Advances in Pulmonary Hypertension Workshop

BPD: Challenges in Lung and Pulmonary Vascular Growth and Development

Moderators:
Drs. Roberta L. Keller + Nicolas Porta

March 9, 2017
Workshop Faculty

- Roberta L Keller MD
  - Professor of Pediatrics, UCSF. Neonatologist, Director of ECMO, Attending Pulmonary Hypertension Service (Benioff SF)

- Hythem Nawaytou MD
  - Assistant Professor of Pediatrics, UCSF. Cardiologist, Attending Echocardiography + Pulmonary Hypertension Service (Benioff SF)

- Jonathan Rome MD
  - Professor of Pediatrics, Penn. Cardiologist, Director of Cardiac Catheterization Laboratory + Interventional Cardiology, Director of Cardiac Procedure + Recovery Unit (CHOP)

- Peter Oishi MD
  - Associate Professor of Pediatrics, UCSF. Critical Care, Medical Director PICU, Director of Pediatric ECLS (Benioff SF)

- Nicolas Porta MD
  - Associate Professor of Pediatrics, Northwestern. Neonatologist, Attending Pulmonary Hypertension Service (Lurie Children’s)
Workshop = Interactive!

Although we have to submit a schedule, the timing + format are meant to be open to questions + discussion throughout...
Workshop Schedule

• 1-1:15  
  Introduction: BPD and Pulmonary vascular disease (Keller)

• 1:15-1:55  
  How I do it: Echocardiographic evaluation of the infant with BPD and concern for pulmonary hypertension (Nawaytou)

• 1:55-2:35  
  How I do it: Diagnostic cardiac catheterization for the infant with BPD and concern for pulmonary hypertension (Rome)

• 2:35-2:55  
  Break

• 2:55-5:00  
  Case presentations (Porta, Moderator)  
  NICU (Keller), PICU (Oishi)
Introduction:
BPD and Pulmonary Vascular Disease

Roberta L. Keller, MD
UCSF Benioff Children’s Hospital
San Francisco CA
March 9, 2017
Overview

• Bronchopulmonary dysplasia (BPD)
• Pulmonary hypertension in BPD
• Consideration of co-morbidities in BPD
  – Functional Class
  – Severity of lung disease, airway obstruction
  – Cardiovascular—structural/hemodynamic factors
  – Other factors—gastroesophageal reflux, feeding difficulties, liver disease, neurologic (abnormal control of breathing due to injury or dysmaturity)
WHAT IS BRONCHOPULMONARY DYSPLASIA?
Prematurity + stages of human lung development

• **Embryonic:** up to 7 weeks
  Lung bud from foregut & growth to bronchi

• **Pseudoglandular:** 5-17 weeks
  Airway and vascular branching to acinus
  Airway epithelium present

• **Cannalicular:** 16-27 weeks
  Formation of respiratory airways (acinus)

• **Saccular:** 24-36 weeks
  Formation & growth of gas exchanging unit

• **Alveolar:** 30-36 weeks on

Hislop 2002
What is BPD?

• Chronic lung disease of prematurity
• “Old” BPD
  Scarring and fibrosis of the lung, severe airway disease in surviving preterm babies in association with high ventilator pressure + FiO\(_2\) (Northway 1967)
• “New” BPD
  Impaired lung and vascular development due to extreme prematurity (< 28-30 weeks’ gestation) (Jobe 1999)
What is BPD?
Definition, physiology, pathology

• Definition:

< 32 weeks’ PMA
Assessed at 36 weeks’ PMA

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Room air</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt; 30% (effective) FiO₂</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 30% (effective) FiO₂ or positive pressure (PPV or NCPAP)</td>
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Treatment with oxygen for at least 28d plus

• Physiology?
  – Abnormal lung/microvascular development
  – Apnea/hypopnea
  – Airway obstruction/disease

• Pathology (Bhatt AJRRCM 2001):

NICHD/NHLBI/ORD Workshop Summary June 1-2, 2000, Jobe and Bancalari, 2001
What is BPD?
Definition, physiology, pathology

