Bronchopulmonary Dysplasia

Christopher D. Baker, MD
Associate Professor of Pediatrics
University of Colorado School of Medicine
Bronchopulmonary Dysplasia

Relevant financial relationships with a commercial interest:
No relevant commercial interests.
BPD: Learning Objectives

- After this lecture, participants will be able to:
  - Review the *pathogenesis* of Bronchopulmonary Dysplasia (BPD)
  - Summarize the *vascular hypothesis* of lung development
  - Differentiate between *protective* and *supportive (chronic) ventilation* strategies in preterm infants
  - Recognize the indications for *chronic mechanical ventilation* in infants with severe BPD
  - Determine *which patients would benefit* from chronic ventilatory support (potentially via tracheostomy)
BPD: Lung Development

- Preterm Birth

- Alveolar
  - Secondary septation results in the division of alveolar ducts into terminal alveoli
  - Pulmonary capillary bed expands by angiogenesis

- Saccular

- Alveolar type II differentiation allows for surfactant production

- Primitive terminal airspaces form, consisting of thin walled saccules

References:
Baker / Alvira 2014 Curr Opin Pediatr 26:306;
Coalson 1999 CLD of Early Infancy 85-124
Bronchopulmonary Dysplasia

- Bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is associated with mechanical ventilation and oxidative stress.  
  Northway 1967 NEJM 276:357

- In infants born at 23-26 weeks gestation, BPD consists of an arrest in lung vascular and alveolar growth.  
  Jobe 1998 Early Hum Dev 53:81
Pathogenesis of BPD

- Genetic Factors
- Premature Birth
  - Prenatal factors
  - Preeclampsia
  - Chorioamnionitis
  - Growth Restriction
  - Fetal infection
  - Smoking, drug use

- Hyperoxia
- Inflammation
- Infection
- Ventilator Induced Injury

Disruption of growth factor signaling pathways

- Alveolarization
- Vascular Growth
- Lung Function

Adapted from Robbins 2012 AJRCCM 185:1015
Bronchopulmonary Dysplasia

“Old BPD” Pre-surfactant Era

**INJURY TO LUNG**

- Atelectasis/Hyperinflation
- Airway epithelial lesions
- Smooth muscle hyperplasia
- Diffuse fibroproliferation
- Remodeling of pulm arteries
- Decreased alveolarization

*Courtesy of SH Abman*
Bronchopulmonary Dysplasia

“New BPD” Post-surfactant ARREST OF DISTAL LUNG DEVELOPMENT

- Rare fibrosis
- Less regional heterogeneity
- Rare epithelial lesions
- Decreased, dysmorphic lung capillaries
- Alveolar simplification

Coalson 2003 Semin Neonatal 8:73
# BPD Severity: NIH Diagnostic Criteria

<table>
<thead>
<tr>
<th>TABLE 1. DEFINITION OF BRONCHOPULMONARY DYSPLASIA: DIAGNOSTIC CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
</tr>
<tr>
<td>Time point of assessment</td>
</tr>
<tr>
<td>Treatment with oxygen</td>
</tr>
<tr>
<td>Mild BPD</td>
</tr>
<tr>
<td>Moderate BPD</td>
</tr>
<tr>
<td>Severe BPD</td>
</tr>
</tbody>
</table>

*Jobe 2001 AJRCCM 163:1723*
BPD: The Spectrum of Severity

- By these criteria, the following have severe BPD:
  - **3 month old 26-wk F:** 1/8L NC; orally feeding; ready for discharge; $O_2$ reduction test: $FiO_2$ 0.31
  - **3.5 month old 24-wk M:** CPAP 6 ($FiO_2$ 0.21); NG fed; unstable during $O_2$ reduction test
  - **4 month old 24-wk twin M:** early HFOV; still intubated, conventional vent ($FiO_2$ 0.80); frequent desaturation “spells”; pulmonary hypertension; tracheostomy planned
Severe “Type 2” or "Grade 3" BPD

