Overview of Bronchopulmonary Dysplasia

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BPD - Objectives

1. Review the definition of bronchopulmonary dysplasia (BPD).
2. Evaluate different treatment modalities for infants with BPD.
3. Recognize some long term issues for patients with BPD.
BPD - Overview

• Never let data stand in the way of dogma.

• Protocols used to reduce variation in care vs. “personalized medicine” with individual care plan is the way to Nirvana.

• No established guidelines for BPD care post-discharge so lots of room for “personalized medicine.”

Reference 1, 2, and 3
BPD - Diagnosis

- First described by Dr. Northway in 1967
- Oxygen requirement at 28 postnatal days/36 weeks postmenstrual age
- Based on gestational age and severity of disease
  - 2001 National Institute of Child Health and Human Development

References 2, 11, and 14
**Definition of BPD**

**Definition of bronchopulmonary dysplasia: Diagnostic criteria**

<table>
<thead>
<tr>
<th>Time point of assessment</th>
<th>Gestational age</th>
<th>≥32 week</th>
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<tbody>
<tr>
<td></td>
<td>&lt;32 week</td>
<td>≥32 week</td>
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<tr>
<td>36 weeks PMA or discharge to home, whichever comes first</td>
<td>&gt;28 days but &lt;56 days postnatal age or discharge to home, whichever comes first</td>
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**Treatment with oxygen >21 percent for at least 28 days plus**

<table>
<thead>
<tr>
<th>Mild BPD</th>
<th>Breathing room air at 36 weeks PMA or discharge, whichever comes first</th>
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</thead>
<tbody>
<tr>
<td>Moderate BPD</td>
<td>Need* for &lt;30 percent oxygen at 36 weeks PMA or discharge, whichever comes first</td>
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<tr>
<td>Severe BPD</td>
<td>Need* for ≥30 percent oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks PMA or discharge, whichever comes first</td>
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<tr>
<td></td>
<td>Breathing room air by 56 days postnatal age or discharge, whichever comes first</td>
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BPD: bronchopulmonary dysplasia; NCPAP: nasal continuous positive airway pressure; PMA: postmenstrual age; PPV: positive-pressure ventilation.

* A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) are considered common to the broad description of BPD and have not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen >21 percent and/or positive pressure for nonrespiratory disease (eg, central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung
BPD - Incidence

- Over time the changes in incidence are unclear
  - Decreased mortality and clarification of definition
- Birth weight <1250 grams account for 97% of BPD cases
- Incidence increases with decreasing gestational age
- Less severe BPD over time

Reference 2
BPD - Pathogenesis

- Three key factors
  - Lung immaturity
  - Acute lung injury
  - Inadequate repair of the initial lung injury

Reference 8
BPD – Risk Factors

• Prematurity especially birth during saccular stage of lung development (23-32 weeks gestation)
• Mechanical ventilation
• Oxygen toxicity
• Infection and inflammation

Reference 2
BPD – Risk Factors

- Fluid overload/PDA
- Genetic factors
- Late surfactant deficiency
- Fetal growth restriction/small for gestational age (SGA)

Reference 2
BPD - Pathogenesis

- Prematurity
  - Poor airway support structures
  - Surfactant deficiency
  - Decreased compliance
  - Underdeveloped antioxidant mechanisms
  - Inadequate fluid clearance

- Inflammation
  - Mechanical injury
  - Oxygen toxicity
  - Infection

Reference 2
BPD - Oxygen Toxicity

- Exact level or duration of supplemental oxygen for damage unknown
- Enzyme inactivation and lipid peroxidation
- Oxygen metabolites and inadequate antioxidant defenses
  - Superoxide free radical, hydrogen peroxide, hydroxyl free radical, singlet oxygen

Reference 2
BPD-Pathology

• Pre-surfactant treated era (pre-1980s)
  – Airway injury
  – Inflammation
  – Parenchymal fibrosis

Reference 2
BPD-Pathology

• Surfactant treated era (post-1980s) with disruption of lung development
  – Alveolar simplification
    • Decreased septation and alveolar hypoplasia, fewer and larger alveoli, reduction of surface area for gas exchange
  – Minimal small airway injury
    • Unless severe BPD

