Long-term Care of Children with Chronic Lung Disease of Prematurity

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Objectives

- Describe the factors affecting development of chronic lung disease of prematurity (CLDP)
- Describe the variety of phenotypes in CLDP
- Discuss the management of CLDP in the outpatient setting
Overview

- Definition and Pathogenesis of BPD
- Illustrative cases with differing phenotypes
  - Alveolar hypoplasia
  - Vascular disease
  - Airway disease
  - Control of breathing disorders
## NIH Definition of BPD

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>&lt;32 weeks</th>
<th>&gt;32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point of assessment</td>
<td>36 weeks post-menstrual age or discharge *</td>
<td>&gt;28 days but &lt;55 days postnatal age or discharge *</td>
</tr>
<tr>
<td>Treatment with oxygen</td>
<td>&gt;21% for at least 28 days</td>
<td>&gt;21% for at least 28 days</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Breathing room air at 36 weeks post-menstrual age, or discharge *</td>
<td>Breathing room air by 56 days postnatal age, or discharge *</td>
</tr>
<tr>
<td>Moderate</td>
<td>Need for &lt;30% O2 at 36 weeks post-menstrual age, or discharge *</td>
<td>Need for &lt;30% O2 to 56 days postnatal age, or discharge *</td>
</tr>
<tr>
<td>Severe</td>
<td>Need for &gt;30% O2, with or without positive pressure ventilation or continuous positive pressure at 36 weeks post-menstrual age, or discharge *</td>
<td>Need for &gt;30% O2 with or without positive pressure ventilation or continuous positive pressure at 56 days postnatal age, or discharge *</td>
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</table>

*Whichever comes first
In the United States

- 4,317,119 live births in 2007
  - 12.7% born prematurely
  - 6.7% had low birth weight (1500-2499 g)
  - 1.48% had very low birth weight (<1500 g)
    - ~64,000 infants at risk for BPD

- About 25% of VLBW infants (<1250 g) will have BPD

Birth weight: well established risk factor

Ehrankranz et. al. Pediatrics, 2005
Factors influencing CLD

- Genetic
- Prenatal environment
  - Chorioamnionitis
  - Preeclampsia
  - Smoking
  - Drug use
- Premature
  - Hyperoxia
  - Inflammation
  - Ventilator induced injury
- Comorbid conditions
- Home Environment
- BPD
- CLD
Results

- Impaired alveolar growth
- Large and/or small airway dysfunction
- Pulmonary vascular disease

Phenotypic Variability

Symptoms of CLD

tachypnea, cough, wheezing, retractions, crackles, dyspnea, exercise or feeding intolerance, failure to thrive, right heart failure
Radiologic changes in BPD

From Vivek Balasubramaniam, MD Lecture: Neonatal Chronic Lung Disease
Alveolar hypoplasia: BPD and chronic CO$_2$ retention

- AA boy born at 24 weeks gestation BW 590 g
- Required intubation and surfactant within a few hours after birth
  - CPAP at 10 weeks of age
  - HFNC at 12 weeks
- Evidence of pulm HTN, ASD diagnosed by ECHO
  - Started on sildenafil empirically prior to cardiac cath due to concerns for being unable to extubate
BPD and chronic CO$_2$ retention

- Persistent tachypnea and poor weight gain
  - Swallow study: aspiration
  - Bronchoscopy: severe tracheobronchomalacia that improved with PEEP of 10

- Tracheostomy placed at 5 months of age
  - Ventilator settings:
    - high tidal volume (10 ml/kg)
    - High PEEP (10)
    - Decreased rate
    - Decreased I-time

- Discharged home after parent education
Alveoli count

Degree of infant to recover from BPD may depend on postnatal alveolar “catch up” growth

Dysanaptic airway growth in preterm lungs

Environmental factors

- Nutrition
- Hyperoxia
- Socio-economic factors
  - Caregiver education
  - Insurance
  - Income
  - Race/ethnicity
  - Access to Care
- Medications
- Infectious factors
  - Daycare
  - Siblings
  - Immunoprophylaxis
  - Breastfeeding
- Airborne pollutants
  - Second hand smoke
  - Pests/pets
Daycare attendance and respiratory comorbidities