- **Definition:**
  - < 32 weeks’ PMA
  - Assessed at 36 weeks’ PMA
  - Treatment with oxygen for at least 28d plus

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<tr>
<th>Severity</th>
<th>Oxygen Requirement</th>
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<tr>
<td>Mild</td>
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- **Physiology?**
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  NICHD/NHLBI/ORD Workshop Summary June 1-2, 2000, Jobe and Bancalari, 2001
WHAT IS PULMONARY HYPERTENSION IN INFANTS WITH BPD?
### Defining PH in BPD

**Cardiac catheterization is the gold standard!**

**Understanding contribution of pulmonary vascular disease challenging without cath**

<table>
<thead>
<tr>
<th>Echo measurement</th>
<th>Criteria used for classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid regurgitant (TR) jet velocity**</td>
<td>Right ventricular systolic pressure (RVsp) &gt; 40 mmHg [right atrial pressure (RAp) = 0]</td>
</tr>
<tr>
<td></td>
<td>RVsp:SBP ratio ≥ 1/2 or 2/3 (RAp = 0 or 5 mmHg)</td>
</tr>
<tr>
<td>Non-restrictive cardiac shunt (PDA, VSD, atrial septum)</td>
<td>Right-to-left or bidirectional flow</td>
</tr>
<tr>
<td></td>
<td>RV or PA pressure ≥ 1/2 or 2/3 systemic</td>
</tr>
<tr>
<td>Interventricular septum (IVS) position</td>
<td>D-shaped or convex into LV</td>
</tr>
<tr>
<td></td>
<td>Flattened throughout the cardiac cycle</td>
</tr>
<tr>
<td></td>
<td>Any flattening</td>
</tr>
</tbody>
</table>

*Assumes no RV outflow tract obstruction  
**By modified Bernoulli equation: RVsp = 4 x velocity² + RAp (assumed RAp noted)  
**PH by echocardiogram: validity**

- PH classified by IVS position
- Severe = systemic-to-suprasystemic at any time
- Survival lower if Severe (37% vs 78% at 1y from Dx)

- Any PH (> 50% systemic) in former preterm infants at 36 weeks associated with higher mortality (10% vs. 1%) (Mourani 2015)

- Any PH (≥ 2/3 systemic) in infants with CDH at ≥ 2 weeks associated with higher mortality and prolonged ventilation and respiratory support (Lusk 2015)
HOW DOES PULMONARY HYPERTENSION IN BPD RELATE TO LUNG DISEASE?
Defining PH—echocardiogram

• Classification schemes based on presence of any or a hierarchy of criteria
  – Investigators have different approaches
• Compare estimated RV or PA pressure estimates to systemic pressure (RV:SBP)
  – PH due to increased pulmonary vascular resistance
• Severity (ratio to systemic)
  – Severe: ≥ 1.0 (systemic-to-suprasystemic)
  – Moderate: ≥ 1/2 - 2/3 and < 1.0
  – None/mild/minimal: < 1/2 – 2/3
<table>
<thead>
<tr>
<th>Publication</th>
<th>Criteria</th>
<th>Early PH</th>
<th>Late PH (36 wks)</th>
</tr>
</thead>
</table>
| **Mirza et al 2014** <28 wks| $P_{PA}/SBP$ ratio $\geq 0.5$  
1. TR (RAP=5)  
2. Cardiac shunt (PDA/VSD)  
3. IVS flattening | 10/120 (8%)  
12±2 d | 5/118 (4%) |
| **Mourani et al 2015** <34 wks, 500-1250g, Echo @ 36 wks | TR: Elevated RVsp $\geq 40$ mmHg or RV/SBP ratio $>0.5$ (RAP=0)  
Any cardiac shunt  
Any IVS flattening | 115/274 (42%)  
7d | 39/277 (14%) |
| Alternate-1                 | Moderate-severe IVS flattening only                                      | ~13%              | ~5%              |
| Alternate-2                 | Exclude IVS flattening                                                   | ~12%              | ~3%              |
Factors associated with Early PH (7-14d)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Respiratory</th>
<th>Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age and birth weight (NS)</td>
<td>MV &gt; 7d by 10d/ MV at 7d*</td>
<td>PDA</td>
</tr>
<tr>
<td>Any PDA treatment</td>
<td>FiO2 &gt; 0.3 by 10d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration of MV</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Severity of BPD</strong>*</td>
<td></td>
</tr>
</tbody>
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*Finding in both Mirza and Mourani studies
## Factors associated with Late PH (36 wks)

