Pulmonary Vascular Disease in Bronchopulmonary Dysplasia

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Disclosures

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• Research Support from: Shire Pharmaceuticals for laboratory research

• Not related to today’s presentation

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Learning Objectives

• To understand the pathogenesis and physiology of pulmonary hypertension (PH) in preterm infants with BPD;
• To develop a diagnostic strategy to evaluate PH in preterm infants with BPD;
• To understand the role of PH-specific drug therapy in the management of PH in BPD.
Physiology and Treatment of PAH

Endothelin-1

Nitric Oxide

Prostacyclin (PgI₂)

Endothelial cells

Preproendothelin → Proendothelin

Endothelin-1

arginine

Arachidonic acid → Prostaglandin I₂

Nitric oxide

Endothelin-1

Endothelin-receptor A

Endothelin-receptor B

Vasoconstriction and proliferation

Exogenous nitric oxide

Vasodilatation and antiproliferation

sGC Activators and Stimulators

Endothelin-receptor antagonists

Phosphodiesterase type 5 inhibitor

Vasodilatation and antiproliferation

Survival in Children with PAH Before and After the Use of Approved Drug Therapies for Adults

1, 3 and 5 year survival: ~85-95%, 70-95% and 50-95%, respectively vs prior to therapies: ~40-65%, 45% and 30% (Robyn Barst, 2012)
Basic Pathways and Novel Targets in PAH: “Beyond Vasodilation”

• Dysregulated cellular growth ("the cancer paradigm")
• Abnormal metabolic regulation
• Inflammation (macrophages, mural cells, fibroblasts)
• Extracellular matrix regulation (structure, function)
• Circulating and Endogenous Progenitor Cells ("resilience factors")
• Hemodynamic Stress
• Right ventricular (RV) performance
  - Adaptation versus Maladaption
  - RV- PA coupling, impedance
  - RV – LV interactions
Pediatric Pulmonary Vascular Disease - Understudied and Poorly Understood

- Limited understanding of disease-specific mechanisms in pediatric PVD;
- Heterogeneity of conditions;
- Lack of organized, multidisciplinary care;
- Small number of patients at each center;
- Anecdotal-based strategies, often based on adult data;
- Lack of care guidelines and quality endpoints for assessing clinical course and response to therapy.
Goals of this Presentation

• Factors that contribute to the development and progression of *pulmonary hypertension* (PH) in BPD;

• *Diagnostic approaches* to infants with BPD and PH;

• *Therapeutic strategies* of PH in infants with BPD.
Bronchopulmonary Dysplasia (BPD)

(from Stenmark KR, Abman SH. 2005)
Pulmonary Vascular Disease in BPD

Placental Dysfunction

Lung Injury
- Hyperoxia
- Mechanical Ventilation
- Infection
- Inflammation
- Hypoxia
- Hemodynamics (PDA)

Epigenetic and Genetic Factors

Premature Birth
- Incomplete vascular growth
- Immature vascular function
- Decreased antioxidant defenses

Developing Lung Circulation

Abnormal Structure
- Smooth muscle cell and fibroblast hyperplasia
- Altered extracellular matrix

Abnormal Function
- High vascular tone
- Altered vasoreactivity
- Impaired metabolic function

Decreased Growth
- Angiogenesis (Alveolarization)
Late Cardiopulmonary Disease in a Young Adult with BPD
Low $D_L CO$ in Adult Survivors of BPD

(Wong PM et al. Eur Respir J, 2008)
Late Pulmonary Hypertension is Associated with Poor Survival in BPD

(from Khemani et al, 2007)
Relationship of PH with Severity of BPD

<table>
<thead>
<tr>
<th>BPD Severity</th>
<th>Seoul</th>
<th>Alabama</th>
<th>CU/IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3.3%</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Mild</td>
<td>1.7%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Moderate</td>
<td>9.2%</td>
<td>36.1%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Severe</td>
<td>58.2%</td>
<td>50%</td>
<td>29.2%</td>
</tr>
<tr>
<td>All Patients</td>
<td>25%</td>
<td>17.9%</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

Seoul Cohort n=116
Alabama Cohort n=145
CU/IU Cohort n=277
Issues in the Diagnosis and Management of Pulmonary Hypertension in BPD

• Whom to screen?
• How to screen?
• When to screen?
• What is the diagnostic evaluation?
• What is the role of cardiac catheterization?
• Which therapies are effective in BPD?
Whom to Screen?

