventilation on a structurally and functionally immature lung. It is characterized primarily by prolonged O_2 requirements.
  The pathological condition of bronchopulmonary dysplasia (BPD) is frequently used interchangeably with CLD

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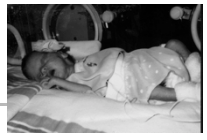
BPD



- The extremely preterm infant can be acutely injured by oxygen and/or CMV.
- Resulting in interference with or inhibition of alveolar and vascular development.
- Smaller and more immature infants constitute the majority of infants who develop BPD.

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Working Definition

- Pulmonary condition affecting premature infants who, after requiring mechanical ventilation during the first week of life, remain oxygen dependent for more than 28 days and have persistent increased densities on chest radiographs, less than 1200 grams.
- Oxygen requirements beyond 36 weeks post-conceptual age

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Incidence

- Inversely related to birth weight.
- 85% incidence in 500 - 699 grams.
- Approximately 5% in > 1500 grams.
- 20% of survivors of Mechanical ventilation develop BPD.
- Approximately 7K deaths each year, 10-15% die in the first year.

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Incidence/Risk Factors

- High FIO2, PPV, intubation, duration of therapy, degree of prematurity, genetic predisposition, inflammation, RDS, PDA, sepsis, and excessive fluid administration.

Who Gets BPD?

- The risk of getting BPD increases as the baby's weight and time in the mother's womb decreases. Today, most babies with BPD (9 out of 10) weighed 1,500 grams (about 3 and a half pounds) or less at birth. Babies born weighing less than 1,000 grams (about 2 pounds) are at very high risk. About 1 out 3 of these gets BPD. These small babies can get BPD even if they do not have RDS or need a breathing machine.

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Who Gets BPD?

- Today, larger and more mature babies rarely get BPD, due to better treatment of breathing problems in newborns. The larger and more mature babies who get BPD have had serious and prolonged breathing problems in the first days of life.

  About 5,000 to 10,000 babies in the U.S. get BPD each year. Because more babies weighing less than 3 pounds live past 4 weeks, more babies get BPD today than 30 years ago.

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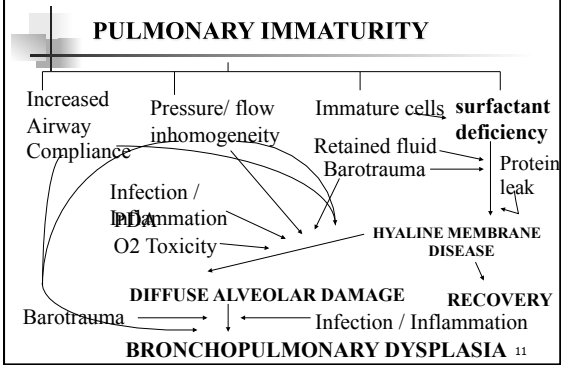
Pathogenesis



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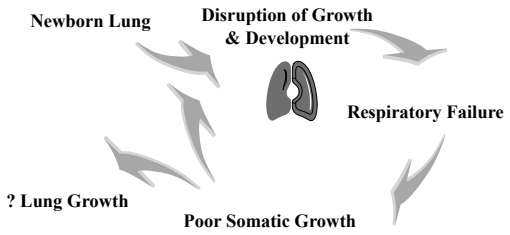
Development of BPD



Pathogenesis

- Features of the immature lung increasing susceptibility:
  - **Barotrauma** : Poorly compliant airspaces, but highly compliant airways
  - **Hyperoxia** : Poorly developed antioxidant defenses
  - **Infection** : Altered airway clearance, immature macrophages & WBC
  - **Inflammation** : Poorly developed anti-oxidant, antiproteolytic and antielastolytic systems
  - **Increased permeability** of the alveolo-capillary membrane with decreasing gestational age.

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Pathogenesis (contd.)

- Complications of Hyperoxia:
- Cytotoxicity → epithelium & endothelium → Pulmonary edema and hemorrhage
- Cytotoxicity on airway lining & macrophages → Poor airway clearance and increased infection
- Pulmonary edema + inhibition of surfactant synthesis leads to worsening compliance
- Inhibition of pulmonary vascular response to hypoxia leads to shunting , V/Q mismatch
- Inhibition of normal lung repair, healing by fibroblast proliferation
- Inhibition of normal lung development, decreased alveolarization
- Loss of pulmonary endothelial functions

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Pathophysiology

- Necrosis of respiratory mucosa and alveolar ducts filled with exudate and debris; then thickened septa and fibroblastic proliferation. Increased mucous production, scarring and fibrosis. Blebs and bullae alternating with areas of atelectasis due to airway obstruction

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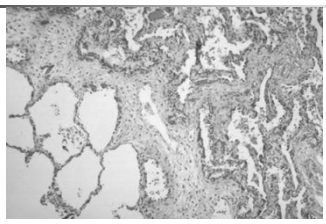
Histology BPD



- Low power of lung with BPD; severe fibrosis at upper right, compensatory emphysema of less damaged area at bottom left.