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<thead>
<tr>
<th>Clinical</th>
<th>Respiratory</th>
<th>Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>Duration of mechanical ventilation (MV)</td>
<td>IVS flattening at 7d</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>CPAP or MV at 36 wks</td>
<td>RV dilation at 7d</td>
</tr>
<tr>
<td><em>Mortality (post-echo)</em></td>
<td>Duration of $O_2$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severity of BPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Discharge on $O_2$</td>
<td></td>
</tr>
</tbody>
</table>

Mourani et al 2015
**PH in BPD: lung + vascular development track together**

<table>
<thead>
<tr>
<th></th>
<th>BPD severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td><strong>Mirza et al</strong></td>
<td></td>
</tr>
<tr>
<td>Early PH</td>
<td>1/59 (2%)</td>
</tr>
<tr>
<td>Late PH</td>
<td>0/35</td>
</tr>
<tr>
<td><strong>Mourani et al</strong></td>
<td></td>
</tr>
<tr>
<td>Early PH</td>
<td>18/50 (36%)</td>
</tr>
<tr>
<td>Late PH</td>
<td>5/50 (10%)</td>
</tr>
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</table>
CONSIDERATION OF FUNCTIONAL CLASS + COMORBIDITIES
PVRI: Functional class (0-2 y)

I. Asymptomatic. Growing + developing normally, no limitation of physical activity.

II. Slight limitation of activity, dyspnea + fatigue, comfortable at rest. Growing on centiles, behind on motor milestones.

III. a—Less than ordinary activity causes undue fatigue or syncope; frequent naps, quiet. Growth compromised, poor appetite, regression of learned motor activities. Requires excessive medical attention.
   b—IIIa, plus growth severely compromised; supplemental feeding.

IV. IIIb, plus syncope and/or right heart failure. Unable to carry out any activity without dyspnea, fatigue or syncope. Not interacting with family.

Lammers 2011
Most children with PH in this cohort improve FC during follow up/treatment

Improvements in FC are associated with survival

Balkin et al, 2016
Co-morbid cardiovascular conditions

• Occur in ~50% of infants with BPD and PH (del Cerro 2014)

• Prevalence (from highest to lowest)
  – pulmonary vein stenosis = PDA
  – aorta-pulmonary collaterals
  – atrial septal defect (ASD)
Additional clinical considerations

- Severity of parenchymal lung disease, airway obstruction/malacia, provision of adequate respiratory support
- Gastroesophageal reflux, aspiration
  - Feeding problems + reflux common in lung disease
  - May be associated with PH-specific therapy
- Neurologic dysfunction
  - Abnormal/dysmature control of breathing
  - Neuromuscular weakness
- Thyroid dysfunction
  - Hyper- and hypothyroidism associated with PH in case reports
  - Hyperthyroid associated with decompensation in those with known PH
- Acute respiratory infections
  - May be initial presentation of PH in former preterm
  - Increase in severity of PH by echo (del Cerro 2014)
Summary of approach

Moderate-severe PH by high quality echo

Clinical assessment:
1. Pulmonary status
2. Functional class
3. Co-morbidities, including thyroid + airway

Chest CT with contrast

Cardiac catheterization

Pulmonary vascular disease confirmed

Assess any CV lesions for intervention vs. monitoring

Treatment plan based on:
1. Severity of PVD
2. Assessed contribution to status
3. Side effects of Rx

