Nutrition & Bronchopulmonary Dysplasia

Camilia R. Martin, MD MS
Associate Professor of Pediatrics, Harvard Medical School
Associate Director, Neonatal Intensive Care Unit
Director for Cross-Disciplinary Research Partnerships, Division of Translational Research
Beth Israel Deaconess Medical Center, Boston MA
Disclosures

Scientific Advisor Board:
Sancilio, Laurent, Alcresta, Prolacta

Research Funding:
Sancilio, Alcresta, Abbott (lipid delivery strategies)
Review
Review current evidence on nutritional practices with regard to BPD

Determine
Determine nutritional strategies that can be applied now

Identify
Identify clinical challenges and knowledge gaps moving forward

Outline
Epidemiologic Data Demonstrate that Growth Attainment in NICU is Associated with BPD Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartile 1 (n = 124)</th>
<th>Quartile 2 (n = 122)</th>
<th>Quartile 3 (n = 123)</th>
<th>Quartile 4 (n = 121)</th>
<th>P^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain, mean (SD), g/kg per d</td>
<td>12.0 (2.1)</td>
<td>15.6 (0.8)</td>
<td>17.8 (0.8)</td>
<td>21.2 (2.0)</td>
<td>—</td>
</tr>
<tr>
<td>BPD, %</td>
<td>56</td>
<td>41</td>
<td>30</td>
<td>31</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Nutrition & BPD: Mechanisms?

- Is nutrition driving the lung disease (A), or is the lung disease driving the nutritional intake (B)

Role of nutrition:
- **Primary** – direct evidence of that a specific nutritional parameter or nutrient is in the pathway of lung injury or repair
- **Secondary** – a proxy to our practices around lung disease (fluid restriction, diuretics, steroids)
Approach to Understand Role of Nutrition in the Prevention and Management of BPD

- Total Daily Fluids
- Energy (Kcals, growth)
- Macro-, Micronutrients
- Base Diet (Human Milk)
- Targeted Nutrients

Preclinical Animal Data
Human Cohort Studies
Randomized Clinical Trials
Targeted Nutrients
Base Diet (Human Milk)
Macro-, Micronutrients
Energy (Kcals, growth)
Total Daily Fluids
<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary hemodynamics in lambs during induced capillary leakage immediately after preterm birth.</td>
<td>Preterm lambs, C v Vol Load (50 mL/k), then PEEP challenge</td>
<td>- Increased protein in BAL fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Interstitial fluid retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Decreased PBF, P/SBP, oxygenation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increased pulm hemorrhage</td>
</tr>
</tbody>
</table>

Human Cohort Studies

**Study**
Hydration during the first 4 days of life and the risk of bronchopulmonary dysplasia in low birth weight infants.

*Van Marter, et al. JPeds 1990*

**Protocol**
Case-Control

**n=76/147**

**Findings**
- Infants w/ BPD rec’d greater total, crystalloid, and colloid fluids per kilogram per day in the first 4 days of life
- Greater net weight gain in the first 4 days of life
- More likely to be given a clinical diagnosis of patent ductus arteriosus
<table>
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<th>Protocol</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association between fluid intake and weight loss during the first 10 days of life and risk of BPD in ELBW infants. <em>Oh et al (Neonatal Network), JPeds 2005</em></td>
<td>Retrospective cohort n=1382</td>
<td>- higher fluid intake and less weight loss during the first 10 days of life associated with an increased risk of BPD</td>
</tr>
</tbody>
</table>
Analysis 1.5. Comparison 1 Restricted versus liberal water intake, Outcome 5 Bronchopulmonary dysplasia.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 5 Bronchopulmonary dysplasia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restricted n/N</th>
<th>Liberal n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell 1980</td>
<td>751-2000</td>
<td>5/85</td>
<td>119</td>
<td>11.9 %</td>
<td>0.63 [0.21, 1.83]</td>
</tr>
<tr>
<td>Kavadia 2000</td>
<td>&lt;1500</td>
<td>21/84</td>
<td>-11 %</td>
<td>32.8 %</td>
<td>0.95 [0.57, 1.60]</td>
</tr>
<tr>
<td>Lorenz 1982</td>
<td>750-1500</td>
<td>10/44</td>
<td>80-140</td>
<td>17.9 %</td>
<td>0.83 [0.40, 1.73]</td>
</tr>
<tr>
<td>Tammela 1992</td>
<td>&lt;1751</td>
<td>21/50</td>
<td>50-120, 150, 200</td>
<td>37.3 %</td>
<td>0.84 [0.55, 1.29]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>263</strong></td>
<td><strong>263</strong></td>
<td></td>
<td>100.0 %</td>
<td><strong>0.85 [0.63, 1.14]</strong></td>
</tr>
</tbody>
</table>