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Pathophysiology

- Formation of hyaline membrane, regeneration of and repair of alveolar epithelium, necrosis of alveolar epitheilium, bronchial smooth muscle metapplasia, intestinal fibrosis, formation of emphysematous blebs and bullae, pulmonary hypertension.

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Pathophysiology

- Pathologists can recognize changes in the lungs of infants soon after birth including airway epithelial necrosis and squamous metaplasia, organization of hyaline membranes, and fibroblastic proliferation in the lung interstitium, of those receiving CMV/02. This leads to eventual lung fibrosis and emphysematous changes.
  In practice the clinical course is usually a combination of these and may be prolonged with persisting pulmonary insufficiency.

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Pathophysiology, Lung Mechanics

- Decreased pulmonary compliance and increase airway resistance
- V/Q mismatching
- Excessive mucous secretion, interstitial edema, excess lung fluid.
- Lobar atelectasis due to mucous plugging.
- Hypercarbia and difficulty maintaining adequate PaO2

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Clinical Findings

- Failure to improve/thrive
- Persistent respiratory insufficiency
- Pulmonary edema with crackles
- Persistent retractions and tachypnea
- Difficult to wean, sensitive to FI02 changes
- ABG's, Partially compensated respiratory acidosis and hypoxemia
- Increased airway resistance

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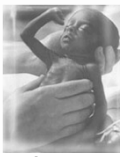
Pulmonary Function



- Decreased FEF
- Increased airway reactivity (persistent respiratory symptoms)
- Increased RV
- Normal TLC
- Carbon dioxide diffusion capacity maybe decreased.
  - Most normalized by 3 years of life, except for FEF that remains decreased.

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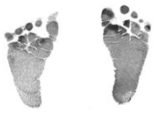
Chest X-Ray Findings

- Small rounded radiolucent areas alternating with radiopaque areas. Cystic lesaions, intersitital fibrosis, pulmonary edema, blebs and bullae.



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Radiographic Evidence

- Predictive for BPD at 36 weeks gestation: rehospitalization within one year, asthma meds., wheezing at age 8,
- Not a long term predictor of outcome or morbidity or mortality.
- Predictive with PDA
- Staging utilizing radiographic findings.

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Radiographic Evidence

- Staging utilizing radiographic findings (Northway, et al).
  - Stage I
    - First 3 days, RDS like
  - Stage II
    - 3-10 days, opaque, granular infiltrates, obscure cardiac markings
  - Stage III
    - 10-20 days, multiple small cysts, visible cardiac shadow
  - Stage IV
    - Greater than 28 days, ⇑ density, larger cysts

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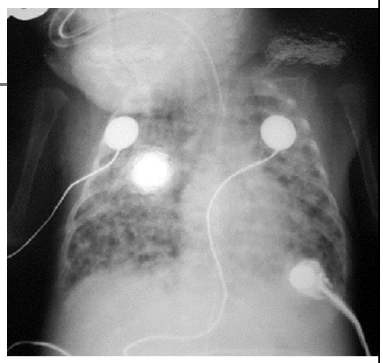
CXR

1. Severe diffuse bilateral atelectasis with pockets of trapped air (Swiss Cheese appearance)

2. Hazy heart borders

3. Et tube tip at T 3 (good placement).

4. Possibly Stage 3 BPD



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Pathophysiology, pre-Surfactant replacement Therapy

- Airway injury, inflammation, parenchymal fibrosis, mismatched ventilation, epithelial metaplasia, smooth-muscle hypertrophy
- Proteases produced by activated WBC's may contribute to the progression of lung injury.
- Neutrophils indicates an increase risk of BPD
- Primary findings in BPD.

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Pathophysiology

- 1. Abnormalities of surfactant
- 2. Barotrauma
- 3. Oxygen toxicity
- 4. Abnormalities in Protease-anti-protease activity
- 5. Pulmonary edema
- 6. Infection

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BPD, Airways and Septation

- Large and small airways that have fewer and larger and larger alveoli
- Septation interference and decreased pulmonary microvascular development
- Decreased Alveolarization

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Clinical presentation

- After extubation, retractions, tachypnea, and crackles persist for variable periods. Atelectasis occurs frequently.
- Infants with more severe lung damage may die of progressive respiratory failure, cor pulmonale, or infections.