Oxygen

- Appropriate oxygenation essential
- Suggested goal is 92-94%  
  - Prevent harm from hypoxemia and excess oxygen  
    - Free radical damage on airway epithelium  
  - Pulse oximeter for monitoring is vital  
  - Continue monitoring for 2-3 months after discontinuation of oxygen

Bronchodilators

- Pathologic changes include smooth muscle hypertrophy
  - Preterm infants had clinical and physiologic benefit \(^1\)

- Concern for decreased smooth muscle tone and increased airway collapsability
  - 1 year olds with CLD did not have a change in airway resistance, some had clinical deterioration, some improved \(^2\)

- Effect of long-term stimulation of receptors during a time of rapid growth is unknown

Inhaled steroids

- Very limited trials regarding their long term use
- Usual approach: Use only if clear clinical benefit in symptomatic infants
- Side effects to consider:
  - Adrenal suppression
  - Cataracts
  - Somatic growth
  - Lung growth
Caregiver Education

- Maternal education does not impact rehospitalizations or respiratory morbidity
  - It maybe that education received in NICU provides families with adequate skill set

Smith VC et al. J Pediatr 2004
Collaco JM et al Pediatr Pulmonol 2011
BPD and Pulmonary vascular disease
Case # 1

AA girl born at 26 weeks gestation, BW: 978 g

No prenatal care. Mother with chorioamnionitis and smoked during pregnancy.

NICU stay for 5 months. Required mechanical ventilation for 3 months, including HFOV. Echocardiograms in NICU showed ASD, otherwise normal.

Comorbidities
Had NEC and required colostomy
RLL pulmonary sequestration
Umbilical hernia repair
BPD and Pulmonary vascular disease Case # 1

3 weeks after discharge had cardiac arrest in ER

Prolonged hospitalization with respiratory failure complicated by rhinovirus respiratory infection and gram negative septic shock

Echocardiograms with indirect evidence of elevated pulmonary pressure
  – Dilated RA and RVH
  – Dilated main pulmonary artery
  – ASD with biderectonal flow
Pathology in PH

Arrest of lung vascular development + Vascular injury and remodeling = Resistance ↔ Compliance
Pulmonary Hypertension

- Risk factors:
  - Earlier gestational age
  - IUGR
  - ASD

- Exacerbated by:
  - LRI
  - Surgery
  - Airway aspiration
Decreased Vascular Density
Echocardiography

- **Advantages**
  - Non-invasive tool to examine cardiac anatomy, function, and to estimate sPAP in the absence of RVOT obstruction

- **Limitations**
  - It does not allow estimations of LV pressures and Q
  - Low sensitivity in diagnosing PVS
  - Limited ability to measure RV function
  - TRJV in ~61% of cases
  - Estimation of sPAP:
    - Sensitivity: 88%; Specificity: 33%; PPV: 88%; NPV: 33%
  - Presence of >1 qualitative abnormality suggesting PH:
    - Sensitivity: 96%; Specificity: 33%; PPV: 86%; NPV: 67%

Differential Diagnosis

- **Arterial**
  - BPD
  - Systemic to pulmonary collateral vessels
  - Pulmonary artery stenosis
  - Portopulmonary HTN

- **Venous**
  - Pulmonary vein stenosis

- **Cardiac**
  - Left heart failure

- **Hypoxic**
  - Recurrent hypoxemia
    - OSA
    - Airway malacia/stenosis

- **Thromboembolic**
  - Pulmonary embolism

- **Miscellaneous**
  - Infection
  - Portal Hypertension
Diagnostic evaluation in PH

- **Screening tests**
  - ECG; echocardiography
  - Serum NT-proBNP

- **Pivotal tests**
  - Cardiac catheterization and testing of pulmonary vasoreactivity
  - Polysomnography
  - HR TS CT of the chest (to assess lung interstitium)
  - V-Q scan (to rule out pulmonary emboli)
  - Liver ultrasound (to rule out portal hypertension, venous shunts such as Abernathy malformation)
  - Thrombophilia studies, LFTs, TFTs, HIV, hepatitis C, HHV6

- **Optional studies**
  - Bronchoscopy
  - Cardiac MRI
  - Lung biopsy
Cardiac catheterization in infants with BPD

- **Goals of cardiac catheterization in BPD**\(^1-3\)
  - To confirm the diagnosis of pulmonary hypertension
  - To assess effects of vasoactive drugs on pulmonary vasoreactivity and left-sided heart pressure
  - To rule out anatomical cardiac lesions, left ventricular diastolic dysfunction, pulmonary vein stenosis