References 2 and 4
BPD-Pathology

• Surfactant treated continued
  – Dysregulation of pulmonary vascular development
    • Abnormal distribution of alveolar capillaries
    • Thickened pulmonary arteriole musculature
      – Increased pulmonary resistance
      – Reduced microvascular development

Reference 2 and 4
BPD-Natural History

• Not well reported
• Variation over time
  – More and younger gestational age survivors
  – Management changes
  – Inconsistency in definitions

Reference 2
BPD - Signs & Symptoms

• Tachypnea
• Wheezing
• Chest wall retractions
• Paradoxic respirations
• Prolonged expiratory phase

References 2 and 8
BPD - Signs & Symptoms

• Increased functional dead space
  – Small and fast tidal volume

• Increased muscle activity
  – Compliant chest wall with wasted energy

• Reactive airways
  – Exercise (crying, feeding), cold air, infection

References 2 and 8
BPD - Signs & Symptoms

• Tracheomalacia/Bronchomalacia/Tracheo megaly
  – More common in “old BPD” pre-surfactant
  – Large airway collapse
    • From barotrauma, infection, intubation
  – Positional (worse lying on back)
  – Increase wheeze with bronchodilator

Reference 2
BPD - Signs & Symptoms

• Cyanosis/hypoxemia
  – Pulmonary hypertension a consideration
  – Sleep related especially during REM
    • Consider polysomnogram
  – Poor growth

Reference 2
BPD - Signs & Symptoms

- BPD spells
  - Cyanosis/life-threatening
  - Reduction in tidal volume
  - Increase in airway resistance
  - Worse Ventilation/Perfusion mismatch

Reference 2
BPD - Signs & Symptoms

• Stridor
  – Glottic and subglottic damage
  – Intubation for >1 week or 3 or more times
    • Stenosis/granuloma
    • Trauma related to tube and suctioning

Reference 2
BPD - CXR

- Diffusely hazy
- Patchy infiltrates
- Pulmonary edema

Reference 2
BPD - CXR

- Atelectasis
- Lung volumes
  - Normal or low initially
  - Hyperinflation/cystic/streaky later

Reference 2
BPD – Overview of Therapy

- Supportive
  - Survival of younger gestational age
- Minimize injury
  - Less aggressive ventilation/oxygen
- Antenatal steroids
- Surfactant

Reference 2
BPD - Overview

• Studies of long term outcomes are difficult to compare and extrapolate
  – Non-standardized care in units
  – Different definitions
  – Changes in clinical care over time
  – Small numbers of patients studied

Reference 2
BPD - Therapy

- Assisted ventilation
- Oxygen
- Monitoring
- Diuretics and fluid balance
  - PDA closure

Reference 2
BPD - Therapy

- Bronchodilators
- Corticosteroids
- Antibiotics/RSV prophylaxis
- Nutrition

Reference 2
BPD - Therapy

• Mechanical ventilation (optimal strategy unknown)
  – Wean gradually from SIMV
  – Small tidal volumes (avoid injury) (4-6 ml/kg)
  – PEEP 5-7 cm water (avoid atelectasis)

Reference 2
BPD - Therapy

- Prolonged inspiratory time (0.4-0.5 sec)
  - Promote uniform lung inflation
- Permissive hypercapnia with pH 7.3-7.4 (pCO₂ 55-65+)
  - Caffeine?
    - Less BPD in <1250 gram babies
      - Not consistent data

Reference 2
BPD - Therapy

• Inhaled nitric oxide (iNO)
  – No significant benefit

• Vitamin A supplementation
  – Data conflicting

Reference 2
BPD - Therapy

• No clear reduction in bronchopulmonary dysplasia
  – High frequency ventilation
  – Nasal intermittent positive pressure ventilation
  – Nasal CPAP
  – Neurologic adjusted ventilatory assist (NAVA)

Reference 2
BPD - Therapy

• Tracheostomy
  – Optimal timing unclear
  – 40-42 weeks PMA and expected ongoing MV

• “Calibrated suctioning”
  – To distal tip of tube

Reference 2
BPD - Therapy

• Oxygen
  – Therapeutic range
    • Optimal saturations unknown
    • Mature versus immature retina
      – 89-95% saturation in less than 30 weeks post menstrual age
      – Greater than 95% with pulmonary hypertension and mature retina