**Table I. BPD definition with severity**

<table>
<thead>
<tr>
<th>BPD severity</th>
<th>Definition (Modified from Jobe and Bancalari)</th>
<th>Relative incidence (Data from Ehrenkranz et al)</th>
<th>Postdischarge mortality (Data from Ehrenkranz et al)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>$O_2$ treatment $&lt;28$ d and breathing room air at $36$ wk PMA or discharge home, whichever comes first</td>
<td>23.1%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Mild</td>
<td>$O_2$ treatment at least $28$ d and breathing room air at $36$ wk PMA or discharge home, whichever comes first</td>
<td>30.3%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Moderate</td>
<td>$O_2$ treatment at least $28$ d and receiving $&lt;30%$ $O_2$ at $36$ wk PMA or discharge home, whichever comes first</td>
<td>30.2%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Severe (type 1)</td>
<td>$O_2$ treatment at least $28$ d and receiving $\geq 30%$ $O_2$ or nasal CPAP/HFNC at $\geq 36$ wk PMA</td>
<td>16.4%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Severe (type 2)</td>
<td>$O_2$ treatment at least $28$ d and receiving mechanical ventilation at $\geq 36$ wk PMA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HFNC, high flow nasal cannula; $O_2$, oxygen.*

*Abman 2017 J Pediatr 181:12
Higgins 2018 J Pediatr 197:300*
A New Baby with “Old” BPD

Severe “Old” + “New” BPD

“Old BPD”
INJURY TO LUNG
- Altered inflation pattern of atelectasis and overinflation
- Severe airway epithelial lesions (hyperplasia, squamous metaplasia)
- Airway smooth muscle hyperplasia
- Extensive fibroproliferation
- Prominent vascular hypertensive lesions
- Decreased internal surface area and alveoli

“New BPD”
ARRESTED LUNG DEVELOPMENT
- Decreased, large and simplified alveoli (alveolar hyperplasia, decreased acinar complexity)
- Decreased, dysmorphic capillaries
- Variable interstitial fibroproliferation
- Less severe arterial/arteriolar vascular lesions
- Negligible airway epithelial lesions
- Variable airway smooth muscle hyperplasia

Severe BPD = “the worst of both worlds...”

Coalson 2003 Semin Neonatol 8:73
Severe “Old” + “New” BPD

Increased Fibro-proliferation

Alveolar Simplification

Coalson 2003 Semin Neonatal 8:73
BPD: A Vascular Hypothesis

- The lungs of preterm infants who die from BPD have markedly decreased vessels.

Bhatt 2001 AJRCCM 164:1971

- Disrupted vascular growth impairs alveolarization.

Abman 2001 AJRCCM 164(10):1755

- In neonatal rats, angiogenic inhibitors decrease pulmonary vascular growth and alveolarization.

Jakkula 2000 AJP Lung 279:L600

- Can we augment vascular growth to prevent/treat BPD?
BPD: Prevention and Treatment
BPD Prevention

• **Delay preterm birth**
  • Degree of prematurity and birth weight are the two biggest risk factors

• **Antenatal steroids**
  • Decreases respiratory distress syndrome, intraventricular hemorrhage, mortality
  • BPD incidence unchanged (due to increased survival)

• **Exogenous surfactant**
  • First dose during the first hour
  • Consider less invasive approaches
  • Can give up to two more additional doses if unstable during the first 72 hours of life
BPD Prevention

• **Protective ventilation strategies**
  - CPAP (even if must forego surfactant), high-frequency oscillatory/jet ventilation, noninvasive ventilation

• **Judicious fluid management**
  - Moderate fluid restriction (negative balance), higher fluid intake associated with BPD and death

• **Caffeine**
  - Not only for apnea of prematurity, but early caffeine therapy may reduce the risk of developing BPD

• **Vitamin A**
  - Some meta-analyses and multicenter studies show modest benefit, injections (3x/week)
BPD Treatment

- **Ventilation strategies**
  - Approach differs for chronic ventilation
  - Support breathing (rather than avoid injury)
  - For established disease: larger tidal volume, lower rate
  - Ideal time to stop weaning attempts?

- **Oxygen Therapy**
  - Avoid toxicity, optimal SpO2 target unclear (91-95%?)

- **Diuretics**
  - Improve lung compliance
  - Side effects: osteopenia, nephrocalcinosis, hearing loss
  - Long-term benefit unclear (avoid when possible)
Respiratory Outcomes in BPD
Respiratory Outcomes in Children

- **7-8y**: VLBW have ↓ FEV₁, ↑ RV/TLC  
  *Finland*: Korhonen 2004 Acta Paediatr 93:316

- **9.5y**: VLBW+BPD have ↓ FEV₁, FVC, FEF₅₀  
  *Germany*: vom Hove 2014 J Pediatr 164:40

- **11y**: <26wk+BPD have ↓ FEV₁, ↑ bronchoreactivity  
  *EPICure; UK*: Fawke 2010 AJRCCM 182:237