Monitoring
UCSF PH Screening protocol

- **Who:** GA < 32 weeks, moderate-to-severe BPD
- **When:** 36 weeks PMA or prior to discharge if earlier
  - If clinical concerns, echocardiogram can be done earlier (*e.g.*, significant lung disease with elevated PCO2, increasing FiO2 requirement, poor growth)
- **Response**
  - “normal”—Follow up 4-6 mos postnatal age, if possible when off supplemental O2
  - “abnormal”—PH consult with recs for further evaluations + timing of follow up. Parental education regarding close monitoring during illness or any perioperative period.
  - All infants discharged on O2 need eval/echo when it is discontinued
CASE: NICU PRESENTATION OF PULMONARY HYPERTENSION
Case: Female, 24 weeks, 620g (AGA)

- Premature ROM (12d) + unstoppable preterm labor
- Intubated, surfactant, early severe lung disease with pulmonary interstitial emphysema
- Inhaled NO in 1\textsuperscript{st} week for pulmonary hypertension
- RLL lobectomy for pneumatocele at 25d
- Extubated to nasal CPAP at 59d
- 4 LPM HFNC at 81d after hydrocortisone
- Increasing FiO\textsubscript{2} at 145 d
  - Echo: systemic RV pressure estimate, with dilated RA/RV, moderately depressed RV function
Transfer for evaluation of PVD

- Started on sildenafil 1 mg/kg tid prior to transfer
- Transfer at 151 d: 45 5/7 weeks’ postmenstrual age
- HFNC 4 LPM FiO$_2$ 1.0
- CBG 7.41/73/+20
- RR 70s, HR 130s-140s, mild retractions, RV heave, no murmur, liver 2.5 cm
- Diuretics: Furosemide tid/Aldactone bid
- Growing on 10$^{th}$ %ile/ predominantly NG fed
  - Cough/gag with oral feeding, intermittent retching + emesis
  - On Ranitidine and metoclopramide

Admission CXR: Coarse bilateral opacities consistent with CLD.
Labs and imaging

• Echocardiogram (on sildenafil):
  – Flat septum: >50% systemic (systolic SBP = 92 mmHg)
  – TR predicts RVsp 35 mmHg + RAp
  – Moderate RA/RV dilation, severe RVH
  – RV function: normal systolic function, abnormal diastolic function
  – LA/LV without dilation
  – LV function: hyperdynamic
  – tiny PFO with bidirectional flow, predominantly left-to-right
  – No PDA
  – pulmonary veins patent

• BNP 167

• Normal TFTs

CT with contrast:
Diffuse ground glass opacities with cystic changes and mosaic attenuation.
Airways patent.
Cardiac catheterization

- RAp 8 mmHg, LAp 10 mmHg
- Systemic BP 94/34 62
- CI 4 L/min/m²
- Pulmonary vein desaturation
  - 90%, 79%, 77%, 84% (LA sat 86%)
- Qp:Qs 1:1
- No pulmonary vein stenosis
- Reasonable capillary blush

### Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>( P_{PA} )</th>
<th>PVRi (WU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{FiO}_2 \ 0.75 )</td>
<td>51/24 36</td>
<td>7.1</td>
</tr>
<tr>
<td>( \text{FiO}_2 \ 1.0, \text{iNO} )</td>
<td>50/22 33</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Pulmonary angiogram
Summary: 153d

- Severe PH (systemic-to-suprasystemic)
  - due to pulmonary vascular disease
  - moderately elevated PVRi with reactivity
  - reasonably compensated (preserved CI)

- Severe lung disease
  - Requires substantial respiratory support, chronically elevated PCO$_2$, PV desaturation

- Poor functional class
  - Good weight gain but with supplemented tube feeds
  - Decreased endurance, emesis

- GER
  - Despite anti-reflux medications
Treatment plan/clinical course
transfer back at 167d

• Pulmonary vascular disease: dual therapy
  – Bosentan initiated at 1 mg/kg bid. Advanced to 2 mg/kg bid after 1 week
  – Sildenafil changed to 0.75/kg mg qid
  – Diuretics continued
  – Echo: Mildly flattened IVS (improved), persistent RV dilation, mild RA enlargement, normal RV systolic function, abnormal diastolic function, mild RVH, TR not quantifiable, pulmonary veins patent
  – BNP 33

• Respiratory support weaned to 3 LPM, FiO₂ 45%

• Feeds: taking all feeds by mouth without retching or emesis
  – Good weight gain over 7d