Reference 2
BPD - Therapy

- No side effects of low flow oxygen
- Adjustments for feeding, sleeping, and illness
- Typically discontinue supplemental oxygen after diuretics, fluid restriction released, and steroids
- Poor growth may be an indication of oxygen desaturation

Reference 2
BPD - Therapy

- Diuretics
  - 3 to 4 weeks old
  - Mechanical ventilation dependent/fluid restricted
  - Furosemide for more severe, pulmonary edema, after PRBC transfusions

Reference 2
BPD - Therapy

• Distal renal tubule
  – Thiazide and/or spironolactone
    • Improved lung mechanics
    • Did not decrease ventilatory support, length of stay (LOS), long term outcome
    • Combination no difference in lung mechanics, electrolyte balance, need for supplements

Reference 2
BPD - Therapy

• Loop diuretics
  – Furosemide
    • Single IV dose (1 mg/kg) or by mouth (2 mg/kg) with transient improvement
    • Chronic dosing
      – Improved oxygenation and lung mechanics

Reference 2
BPD - Therapy

- No change in ventilatory support, LOS, survival, long term outcome
- Ototoxic especially rapid IV
- Nephrocalcinosis/Nephrolithasis

Reference 2
BPD - Therapy

• Monitor electrolytes
  – unclear guidelines regarding specifics
    • Initiation, increase in dose, at least weekly

• Consider supplementation with sodium chloride, potassium chloride, and calcium

• Also monitor alkaline phosphatase and vitamin D

Reference 2
BPD - Therapy

• MDI vs. Nebulizer
  – Small proportion of medication is delivered to lungs
    • 0.17-0.23 MDI
    • 0.21-0.23 Neb
  • Most in central lung regions
  • MDI may be preferable
    – More cost effective

Reference 2
BPD - Therapy

• Albuterol/levalbuterol
  – May help (observation)
    • Clinical trial
      – Gas exchange
      – Decreased respiratory effort
      – Fewer decompensations
    • Discontinue if no benefit
    • Also for acute exacerbations of airway reactivity

Reference 2
• Bronchodilators may have side effects
  – Tachycardia
  – HTN
  – Possibly arrhythmia
  – Worse symptoms if bronchomalacia

Reference 2
BPD - Therapy

• Systemic steroids
  – 1983 was first randomized trial
  – Peak use 1997–8
  – Lowest usage 2003–4
  – In general: Improves lung function but significant side effects with complications often outweighing benefits

Reference 2
BPD - Therapy

• Systemic steroids---adverse effects
  – Sepsis/infection
  – Adrenal suppression
  – Poor growth
  – Hypertension
  – Cardiac hypertrophy

References 2 and 8
BPD - Therapy

• Systemic steroids---adverse effects
  – Hyperglycemia
  – Bowel perforation and GI bleeding
    • Overlap with indomethacin

Reference 2
BPD - Therapy

• Systemic steroids---adverse effects
  – Decreased bone mineralization
  – Neurodevelopmental abnormalities/cerebral palsy
    • Especially early use and dexamethasone
    • Ongoing evaluation

Reference 2
BPD - Therapy

- Issues with systemic steroid studies
  - Variations in study methodologies
    - Preparation of glucocorticoid used
    - Dosing and timing of administration
    - Length of therapy
  - See the American Academy of Pediatrics/Canadian Pediatric Society recommendations

Reference 2
BPD - Therapy

• Early systemic steroids (< 7 days old)
  – Risk > benefit to give to all
  – Subgroups for benefit > risk not clearly defined

Reference 2
BPD - Therapy

- Late systemic steroids (>7 days old)
  - Improved lung function
  - Reduced need for assisted ventilation/oxygen therapy
  - Reduced extubation failures
  - For acute exacerbations
    - Term and older

Reference 2
BPD - Therapy

• Inhaled steroids
  – Early use does not prevent BPD
  – Treatment for BPD unclear
    • Double dose for 5-7 days versus hydrocortisone burst with exacerbation
    • Greater risk of pneumonia?
    • Appropriate dose is unknown
    • Older infants requiring pulmonary support or airway reactivity