- Extreme prematurity (< 26 weeks)
- IUGR or pre-eclampsia
- Maternal smoking
- Prolonged ventilator course
- Inability to wean FiO$_2$, lack of overall improvement with time, poor growth, recurrent “spells”
- Severity of BPD
- Or, All infants with BPD near term corrected age, even if clinically stable?
Abnormal Placental Histopathology and High Risk for BPD and PH in Preterm Infants

(Mestan K et al, Placenta, 2014)

|                           | No BPD or PH
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N = 165</td>
</tr>
<tr>
<td>Maternal vascular</td>
<td>56 (34)</td>
</tr>
<tr>
<td>underperfusion (any)</td>
<td></td>
</tr>
<tr>
<td>Severe MVU</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Vessel changes:</td>
<td></td>
</tr>
<tr>
<td>FN/AA</td>
<td>6 (4)</td>
</tr>
<tr>
<td>MBPA</td>
<td>16 (10)</td>
</tr>
<tr>
<td>MHMA</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Villous changes:</td>
<td></td>
</tr>
<tr>
<td>Infarcts</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Increased syncytial knots</td>
<td>53 (32)</td>
</tr>
<tr>
<td>Villous agglutination</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Increased perivillous fibrin</td>
<td>7 (4)</td>
</tr>
<tr>
<td>DVH/STV</td>
<td>36 (22)</td>
</tr>
</tbody>
</table>

*P < 0.01, versus No BPD or PH; **P < 0.001, versus No BPD or PH.

(MVU = maternal vascular underperfusion)
Intrauterine Growth Restriction and the Risk of PH in BPD Infants

(Check et al, 2013)
## Potential Risk Factors for PH in BPD

<table>
<thead>
<tr>
<th></th>
<th>Minimal Risk</th>
<th>Higher Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age</strong></td>
<td>&gt; 28 weeks</td>
<td>&lt; 28 weeks</td>
</tr>
<tr>
<td><strong>Perinatal risk factors:</strong></td>
<td>preeclampsia, chorio, IUGR, maternal smoking</td>
<td></td>
</tr>
<tr>
<td>Echocardiography at dx</td>
<td>Mild septal flattening</td>
<td>RV enlargement, effusion</td>
</tr>
<tr>
<td>Pulmonary Vein Stenosis</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>LV Diastolic Dysfunction</td>
<td>LVEDP &lt; 12</td>
<td>LVEDP ≥ 12</td>
</tr>
<tr>
<td>Catheterization: AVT</td>
<td>+ reactivity</td>
<td>- reactivity</td>
</tr>
<tr>
<td>Catheterization: PVRI, CI, RAP, PA/AoP ratio</td>
<td>PVRI &lt; 7 WU x m²; CI ≥ 3 L/min/m²; RAP &lt; 4 mmHg; Ratio &lt; 0.5</td>
<td>PVRI ≥ 7 WU x m²; CI &lt; 3 L/min/m²; RAP &gt; 4 mmHg; Ratio &gt; 0.5</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>low, decreasing levels</td>
<td>High, sustained levels</td>
</tr>
<tr>
<td>Prolonged ventilator tx</td>
<td>Ventilation ≤ 1 month</td>
<td>Ventilation &gt; 1 month</td>
</tr>
</tbody>
</table>

**Abbreviations:** AVT, acute vasoreactivity testing; BNP, brain natriuretic peptide; CI, cardiac index; dx, diagnosis; LV, Left ventricular; PVRI, pulmonary vascular resistance index; PA/AoP, pulmonary artery to aortic pressure ratio; RAP, right atrial pressure; RV, right ventricular.
How to Screen?