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BPD and Pulmonary Hypertension

- In severe involvement, there is abnormal vascular development.
- The chronic hypoxia associated with BPD and PHT results in a proliferation of inflammatory mediators that directly affect the lung.
- The result is a further deterioration and progression of both BPD and PHT

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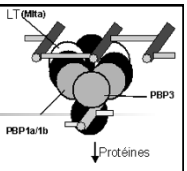
Early Lung Development



- Genetic polymorphisms
- Fibro-blast growth factors-10, Bmp-4 (bone morphogenetic protein 4), NKx2.1 (gene- septation of airways), and enzymes essential for lung growth. Pro-Bombesin-like peptides (BLP)
- Signaling cascade affects of morphoregulations has an important timing effect on the growth and development of the gas exchange unit.

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Morphoregulators and Inflammatory Mediators

- Factors present in the injured lung:
  - Transforming growth factor (TGF)-β
- Could be used as predictor for BPD and home O2 use.

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Mechanism of Injury

- Additively or synergistically to promote lung injury.
- Traditional view-oxidant and ventilation-mediated injury.
- Oxygen can delay septation during saccular development O2 as a drug.

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Mechanism of Injury

- CMV causes proinflammatory response (injury)
- Avoiding intubation and CPAP use associated with lower incidence of BPD
- Granulocytes appear soon after CMV is initiated in the lung, (though decrease systemically)
  - The appearance of granulocytes correlates with pulmonary edema.
  - A decrease in circulating granulocytes at 1 hour have an increased risk of BPD

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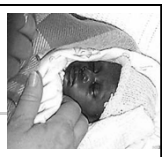
Inflammatory Response



- Multiple pro-inflammatory and chemotactic factors
- Macrophage inflammatory protein-1 and interleukin (IL)-8, TGF- β (transforming growth factor-beta) production and fibrosis
- Counterregulatory cytokines: IL-10 may be decreased.

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Inflammatory Response

- Bombesin-like peptides (BLP)
  - Produced by neuroendocrine cells as mediators in BPD
  - Increased;Neuroendocrine cells, mast cells, and eosinophils in the BPD lung.
  - Anti BLP decrease number of immunologic cells and cause less injury. ↓
  - Urinary BLP levels correlate with BPD severity.

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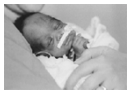
Other factors



- Hyperoxia (inhibited DNA synthesis), hypoxia, or poor nutrition can cause septation as can glucocorticoid treatment.
- Increased cytokines tumor necrosis factor-alpha, TGF-B, IL-6, or IL-11 can also interfere with alveolarization, furthering inflammatory process and altered septation.

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Other factors

- Retinoic acid receptor (RAR)B, needed for organogenesis from steroid/thyroid RAR.
  - Promotes septation
  - Glucocorticoids inhibition of septation reversed

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Treatment/Interventions

- Prevention of prematurely
  - Surfactant therapy
  - "Gentle" ventilator parameters and ABG's
    - PaCO2 50-70 mmHg
    - Increased expiratory times to decrease airtrapping
    - CPAP therapy
    - Maintain PaO2 55-60 mmHg: SaO2 85-90%

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Treatment/Interventions

- Nutrition
  - Malnutrition, especially decreased proteins increase preterm infants to oxidant-induced lung injury, and interfere with lung growth and DNA synthesis
  - Polyunsaturated fatty acids suggests some protective effects, yet to be validated (commercial lipid peroxidation problems)

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Treatment/Interventions

- Nutrition
  - Vitamin A important to cell growth, differentiation and airway epithelial cell integrity. Studies have shown a significant reduction in BPD.
  - Inositol, sulfur-containing amino acids, and selenium may provide protection against BPD.
  - Vitamin E deficiency ⇑ 02 toxicity, with V-E ⇓ lung injury of 02 administration, but not BPD.

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Nutrition

- Caloric needs
  - Anabolism
- Special nutrient needs
  - More fat
  - Less carbohydrate

Treatment/Interventions

- Oxygen toxicity
  - Recombinant human superoxide dismutase (rhSOD)
  - Encouraging long term effects only, ⇓ meds, less IVH
- Monitor fluid administration and diuretics, (I and O)

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Treatment/Interventions

- Glucocorticoids/Corticosteroids
  - Accelerate the maturation of lung tissue and structures, increase surfactant production and lung compliance, reduce vascular permeability, and increase lung water clearance
  - Improved lung function.