- **1991-92 vs. 1997 vs. 2005** (at 8y)  
  - 2005: ↓ MV / ↑ CPAP, lung function unchanged  
  *Australia*: Doyle 2017 NEJM 377:329
Young Adults with “Old” BPD Have Airways Disease

AIRWAYS DISEASE AT ~18 YRS

Normal
+Methacholine
Reversible Obstruction
Fixed Obstruction

BPD (n = 25)
Matched Cohort (n = 26)
Normal (n = 53)

24%
8%
44%
24%
69%
31%
83%
17%

Northway 1990 NEJM 323:1793
Respiratory Outcomes in Young Adulthood

- 17y: ↑ asthma, ↓ FEV₁
- 25y: ↓ lung function, ↑ RV/TLC, +methacholine response
  \[ \text{Norway: } \text{Halvorsen 2004 Acta Paediatr 93:1294} \]
  \[ \text{Norway: } \text{Vollsæter 2015 ATS Annals 12:313} \]
- 19y: ↓ FEV₁, FVC, FEV₁/FVC; normal lung volumes
  \[ \text{Australia: } \text{Doyle 2006 Pediatrics 118:108} \]
- 25y: persistently ↓ airflows, no air trapping
  \[ \text{Australia: } \text{Gibson 2015 Pediatr Pulmonol 50:987} \]
Ventilation Strategies: Protective vs. Supportive
Protective Ventilation

• **GOAL:** avoid lung injury
  • “Gentle-ation”, early extubation
• Appropriate in the immediate postnatal period
• Consider less-invasive approaches:
  • Continuous positive airway pressure (CPAP)
  • High-frequency oscillatory ventilation
  • Small tidal volume / high rate vent strategy
• Delivery room CPAP (in lieu of postnatal surfactant)
• Minimally-invasive surfactant therapy (by catheter)
• Treatment of acute respiratory distress in children
Supportive Ventilation

- **GOAL:** support breathing, promote growth and development, stability, baby is happy
- Appropriate for established / chronic lung disease
- Heterogeneous lung: regions of fibrosis/atelectasis as well as regions of marked hyperinflation
- Supportive approaches to ventilation:
  - Larger tidal volume / lower rate vent strategy
  - PEEP to overcome dynamic airway collapse
- Support breathing for months/years; defer weaning
- Consideration of tracheostomy
Tracheobronchomalacia

Counterintuitively, less PEEP may worsen hyperexpansion!

- Malacia = dynamic collapse of the airways
Ineffective Chronic Ventilation

(T = Resistance × Compliance)

Low tidal volume
Short insp times

Adverse effects:
- Worse distribution of gas
- Increased dead space ventilation
- Higher PCO₂
- Higher FiO₂
- Progressive atelectasis
- Regional overdistension

Effective Chronic Ventilation

Chronic Ventilation: Other Factors

- Optimal nutrition for linear growth without obesity
- Aspiration – need for gastric fundoplication?
- Airway clearance / suctioning of secretions
- Medications (e.g., inhaled/enteral steroids, bronchodilators, diuretics)
- Pulmonary hypertension – screening, treatment
- Bedside emergency management – still A-B-C!
- Agitation, dyssynchrony – sedation, NAVA
- Developmental therapy – PT, OT, speech, feeding
Interim Summary

- The respiratory sequelae of BPD persist into young adulthood
- Strategies for protective and supportive ventilation differ dramatically
- More importantly, the goals of care are very different
- Chronic ventilation gives a baby with (Type 2) severe BPD the best chance at a positive outcome
Case: NICU Consult
Case: NICU Consult

3 month-old 24-week preterm twin girl, failed extubation multiple times despite aggressive steroid therapy (dexamethasone), has frequent desaturation spells.

**Current ventilator settings**: volume control, Vt 5ml/kg, i-time 0.4 sec, rate 35, PEEP 5 cm H₂O, PS 12 cm H₂O, FiO₂ 0.50

**Blood gas**: pH 7.36, pₐCO₂ 64, pₐO₂ 118

**Medications**: Lasix 1 mg/kg BID, prednisolone 0.5 mg/kg every 48 hours, albuterol q4h PRN

**Studies**: 
- **CXR**: hyperinflation, patchy atelectasis
- **Echocardiogram**: no interventricular septal flattening
- **Flexible bronchoscopy**: severe tracheobronchomalacia
What changes in ventilator strategy do you suggest?