Total events: 57 (Restricted), 67 (Liberal)

Heterogeneity: $\chi^2 = 0.51$, df = 3 ($P = 0.92$); $I^2 = 0.0\%$

Test for overall effect: $Z = 1.08$ ($P = 0.28$)

Test for subgroup differences: Not applicable


Targeted Nutrients

Base Diet (Human Milk)

Macro-, Micronutrients

Energy (Kcals, growth)

Total Daily Fluids
Energy - Overview

• In experimental models, evaluation of nutritional energy modeled as growth restriction.
  • There remains a high incidence of postnatal growth restriction
  • Growth failure is associated with BPD, including perinatal growth restriction (IUGR)
Preclinical Animal Data

Restricted Nutrition/Postnatal Growth Restriction

Alveolar formation is dysregulated by restricted nutrition

(Joss-Moore et al, Pediatric Research 2016)

- Lamb
- NIS vs NIS + RN; RN = lower fluids, fat, protein, calories (150 kcal/k/d v 60 kcal/k/d)
- 21 day model
- RN = reduced alveolar count, increased septal wall thickness, decreased caspase-3 (apoptosis), decreased PCNA (proliferation)
- Unable to determine specific nutrient effects; or windows of opportunity/vulnerability
**Preclinical Animal Data**

**Restricted Nutrition/Postnatal Growth Restriction**

  - New Zealand white rabbits
  - C= control; M= malnutrition (30% reduction in all nutrients); A= room air; H=hyperoxia (95% \( O_2 \))
  - 7 day model
  - H = reduced alveolar count; M = enhances hyperoxia effect, Unable to determine specific nutrient effects; or windows of opportunity/vulnerability
Preclinical Animal Data

Restricted Nutrition/Postnatal Growth Restriction

- Postnatal growth restriction augments oxygen-induced pulmonary hypertension
- (Wedgwood et al, Pediatric Research 2016)
  - Rat
  - PNGR induced by increasing litter size
  - 14 day model; Hyperoxia 75% O₂
  - PNGR induces specific mechanistic changes in lung injury – some similar, some additive
  - Unlike previous models, did not play a role in RAC and/or alveolar area
  - Unable to determine specific nutrient effects; or windows of opportunity/vulnerability

Cardiac/Pulmonary Vascular Development

<table>
<thead>
<tr>
<th>Table 1. Summary of similarities and differences between hyperoxia and PNGR in neonatal rat pups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive effects</td>
</tr>
<tr>
<td>Fulton’s index ↑</td>
</tr>
<tr>
<td>RV weight/body weight ↑</td>
</tr>
<tr>
<td>Medial wall thickness ↑</td>
</tr>
<tr>
<td>Vessels per HPF ↓</td>
</tr>
<tr>
<td>BCAA ↓</td>
</tr>
<tr>
<td>Effects unique to hyperoxia</td>
</tr>
<tr>
<td>Mean alveolar area ↑</td>
</tr>
<tr>
<td>Radial alveolar count ↓</td>
</tr>
<tr>
<td>Effects similar but not additive</td>
</tr>
<tr>
<td>VEGF/VEGFR2 ↓</td>
</tr>
<tr>
<td>HIF1α/HIF2α ↓</td>
</tr>
<tr>
<td>P-4E-BP1 ↓</td>
</tr>
<tr>
<td>eNOS ↓</td>
</tr>
<tr>
<td>Nitrate+nitrite ↓</td>
</tr>
</tbody>
</table>

BCAA, branched chain amino acids; eNOS, endothelial nitric oxide synthase; HPF, high-power field; PNGR, postnatal growth restriction; RV, right ventricle.
Human Cohort Studies

Energy Delivery

- Early Nutrition Mediates the Influence of Severity of Illness on Extremely Low Birth Weight Infants (Ehrenkranz et al, Pediatr Res 2011)
  - NICHD Neonatal Network
  - n=1366
  - During the first 7 days of life, the OR of NEC, late-onset sepsis, BPD, and NDI decreased by about 2% for each 1 kcal/ kg/d of total energy intake
  - Concept of early energy provision in reducing neonatal morbidities has been reinforced in other cohort studies, including ROP
To date, no randomised controlled trials are available that examine the effects of increased versus standard energy intake for preterm infants with (or developing) CLD/BPD.