• EKG lacks sensitivity for identifying premature infants at risk for pulmonary hypertension (PH).

• Echocardiogram is currently best non-invasive approach, but its efficacy in determining the presence or severity of PH in BPD as applied in clinical practice is uncertain.
Utility of Echocardiograms in Assessments of Pulmonary Hypertension in BPD

(Mourani et al, Pediatrics, 2008)
Diagnosis of PH in BPD: An Approach

(from Mourani PM, Abman SH. Clin Perinatol, 2015)
Elements of Pulmonary Hypertension in BPD

- Lung Disease
  - Hyperinflation
  - Atelectasis
  - Hypoxemia
  - Hypercarbia

- Heart Disease
  - RV Dysfunction
  - Impaired LV Contractility
  - LV Diastolic Dysfunction
  - Shunt (ASD, PDA, VSD)

- Pulmonary Vascular Disease
  - High tone and reactivity
  - Hypertensive arterial remodeling
  - Decreased vascular growth

- High Pulmonary Artery Pressure
Diagnostic Approach to Infants with Pulmonary Hypertension in BPD

• Evaluation of Underlying Lung Disease:
  - Prolonged monitoring of O₂ (awake, asleep, feeds)
  - PaCO₂ – contribution to PH or marker of disease severity, need for chronic (effective) ventilation?
  - Chronic aspiration (barium swallow, swallowing study, pH probe, impedance study)
  - Sleep study
  - Structural airway disease: flexible bronchoscopy
  - Reactive airways disease
  - Chest CT Scan

• Cardiac Catheterization
Role of Cardiac Catheterization

- Assess severity of pulmonary hypertension
- Anatomic heart disease/shunt lesions (esp. assessment of atrial septal defects)
- Structural vascular abnormalities (eg, arterial stenosis, pulmonary vein stenosis, hemangiomatosis, others)
- Assess cardiac function (LV dysfunction)
- Catheter-based interventions (collaterals, stenosis, shunt)
- Acute vasoreactivity/hypoxia testing for selection of chronic therapy
Increased Hypoxic Pulmonary Vasoconstriction in BPD

(Abman et al, 1985)
Left Ventricular Diastolic Dysfunction in BPD
Pulmonary Vein Stenosis in BPD

High Mortality in PVS

(Drossner et al, 2008)
Severe Pulmonary Hypertension in a Preterm Infant with BPD and PVS

Pulmonary Artery Remodeling

Pulmonary Vein Remodeling
Increased Systemic to Pulmonary Collaterals in BPD
Associated Cardiovascular Lesions in BPD Infants with Pulmonary Hypertension

<table>
<thead>
<tr>
<th>FINDING</th>
<th>% of PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- PDA/ASD/PFO</td>
<td>50%</td>
</tr>
<tr>
<td>- Pulmonary Vein Stenosis</td>
<td>27%</td>
</tr>
<tr>
<td>- Aorto-pulmonary Collaterals</td>
<td>35%</td>
</tr>
<tr>
<td>- Left Ventricular End-Diastolic Pressure &gt; 12 mmHg</td>
<td>54%</td>
</tr>
</tbody>
</table>

- Retrospective study of 29 patients
- 21 patients had CT scans, 14 had cath
- 66% with one associated findings

(del Cerro et al. Pediatric Pulmonol, 2013)
Histologic Evidence of Intrapulmonary Vascular Shunt Vessels in BPD

(Normal, ACD/MPV, BPD)

(Galambos C, Sims-Lucas S, Abman SH. Ann Am Thorac Soc. 2013)
Patterns of Abnormal Vasculature in the Distal Lung of Infants Dying with Severe BPD
Persistent Fetal Intrapulmonary “Shunt Pathways” in Severe BPD