Reference 2
BPD - Therapy

• Antibiotics if infection
  – CXR and culture of tracheal aspirate

Reference 2
BPD - Therapy

• RSV prophylaxis
  – Palivizumab per guidelines

Reference 2
BPD - Nutrition

• NG/OG/PG feeds
• High caloric density
  – Avoid malnutrition
• Fluid restricted
  – 140-150 ml/kg/day after day of life 7

Reference 2
BPD - PFT

- Typical—airflow obstruction and air trapping
  - Decreased forced expiratory flow rates
  - Increased functional residual capacity, residual volume, RV/TLC
  - Many bronchodilator responsive
  - Increased respiratory effort and minute ventilation

Reference 2
BPD - PFT

• Long-term for “classic BPD”
  – Airway obstruction
  – Hyperinflation with elevated residual volume
  – Reduced exercise tolerance and oxygen desaturation (some studies)

Reference 2
BPD - PFT

• Long term for “new BPD” (post surfactant/antenatal steroids/iNO) mostly unstudied and unknown
  – Perhaps less airflow limitation
  – Perhaps less hyperinflation and air trapping
  – Perhaps improved exercise tolerance

References 2 and 13
BPD - Long Term

• 35-90% mortality
  – Predictors
    • Mean airway pressure and oxygen concentration
    • Longer duration of mechanical ventilation
    • Sepsis
    • Pulmonary HTN
      – Cor pulmonale

Reference 2
BPD - Long Term

- Recurrent hospitalization (pneumonia, RAD, RSV)
  - 50% in first 2 years
    - Growth/feeding issues
    - Surgical: G-tube, VP shunt, tracheostomy
    - CNS/seizures
    - Viral
      - Can be life threatening

Reference 2
BPD - Long Term

- Systemic hypertension
- Left ventricular hypertrophy
- Pulmonary hypertension
  - EKG may underestimate abnormalities
  - May require cardiac catheterization
    - Gold standard, reactivity, collaterals
  - Echocardiogram
    - Screening and serial follow-up

References 2 and 8
BPD - Long Term

• Airway hyperresponsiveness
  – 40-50% with abnormal exercise, histamine or methacholine response
  – No increase in atopy
    • Not elevated exhaled nitric oxide
  – May respond to inhaled corticosteroids (ICS)

Reference 2
BPD - Long Term

• Neurodevelopmental impairment
  – Motor and cognitive performance
    • Abnormal gross and/or fine motor skills, receptive and expressive language skills
    • Subtle signs or obvious
    • Cerebral palsy
    • Microcephaly
    • Behavioral problems
    • Dysphagia/aspiration

Reference 2
BPD - Long Term

- Blindness and hearing impairment
- Height and weight poor and no ideal growth chart
- Gastroesophageal reflux disease
- Oral aversion
- Need for special services

Reference 2
BPD - Long Term

• Radiography
  – CXR
    • Minor fibrotic changes and generalized hyperinflation
  – CT chest
    • Linear and triangular opacities, mosaic perfusion, and air trapping

Reference 2
BPD - Long Term

• Avoid tobacco smoke
• Avoid respiratory irritants
• Frequent hand washing
• CPR training for caregivers
• Car seat challenge
BPD - Long Term

- Oximeter and cardiorespiratory monitor if home oxygen, tracheostomy
- Alert to maternal depression
- Alert to vulnerable child syndrome
- Daycare exposure
  - Care needs and infection risk

Reference 2
BPD - Long Term

- Higher SIDS risk
- Anemia with lower nadir
- Retinopathy of prematurity
- Refractive errors
- Delayed tooth eruption

Reference 2
BPD – Summary and Thank You

• Never let data stand in the way of dogma.
• Protocols used to reduce variation in care vs. “personalized medicine” with individual care plan is the way to Nirvana.
• No established guidelines for BPD care post-discharge so lots of room for “personalized medicine.”
References and Suggested Reading

1. Chronic Lung Disease in Early Infancy; Marcel Dekker Volume 137, 2000.

2. UpToDate, January 2016.

References and Suggested Reading


References and Suggested Reading


References and Suggested Reading


12. Postnatal Corticosteroids to Treat or Prevent Chronic Lung Disease in Preterm Infants, Committee on Fetus and Newborn Pediatrics. 2002;109;330
References and Suggested Reading