Research should be directed at evaluating the effects of various levels of energy intake on this group of infants on clinically important outcomes like mortality, respiratory status, growth and neurodevelopment.

The benefits and harms of various ways of increasing energy intake, including higher energy density of milk feed and/or fluid volume (clinically realistic target volume should be set), parenteral nutrition, and the use of various constituents of energy like carbohydrate, protein and fat for this purpose also need to be assessed.

Targeted Nutrients
Base Diet (Human Milk)
Macro-, Micronutrients
Energy (Kcals, growth)
Total Daily Fluids
Macronutrients – Protein/Fat

• Unable to find any animal or human studies evaluating total protein using at least the current recommended dose or total fat delivery in neonatal lung injury.

Building Blocks:
Branched chain amino acids and respiratory pattern and function in the neonate.
Blazer et al. J Perinat 1992

N=10, Mean gestational age was 30.6 weeks (range 27 to 33 weeks)

Infants who develop bronchopulmonary dysplasia receive a lower enteral intake of calories and total lipids during the first 14 days of life.


• Increased dynamic compliance
• Decreased pulmonary resistance
• All values returned to baseline with resumption of the routine TPN
Targeted Nutrients
Base Diet (Human Milk)
Macronutrients
Energy (Kcals, growth)
Total Daily Fluids
Human Cohort Studies

Base Diet - Breast Milk

• Beyond Necrotizing Enterocolitis Prevention: Improving Outcomes with an Exclusive Human Milk–Based Diet (Hair et al, Breastfeeding Medicine 2016)
  - Multicenter, retrospective cohort
  - Pre-, Post- exclusive HUM diet
  - n= 1,587
  - BPD defined as need for oxygen at 36 weeks PMA
  - BOV 56.3% vs HUM 47.7% (p=0.0015)

• Does Breastmilk Influence the Development of BPD? (Spiegler et al, JPeds 2016)
  - Multicenter, prospective cohort
  - Exclusive formula vs exclusive breast milk
  - n= 462
  - BPD defined as need for oxygen at 36 weeks PMA + moderate/severe categories as defined by the NIH
  - Formula 20.9% vs BM 11.2% (p=0.005)
Targeted Nutrients
Base Diet (Human Milk)
Macro-, Micronutrients
Energy (Kcals, growth)
Total Daily Fluids
Abrupt cessation of in utero nutrient transfer and insufficient postnatal nutritional delivery results in accrued nutrient deficits.

Can we identify nutrients important in lung development that can be candidates for targeted delivery in sufficient amounts during critical periods?
**Preclinical Animal Data**

**Scientific Rationale in Targeted Nutrient Delivery**

**Poor Postnatal Nutrition Leads to Deficiencies in Important Bioactive Mediators**

Benefits of pre-, pro- and Synbiotics for lung angiogenesis in malnutritional rats exposed to intermittent hypoxia.


- Formula-fed groups were significantly growth suppressed with decreased lung weights
- Lung VEGF was decreased
- All genes involved in angiogenesis were downregulated in the formula-fed groups compared to maternally-fed.

*Same effect with delayed feedings!*
Preclinical Animal/Human Data

Scientific Rationale in Targeted Nutrient Delivery

BPD

Late-Onset Sepsis

CLD 2.5x

LOS 40%

Mouse Model

RvD1 + LXA4

Martin et al. JPeds 2011
Martin et al. Plos One 2014
**Immunonutrients & CLD**

**Preclinical Animal Data**

**Retinoids**

**Effect of Retinoic Acid on Oxygen-Induced Lung Injury in the Newborn Rat**


**L-Citrulline**

L-citrulline attenuates arrested alveolar growth and pulmonary hypertension in oxygen-induced lung injury in newborn rats.