(Galambos C et al. Ann Am Thorac Soc. 2013)
Intrapulmonary Shunt Vessels in BPD

Normal perinatal lung:
- Intrapulmonary Arteriovenous Anastomotic Vessels (IAAV) closed
- Alveolar capillaries with normal blood flow
- Pulmonary artery
- No hypoxemia (rich in O₂)

Bronchopulmonary dysplasia:
- Prominent Intrapulmonary Arteriovenous Anastomotic Vessels (IAAV)
- Alveolar capillaries with decreased blood flow
- Pulmonary artery
- Hypoxemia due to shunt (decreased O₂)

(Galambos C et al. Ann Am Thorac Soc. 2013)
Pulmonary Hypertension Drugs: Therapeutic Approach in BPD

- Inhaled NO (5 - 20 ppm)
- Sildenafil (0.5 - 2 mg/kg/dose q 6 - 8 hours)
- Bosentan (1/4 tab daily initially, then BID)
- Prostacyclin analogues:
  - Epoprostenol (Flolan) (iv)
  - Inhaled Iloprost
  - Remodulin (iv, SQ, inhaled)
- Milrinone
AHA/ATS Consensus Pediatric PAH Treatment Algorithm

Consider: Diuretics, Oxygen, Anticoagulation, Digoxin

Acute Vasoreactivity Testing

Oral CCB

Improved

Lower Risk

ERA or PDE-5i (oral)
Iloprost (inhaled)
Treprostinil (inhaled)

Reassess: consider combo-therapy

Continued CCB

Higher Risk

Epoprostenol IV or Treprostinil (IV/SQ)
Consider Early Combination ERA or PDE-5i (oral)

Atrial septostomy
Lung transplant

Ambrisentan (2aB), Bosentan (1B), CCB (1B), Epoprostenol (1B), Iloprost (2aB), Sildenafil (1B), Tadalafil (2aB), Treprostinil IV/SQ (1B), Treprostinil Inh (2aB)
Chronic Sildenafil Therapy for Late Pulmonary Hypertension in CLD

(Mourani PM et al, J Peds, 2009)
Subcutaneous Treprostinil (Remodulin) for Late Pulmonary Hypertension in BPD

(Ferdman DJ et al. Pediatrics 2014)
Resolution of Pulmonary Hypertension in BPD

29 patients with PH and BPD
69% on drug therapy:
- inhaled NO (45%)
- sildenafil (62%)
- bosentan (10%)
- iloprost (14%)
14% mortality

(An et al, Korean Circ J, 2010)
Poor Survival in BPD Infants with Pulmonary Hypertension

* 95% Confidence Intervals

(Del Cerro et al. Pediatric Pulmonol, 2013)
AHA/ATS Guideline

Pediatric Pulmonary Hypertension
Guidelines From the American Heart Association and American Thoracic Society

Steven H. Abman, MD, Co-Chair; Georg Hansmann, MD, PhD, FAHA, Co-Chair;
Stephen L. Archer, MD, FAHA, Co-Chair; D. Dunbar Ivy, MD, FAHA; Ian Adatia, MD;
Wendy K. Chung, MD, PhD; Brian D. Hanna, MD; Erika B. Rosenzweig, MD;
J. Usha Raj, MD; David Cornfield, MD; Kurt R. Stenmark, MD;
Robin Steinhorn, MD, FAHA; Bernard Thébaud, MD, PhD; Jeffrey R. Fineman, MD;
Titus Kuehne, MD; Jeffrey A. Feinstein, MD; Mark K. Friedberg, MD;
Michael Earing, MD; Robyn J. Barst, MD†; Roberta L. Keller, MD; John P. Kinsella, MD;
Mary Mullen, MD, PhD; Robin Deterding, MD; Thomas Kulik, MD;
George Mallory, MD; Tilman Humpl, MD; David L. Wessel, MD; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society

(Circulation, 2015)
Pulmonary Hypertension in BPD

• Screening for PH by echocardiogram is recommended in infants with established BPD (Class I, Level B).