- **Mortality in children with PH: 0.8 %**\(^4\)

1. Abman S. Arch Dis Child Fetal and Neonatal Ed 2002; 87: 15-18
Cardiac catheterization in infants with BPD

<table>
<thead>
<tr>
<th>CATH might not be indicated</th>
<th>CATH most likely indicated</th>
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<tbody>
<tr>
<td>▪ Non-severe PAH (PAP:sBP &lt;0.67)</td>
<td>▪ Age ≥ 4-6 months</td>
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<tr>
<td>▪ Normal NT-proBNP levels</td>
<td>▪ Severe PH (PAP:sBP ≥ 0.67)</td>
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<tr>
<td>▪ Appropriate somatic growth</td>
<td>▪ ↑ NT-proBNP levels</td>
</tr>
<tr>
<td>▪ ↓ O₂ requirement</td>
<td>▪ ↑→ hypoxemia</td>
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<td></td>
<td>▪ ↑ vent settings</td>
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<tr>
<td></td>
<td>▪ Hx/o HFOV</td>
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<td></td>
<td>▪ Persistent lung edema</td>
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<td></td>
<td>▪ Poor somatic growth</td>
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</tbody>
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Survival in PH

- 42 infants with BPD developed pulmonary hypertension after 2 months of age
  - diagnosed by either echocardiography or cardiac catheterization.
- 38% of infants died during the followup period
- Among the survivors the majority improved after a median follow-up of 9.8 months

PH: Pulmonary vasoactive drugs

- Have not been approved for use in infants with PH
- Their dose and side effects in infants are not known
- Administration without a clear diagnosis is discouraged
- Informed consent is advised in some institutions
BPD and pulmonary vascular disease
Case #2

Caucasian girl born at 32 weeks gestation, BW: 1420 g

Triplet gestation, but one triplet expired. NICU stay for 1 month, intubated 10 days.

Hospitalized 2 weeks later due to “gasping” and turning blue.

- Echocardiogram showed ASD, mild peripheral artery stenosis
  - RVP ~ 54 mmHg, normal RV function and shape

Follow up echocardiograms showed stable RVP estimate (37 and 42 mmHg) in next 4 months.
BPD and pulmonary vascular disease
Case #2

- Routine echocardiogram at 14 months old showed RVP ~131 mmHg, patient crying and moving
- Repeat done with sedation showed RVP ~103 mmHg, ASD with bidirectional flow and RVH
BPD and pulmonary vascular disease
Case #2

10 months

14 months
BPD and pulmonary vascular disease
Case # 2

Cardiac Catheterization showed severe peripheral pulmonary artery stenosis

BPD and pulmonary vascular disease
Case # 3

- Case 1
  - 5-month-old male, RDS, hypoxemia, MV, sPAP/sBP: 0.6
  - twin pregnancy, chorioamnionitis; 28 weeks; 829 g
  - HFOV and iNO for hypoxemia and PH at birth; discharged at 4 months of age on O₂ at 0.5 L/min.

- Case 2
  - 10-month-old infant, recurrent hypoxemia and respiratory distress (systemic and inhaled steroids, diuretics, supplemental O₂), LVH on ECG; good LV function and absence of PH on echocardiogram.
  - PRM at 19 weeks, c-section at 24 weeks, BW: 723 g, surfactant at birth, MV for 63 days, RSV bronchiolitis

Case # 3 Left ventricular diastolic dysfunction

<table>
<thead>
<tr>
<th>Table. Hemodynamic data</th>
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<tbody>
<tr>
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<tr>
<td><strong>Patient 1</strong></td>
</tr>
<tr>
<td>Age at catheterization (mo)</td>
</tr>
<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>sPAP (mm Hg)</td>
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<tr>
<td>Sys sBP (mm Hg)</td>
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<tr>
<td>pctFS (%)</td>
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<tr>
<td>LVEF</td>
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<tr>
<td>Transmitral E (cm/s)</td>
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<td>Transmitral A (cm/s)</td>
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<td>Transmitral E/A</td>
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<td>LV Tdi</td>
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<td>Lateral Ea (cm/s)</td>
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<tr>
<td>Lateral Aa (cm/s)</td>
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<td>Qualitative findings</td>
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<td>Cardiac catheterization</td>
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<td>RAP (mm Hg)</td>
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<td>sPAP (mm Hg)</td>
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<tr>
<td>mPAP (mm Hg)</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
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<tr>
<td>Mean AoP (mm Hg)</td>
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<tr>
<td>PVR/SVR</td>
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<tr>
<td>CI (L/min/M^2)</td>
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</table>