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Treatment/Interventions

- Cortisol-response to lung injury is decrease in preterm infants.
  - The infant is unable to respond to stress effectivily due to the lack or decrease in cortisol.
  - Regulation of blood pressure and cardiovascular function as well as regulation of the body's use of proteins, carbohydrates, and fats.
- Theophylline Therapy
- Chest physical therapy

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Prognosis

- Mortality approximately 30%
- Survivors sent home: frequently require long term O2 therapy, diuretics, bronchodilators, special diets/formula
- Re-admissions common for respiratory symptoms and infections

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BPD vs. Normal

Not conducive to gas exchange	**Conducive to gas exchange**
Thick blood gas barrier	Thin blood gas barrier
Low compliance	Highly compliant
Immature epithelial cells	Mature epithelial cells
Low surfactant levels	Adequate surfactant
Small area for gas exchange	Large area for gas exchange
Poorly vascularized	Highly vascular
High resistance to blood flow	Low resistance to blood flow

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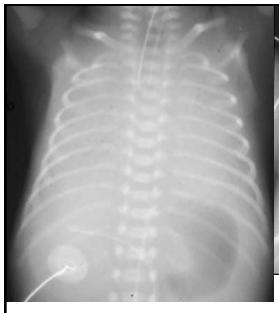
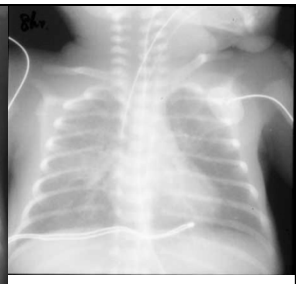


Progression of HMD to BPD (1 hr)



Progression of HMD to BPD (3 hr)

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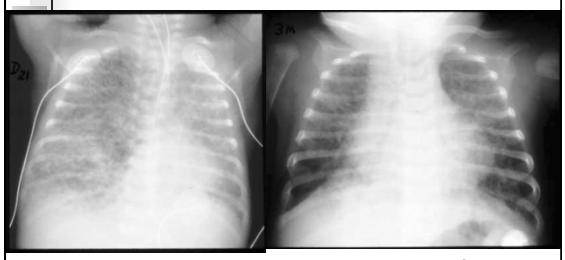

Progression of HMD to BPD (D21)

Progression of HMD to BPD (3m)

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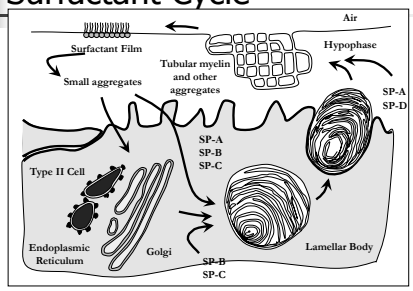
Surfactant Cycle



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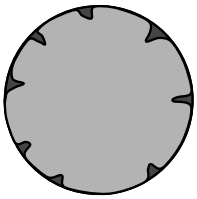
Alveolar Development



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Prevention

- **Prevention of prematurity** (delaying delivery beyond 30 wks would decrease BPD by 75%)
- **Antenatal steroids/dexamethasome**
- Antenatal TRH ?? (Re: ACTOBAT trial)
  - thyrotropin releasing hormone
- Aggressive management of **perinatal infection** - Bacterial / Ureaplasma/
- Tocolysis

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Prevention (contd.)

- **Conservative mechanical ventilation** (limit airway pressures, tidal volume, duration of CMV). HFV not proven better, unless air leak /PIE.
- **Fluid restriction**, early PDA closure.
- **Surfactant** decreases risk of BPD in babies who would otherwise have severe RDS, but it also permits survival of smaller babies who go on to develop CLD. Overall incidence unchanged, but shifted to smaller babies. Does not affect non-BPD CLD incidence.
- Surfactant + Antioxidants undergoing trials.

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Pharmacotherapy

- Diuretics
- Bronchodilators
- Anti-inflammatory agents
  - Steroids ? ? ?
  - Cromolyn
  - Ipratropium

Respiratory Care

- Volume
- Pulmonary function testing
- Tracheostomy
- Discharge planning
  - Home ventilator care
  - Home oxygen therapy
  - Home respiratory medications
  - Home monitoring

Management (contd.)

✷ Treatment is directed towards major pathophysiology:

- Pulmonary edema
- Bronchoconstriction and airway hyperreactivity
- Airway inflammation
- Chronic lung injury and repair

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Management (contd.)