• Evaluation and treatment of lung disease, including assessments for hypoxemia, aspiration, structural airways disease and the need for changes in respiratory support, is recommended in infants with BPD and PH before initiation of PAH-targeted therapy. (Class I, Level B)
Pulmonary Hypertension in BPD

- Evaluation for chronic therapy for PH in infants with BPD should follow recommendations for all children with PH and include cardiac catheterization to diagnose disease severity and potential contributing factors such as LV diastolic dysfunction, anatomic shunts, pulmonary vein stenosis and systemic collaterals. (Class I, Level B)

- Supplemental oxygen therapy is reasonable to avoid episodic or sustained hypoxemia and with the goal of maintaining O2 saturations between 92% - 95% in patients with established BPD and PH. (Class IIa., Level C)

- PAH-targeted therapy can be useful for infants with BPD and PH on optimal treatment of underlying respiratory and cardiac disease. (Class Iia, Level C)
PPHN in Preterm Infants

- iNO can be beneficial for *preterm infants* with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios. (*Class IIa, Level B*)
Conclusions

• Pulmonary vascular disease (PVD) can be identified *early* in preterm newborns and is associated with:
  - an increased risk for developing BPD
  - higher mortality and late respiratory morbidities.

• Primary management is related to comprehensive evaluation and treatment of underlying respiratory disease;

• PH and related cardiovascular abnormalities modulate the clinical course and outcomes of BPD.
Pediatric Heart Lung Center, UCD
Clinical Team

Laboratory Team
Case Studies for AUDIENCE RESPONSE SYSTEM Discussion
Case 1: Late PH in Severe BPD Despite Chronic Mechanical Ventilation

- 9-month-old infant with BPD referred for assessment and treatment of severe PH
- 24 weeks gestation, history of oligohydramnios and IUGR
- Received antenatal steroids, early surfactant
- Mechanical ventilation for first 2 months of life
- transitioned to HFNC for 2 months
- re-intubated and ventilated due to worsening respiratory course despite multiple courses of steroids
- Developed progressive PH despite ventilation, requiring treatment with sildenafil (1 mg/kg q 6 hours) and bosentan (1 mg/kg BID)
- Transferred for further evaluation
Case 1: Late PH in Severe BPD Despite Chronic Mechanical Ventilation

• Initial ECHO = RV dilation, marked septal flattening, insufficient window to determine TRJV

• Ventilation upon arrival
  – FiO₂: 85%
  – TV: 5 mL/kg
  – Peak pressure: 24 cm H₂O
  – PEEP: 6 cm H₂O
  – Rate: 40 bpm
  – VBG: 7.37/78/35

bpm, beats per minute; FiO₂, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; RV, right ventricle; TRJV, tricuspid regurgitation jet velocity; TV, tidal volume; VBG, venous blood gases.
Audience Question 1

• What is the next most important step in managing this preterm infant?
  1. Cardiac catheterization
  2. Evaluation and management of the underlying respiratory disease
  3. Urgent tracheostomy
  4. Lung biopsy
  5. An additional course of steroids
Evaluation of Underlying Lung Disease in Infants With BPD and Comorbid PH

- Prolonged monitoring of $O_2$ (awake, asleep, during feeds)
- $PCO_2$—contribution to PH or marker of disease severity, evaluate the need for chronic (effective) ventilation
- Sleep study to evaluate hypoxemia
- GER with chronic aspiration: radiologic studies (barium swallow, upper GI series), pH or impedance probes, and/or swallow studies
- Structural airway disease: flexible bronchoscopy
- Reactive airway disease
- Chest CT scan may help evaluate lung parenchyma and vasculature
- CATH
Management of Ventilator-Dependent Infants With Severe BPD

• Heterogeneity of lung disease
  – Marked variability in regional time constants
  – Mixed airways and parenchymal disease, with decreased surface area (hypoplasia), edema, atelectasis