LVDD may not be uncommon in BPD
PCWP > 12 mmHg 8/33 (26%)
PCWP > 16 mmHg 4/33 (12%)


O₂

O₂ + iNO
7 yo AA boy born at 27 weeks gestation presents with respiratory distress, rhinovirus positive
- Prenatal course complicated by PROM and maternal alcohol use
- Post natal course
  - Mechanical ventilation for 38 days, discharged on oxygen
  - GER
  - Apnea and bradycardia, caffeine until 36 weeks PCA
- Persistent supplemental oxygen need ½ to 2 LPM
- Poor growth and development
- Frequent respiratory illnesses requiring systemic steroid use
BPD and airway obstruction

- Evaluation included:
  - CBG: normal pH and CO2
  - Bronchoscopy: mild subglottic stenosis, otherwise normal
  - Echocardiogram: normal
  - Sleep study: AHI of 4/hr, all central
  - Swallow study: normal
    - Mom reports intermittent choking with liquids
  - Brain MRI:
    - Small, under-developed left cerebellar hemisphere
    - Gliosis of frontal, parietal, and occipital white matter
Airway obstruction

- 60 VLBW children at age 6-8 years
  - 28 with RDS who did not develop BPD
  - 32 with RDS who developed BPD
  - BPD was graded as mild, moderate or severe

- Spirometry: Those with BPD had FEV1<80% predicted, greater reversibility
  - less than half of these children were symptomatic

- Atopy: normal skin prick testing

But is it Asthma?

- Classical pediatric asthma
  - reversible airway reactivity responsive to bronchodilators

- Children with a history of BPD may have fixed airway obstruction with symptoms of wheeze
  - Small airway caliber size
  - Remodeling

- Reduced diffusing capacity

Lum S. Nature and severity of lung function abnormalities in extremely preterm children at 11 y. Eur Respir J 2010
Exercise

- Children in EPICure study: 38 extremely premature children and 38 controls

- Exercise test showing
  - Reduced peak oxygen consumption
  - Higher respiratory rate
  - Lower tidal volume

- Accelerometer data
  - No difference in physical activity

3 month old Caucasian boy born at 35 weeks gestation with normal birth weight

Noted to have seizure-like activity day of birth

Loaded with phenobarbital and developed prolonged apnea, intubated and mechanically ventilated
  - Over the next 6 weeks, he had apneas and hypercarbia after every attempt at weaning and extubation
  - During this period diagnosed with Hirschprung’s disease and underwent resection and colostomy
Ventilatory control

- Immature respiratory system
  - Chemoreceptor response impaired
    - Larger decrease in minute ventilation when exposed to oxygen
    - Frequent central apneas, specially when asleep

- Environmental factors affect chemoreceptor maturation:
  - Hypoxia
  - Hyperoxia
  - Nicotine exposure

- Increased risk of SIDS

- Poor somatic growth

McGinley and Carroll. Pediatr Allergy, Immuno, and Pulmono 2011, 24(1)
Apnea and bradycardia
Clinical significance of APNEA

- The frequency and duration of apneas
- Consequences of apnea
- Persistent apnea beyond 44 w PCA
- Causes of central apnea
  - Apnea of prematurity
  - Periodic breathing
  - GER
  - Upper/lower RI
  - CNS pathology
  - Metabolic pathology
  - Cardiac pathology
BPD and control of breathing

- Diagnosed with Congenital Central Hypoventilation Syndrome (Ondine’s Curse)
- Tracheostomy placed to support ventilation
Summary

- BPD is influenced by multiple factors
- The disease changes as pulmonary growth continues
- There are variable but overlapping phenotypes in the older infant and child with CLDP
  - Based on airway, alveolar, and vascular abnormalities as well as comorbidities
- There is a lack of disease specific interventions and therapies
  - Network of specialized care centers would allow for large clinical trials and improve patient care
recruitment capacity in response to an increased cardiac output induced by exercise or metabolic stress.

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