A. Change to non-invasive ventilation
B. Increase Vt, i-time, and PEEP; decrease rate
C. Increase Vt and rate
D. Increase pressure support and decrease inspiratory time
E. Change to high frequency oscillatory ventilation (HFOV)
Correct answer:

B. Increase Vt, i-time, and PEEP; decrease rate
Answer Rationale

- Child will likely not tolerate extubation
- In severe BPD, larger Vt with longer i-time optimizes gas distribution
- A slower rate permits adequate exhalation
- PEEP supports dynamic airway collapse
- Increasing the rate may lower the pCO2, but increases V/Q mismatch
- HFOV is challenging in established BPD due to highly variable time constants and heterogeneous lung injury
Interdisciplinary Ventilator Care Program
Ventilator Care Program (VCP)

- **VCP History in CO**: Pulm/Neo collaboration (Abman, Gien)
- **Mission**: Quality inpatient-to-outpatient care
- **Team approach** – many key contributors
- **Transition to PRCU (out of ICU)** before discharge
- **Clinical rounds**: two meetings/week since 2007
  - **NICU rounds**: at bedside, families participate
  - **VCP rounds**: conference room, discharge planning
- **Pulm-NICU Consult team**: since Jan 2019
- **Impact on families**: mortality, LOS/cost, traumatic stress
Ventilator Care Program (VCP)

- **Point-prevalence:** 20+ inpatients, 100+ outpatients (in seven state region)
- **Key discharge barrier:** inadequate in-home private duty nursing (worse in 2018-2019)
- 96% of U.S. survey respondents either “Disagreed” or “Strongly Disagreed” that there was “an adequate supply of home nursing services.”  

  *Sobotka S 2018, Pediatric Pulmonol 54:40-46*
Many Factors Delay Discharge

Sobotka 2016 Hosp Pediatr 6(9):552-7
VCP Standardized Process

- **Quality Improvement** (may not be generalizable)
- **Process map**: increases safety, improves efficiency, defines roles, ensures nothing overlooked
- Focus on **care coordination** (case management)
- Summarizes caregiver **responsibilities**
- **Standarized** process; highly **customized**
- Used to create the family-friendly “**Road Map**”
- **Reduced length of stay** (LOS) by 42% and post-ICU LOS by 55%

*Baker 2016 Pediatrics 137:e20150637*
Process Mapping

Vent Care Program: Ideal state processes for first transition to home with trach and vent

Wednesday, June 05, 2013

Baker 2016 Pediatrics 137:e20150637
VCP Caregiver Education

• Interdisciplinary collaborative: led by RT and Nursing
• Teach-back Method
• Multiple modalities utilized (verbal, written, videos, CPR, high-fidelity SIM)
• Bilingual (English/Spanish)
• Address learning needs (language barriers, dyslexia)
• Timelines, checklists, color-coded medications
High-Fidelity Simulation (SIM)

- AIM: To recreate emergencies in a safe/artificial setting
- Two Complex Scenarios (90 min, including debriefing):
  - Plugged tracheostomy – requires suctioning the trach
  - Ventilator malfunction – requires full CPR and calling 911
- To date: 100+ children (200+ caregivers)
High-Fidelity Simulation (SIM)

• SIM scheduled during week before discharge (to confirm/reinforce skills)
• Families identify gaps in understanding
• Not a pass/fail “test”
• Limitations: cost, time, difficult to repeat
• Subjectively, SIM improved caregiver confidence
  Tofil 2013 Clinical Pediatrics 52(11):1038

• In our population, caregivers ranked post-SIM debriefing the most beneficial element of training
  Thrasher/Baker 2018 J Pediatr Nurs 38:114

• 2018: Expanded to all “tracheostomy” patients (n=20+)
Summary

- BPD consists of an interruption in pulmonary vascular and alveolar growth after preterm birth
- Preterm infants with severe BPD can develop features of both “new BPD” and “old BPD”
- Optimal approaches to preventing and treating BPD remain unclear
- Children and young adults with BPD often have airflow obstruction
- Supportive Ventilation: chronic lung disease can improve over time (years)
- The care of chronically-ventilated children is improved with an interdisciplinary program
Should We Chronically Ventilate Infants with Severe Chronic Lung Disease?
Severe Bronchopulmonary Dysplasia

Age 6 months  Age 14 months  Age 23 months

Abman SH, The Newborn Lung, 2011 (Castile RG)
Thank you.

Christopher.Baker@UCAnschutz.edu