• Tracheomalacia, diffuse bronchomalacia

• Airway secretions

• Aspiration

• PH

Adverse Effects:
- Worse distribution of gas
- Increased dead space ventilation
- Higher $\text{PCO}_2$
- Higher $\text{FiO}_2$
- Progressive atelectasis
- Regional overdistension

Heterogeneity of Lung Disease in Established BPD

Benefits:
- Improved gas distribution
- Lower $V_D/V_T$
- Lower $PCO_2$
- Lower $FiO_2$
- Less atelectasis

Ventilator Strategies in Severe BPD

- Marked regional heterogeneity:
  - Larger tidal volumes (10-12 mL/kg)
  - Longer inspiratory times (≥0.6 sec)

- Airways obstruction
  - Slower rates allow better emptying, especially with larger tidal volumes
  - Complex roles for PEEP with dynamic airway collapse

- Interactive effects of vent strategies
  - Changes in rate, tidal volume, inspiratory and expiratory times, pressure support are highly interdependent
  - Overdistension can increase agitation and paradoxically worsen ventilation

- Permissive hypercapnia
Case 2: PH in BPD—Lung Edema During Pulmonary Vasodilator Therapy

- Male twin B born at 28 weeks gestation, 829 g
- Delivered via C-section due to chorioamnionitis and oligohydramnios
- Poor oxygenation with PH confirmed by ECHO
- Treated with surfactant, high frequency oscillatory ventilation, and inhaled NO
- Extubated to CPAP after 5 weeks
- Discharged home at 4 months on 0.5 lpm oxygen
- ECHO at discharge was normal except for “mild ventricular septal flattening when agitated”
Case 2: (continued)

- Readmitted to PICU 1 month after NICU discharge with severe respiratory distress requiring mechanical ventilation
- ECHO revealed severe PH, which was estimated at 3/4 systemic level with mild biventricular hypertrophy
- iNO therapy (20 ppm) was initiated
- Despite aggressive diuretic use, serial chest radiographs showed worsening pulmonary edema
Case 2: Chest Radiographs Before and During iNO Therapy
Audience Response Question 2

• What would you do next?
  1. Begin sildenafil
  2. Cardiac catheterization
  3. Begin milrinone
  4. Increase PEEP
  5. Begin high dose steroids
Case 2: LV Diastolic Dysfunction Contributing to PH in BPD

- CATH findings revealed
  - mPAP, 41 mm Hg
  - PCWP, 17 mm Hg
- Milrinone added to reduce LV afterload and pulmonary edema and to improve cardiac output
- PH progressively improved over a few weeks to less than 1/3 systemic level
- Transitioned from iNO and milrinone to sildenafil and enalapril and diuretic therapy was reduced
- Discharged from the hospital after 5 weeks on 0.25 lpm oxygen, enalapril, sildenafil, diuretics, and inhaled steroids
- Prescribed prolonged chronic sildenafil therapy as outpatient
Case 3: Late Onset of Severe PH in BPD

- 23-month-old infant referred from out-of-state for further evaluation and treatment of severe PH
- 30 weeks gestation with markedly prolonged PROM
- NICU course included HFOV, iNO therapy and mechanical ventilation x 3 weeks
- ECHO prior to discharge read as “no signs of pulmonary hypertension”
- Discharged on home oxygen therapy, progressively weaned off as outpatient
- First year at home characterized by
  - Multiple hospital readmissions for respiratory exacerbations
  - Need for asthma therapy
  - On and off supplemental oxygen
Case 3: Late Onset of Severe PH in BPD

- ECHO performed at 18 months and showed near systemic PH
- Restarted on supplemental oxygen, initiated sildenafil therapy
- Bosentan added due to lack of improvement in PH
- Chest film and CT scan images
Audience Question 3

Which of the following is evidence-based pulmonary vasodilator therapy in BPD-associated PH?

1. Sildenafil
2. iNO
3. Prostacyclin analogues (e.g., Treprostinil)
4. Bosentan
5. Milrinone
6. None of the above