- DIURETICS

- WHY ?
  - Clinical, XRay & Histologic evidence of interstitial & peribronchiolar pulmonary edema
  - Abnormal regulation of water balance ; hypervolemia
  - Acute and short term diuretics improve pulmonary function and occasionally gas exchange
  - Benefit unrelated to urine output

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Management (contd.)

- DIURETICS:

- Types: Loop diuretics: **Furosemide**
  Thiazides : Chloro/Hydrochlorothiazide
  Spironolactone
- Results with Thiazides and Spironolactone conflicting, though blinded studies did show some improvement
- Furosemide also increases vasodilator PG synthesis, causes systemic and pulmonary vasodilation, increases surfactant synthesis and decreases Chloride transport in the airway epithelium

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Management (contd.)

- BRONCHODILATORS

Pathways controlling airway smooth muscle tone :

1. . Parasympathetic cholinergic : contraction, increase mucus
2. . Beta-adrenergic : relaxation
3. . Nonadrenergic, noncholinergic (NANC) or Peptidergic :
   - Bronchoconstrictor : Substance P
   - Bronchodilator : VIP (possibly deficient in Asthma)

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Management (contd.)

- WHY ?

- Sufficient bronchial smooth muscle, even in tiny premies
- Hyperplastic smooth muscle and metaplastic epithelium in BPD
- Correlation with family history of Asthma

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Management (contd.)

- Types of Bronchodilators:
- Methylxanthines (Theophylline, caffeine)
  - Bronchodilator, diuretic, resp stimulant
  - weak bronchodilator, increased side effects
- β-adrenergic agonists (mainly $\beta 2$, less $\beta 1$)
  - mainly smooth muscle relaxation, also enhance mucociliary transport, redistribute pulmonary blood flow
- Anticholinergics - Atropine, Ipratropium

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Management (contd.)

- Results:
  - Bronchodilators improve pulmonary function in the short-term.
  - No studies on long-term efficacy
  - Long term safety ? - β receptors in the brain.
- Is bronchoconstriction protective ?
  - Focal bronchoconstriction may have protective action by limiting lung injury to distal units
  - May maintain airway wall rigidity

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Management (contd.)

- VASODILATORS
  - WHY ?
    - Alveolar hypoxia leads to pulmonary vasoconstriction and structural remodeling of the pulmonary vascular bed.
  - Oxygen a potent vasodilator, main vasodilator used in BPD. Keep PO_2 60-80, SpO_2 92-95%.
  - Hydralazine, Diltiazem, Nifedipine used in very small trials showed hemodynamic improvement.

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Management (contd.)

- ANTIOXIDANTS
  - No benefit demonstrated with Vit E
  - Vit A supplementation *may* help. VLBW deficient in Vit A and RBP. Babies with BPD have lower Vit A. Studies so far small, but majority show benefit. Potential for toxicity exists.
  - Superoxide dismutase, Catalase, Glutathione peroxidase etc are under investigation.

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Management (contd.)

- EXPERIMENTAL MODALITIES

Enzyme, Gene, Cytokine, Antioxidant, Antiprotease administration

Lung transplant

- ESSENTIAL ELEMENT

Oxygen therapy, avoidance of environmental and infectious hazards

Essential not to underutilize or discontinue O2 too early

(may lead to feeding difficulty, slow growth, bronchoconstriction, Pulmonary hypertension)

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Outcome (contd.)

- Long-term outcome
- Lung function -
  - Poor compliance,
  - increased resistance,
  - expiratory airflow limitation (bronchospastic and bronchomalacic),
  - increased WOB, air trapping, reactive airway disease.
  - May persist into adulthood.

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Outcome (contd.)

- Long-term outcome (contd)
  - Cor pulmonale - usually resolves
  - Reactive Airway disease - 50% will have exercise induced bronchospasm
  - SIDS ? - BPD spells ?- acute obstructive episodes. Some reports of increased SIDS incidence.

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Outcome (contd.)

- Long-term outcome (contd)
  - Growth failure common. 50% < 10th centile at 6 mo. Only 7% > 50th at 2 yrs.
    - Resistance to oral stimulation,
    - forcing food,
    - increased caloric consumption

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Outcome (contd.)

- Long-term outcome (contd)
  - Studies on developmental outcome inconclusive. Most show no relation to BPD but to prematurity and other risk factors. Relationship to time hospitalized, but not with time ventilated.
  - Short stature and airflow obstruction persist into adulthood (Northway's 23 yr follow-up)

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