**Vitamin D**

Vitamin D treatment improves survival and infant lung structure after intra-amniotic endotoxin exposure in rats: potential role for the prevention of bronchopulmonary dysplasia.

# Vitamin A Supplementation for Extremely-Low-Birth-Weight Infants


## Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vitamin A Group (N=405)</th>
<th>Control Group (N=402)</th>
<th>Relative Risk (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease or death by 36 wk post-menstrual age — no. (%)</td>
<td>222 (55)</td>
<td>248 (62)</td>
<td>0.89 (0.80–0.99)</td>
<td>0.03†</td>
</tr>
<tr>
<td>Death by 36 wk postmenstrual age — no. (%)</td>
<td>59 (15)</td>
<td>55 (14)</td>
<td>1.07 (0.76–1.50)</td>
<td>0.72</td>
</tr>
<tr>
<td>Death before discharge — no. (%)</td>
<td>67 (17)</td>
<td>66 (16)</td>
<td>1.01 (0.74–1.38)</td>
<td>0.96</td>
</tr>
<tr>
<td>Survival with chronic lung disease at 36 wk post-menstrual age — no./total no. (%)</td>
<td>163/346 (47)</td>
<td>193/347 (56)</td>
<td>0.85 (0.73–0.98)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

# Table 2. Primary Outcome and Secondary Respiratory-Related Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DHA Group (N = 592)</th>
<th>Control Group (N = 613)</th>
<th>Adjusted Effect (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological BPD: primary outcome — no. (%) †</td>
<td>291 (49.1)</td>
<td>269 (43.9)</td>
<td>1.13 (1.02–1.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>Physiological BPD or death before 36 wk of postmenstrual age — no./total no. (%) † ‡</td>
<td>330/631 (52.3)</td>
<td>298/642 (46.4)</td>
<td>1.11 (1.00–1.23)</td>
<td>0.045</td>
</tr>
<tr>
<td>Clinical BPD — no./total no. (%)</td>
<td>315/592 (53.2)</td>
<td>304/612 (49.7)</td>
<td>1.09 (1.00–1.18)</td>
<td>0.06</td>
</tr>
<tr>
<td>Severity of BPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild — no. (%) ††‡</td>
<td>80 (13.5)</td>
<td>108 (17.6)</td>
<td>0.76 (0.58–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Moderate — no. (%) ††‡</td>
<td>65 (11.0)</td>
<td>50 (8.1)</td>
<td>1.35 (0.95–1.92)</td>
<td>0.10</td>
</tr>
<tr>
<td>Severe — no./total no. (%) †‡</td>
<td>202/592 (34.1)</td>
<td>194/612 (31.7)</td>
<td>1.07 (0.93–1.22)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Successful Bench to Bedside Translation for Targeted Nutrient Delivery

- Bench to Bedside Translation
- Adequate Preclinical Models
- Kinetics & Physiology

- GA-specific
- When to give?
- How to deliver?
- How much to give?
- Markers of success?
Nutrition Interfaces with the Pathogenesis of BPD

Preclinical/animal data strongly link nutrition with lung development and disease pathogenesis

Epidemiology studies and small clinical trials generally supportive (though lots of unknowns)

Bedside translation (except Vitamin A) difficult to establish
- Need adequate numbers of infants at highest risk
- What, why, how, & when —; no biomarkers of nutritional efficacy
- Animal models incomplete not fully representative
Recommendations for Nutritional Delivery for the Prevention of BPD

- **Total daily fluids** – an option for care; do not compromise energy delivery and growth

- **Energy delivery** – avoid postnatal growth restriction; don’t compromise delivery if fluid restriction imposed (mixed evidence); or other practices that might impact growth attainment (diuretics, steroids). No specific evidence/trials on min/max energy intake and role in BPD pathogenesis

- **Macro (total fat/protein)** – meet minimum requirements, dose to meet energy goals; no BPD data

- **Feed the gut** – gut drives systemic health – through modulation of microbiome, innate defenses.

- **Base diet** – human milk; fortification to meet above energy goals; no evidence to preferred fortification strategies

- **Immunonutrients** – Vitamin A; ? Others (not for prime time)
Thank You!