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

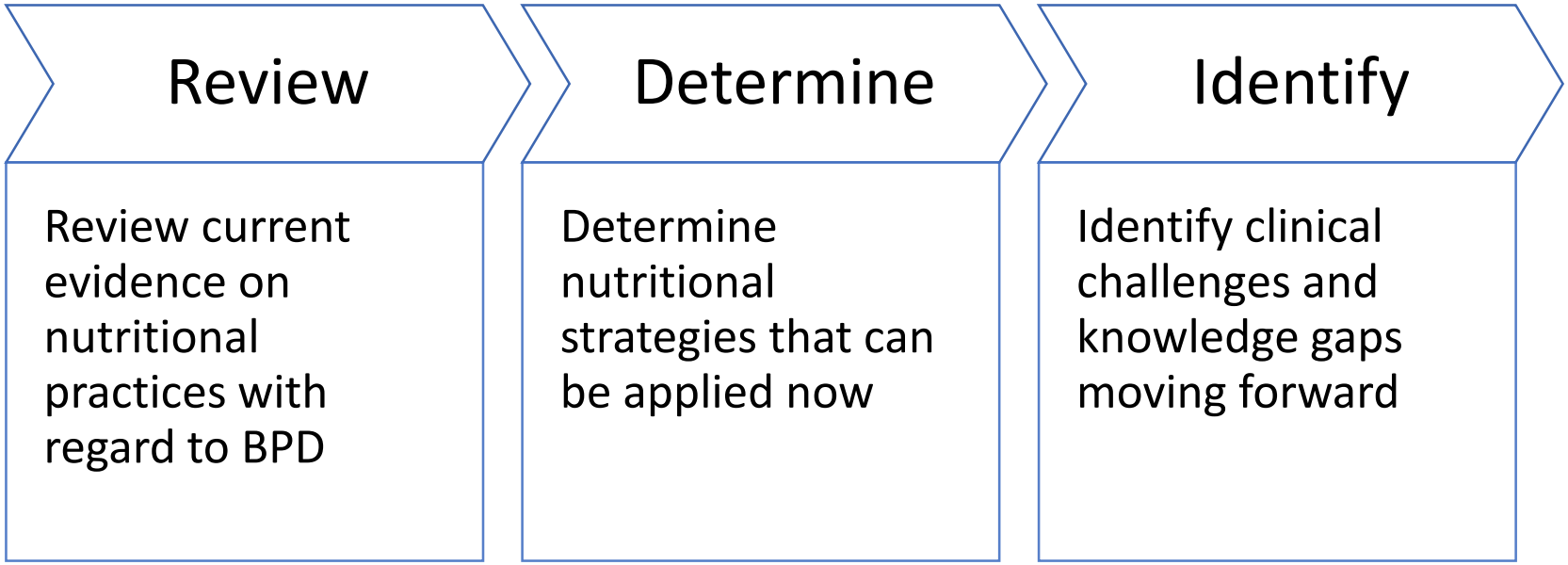
Disclosures

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

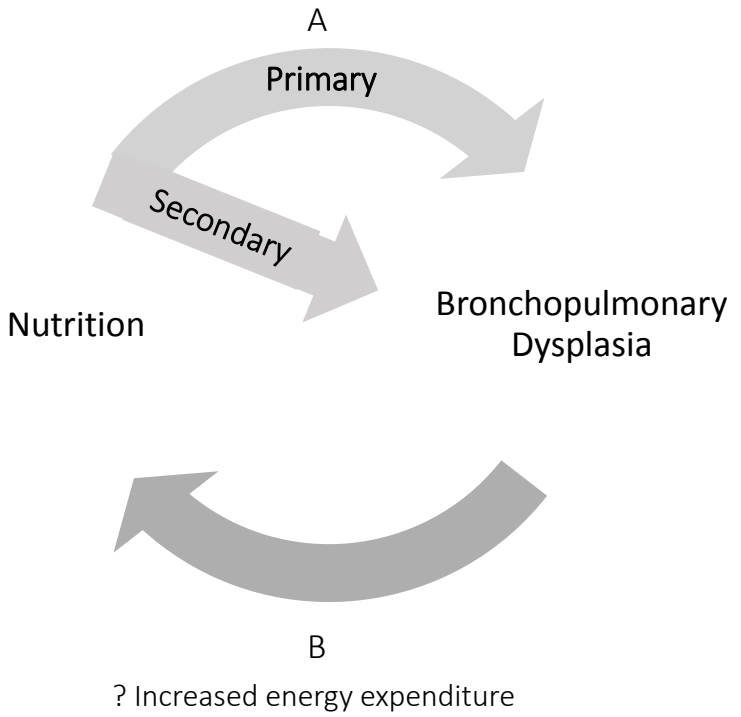
Epidemiologic Data Demonstrate that Growth Attainment in NICU is Associated with BPD Risk

TABLE 2 Characteristics of Follow-up Cohort by Weight Gain Quartile

Variable[a]	Quartile 1 ($n = 124$)	Quartile 2 ($n = 122$)	Quartile 3 ($n = 123$)	Quartile 4 ($n = 121$)	P[b]
Weight gain, mean (SD), g/kg per d	12.0 (2.1)	15.6 (0.8)	17.8 (0.8)	21.2 (2.0)	—
BPD, %	56	41	30	31	<.001

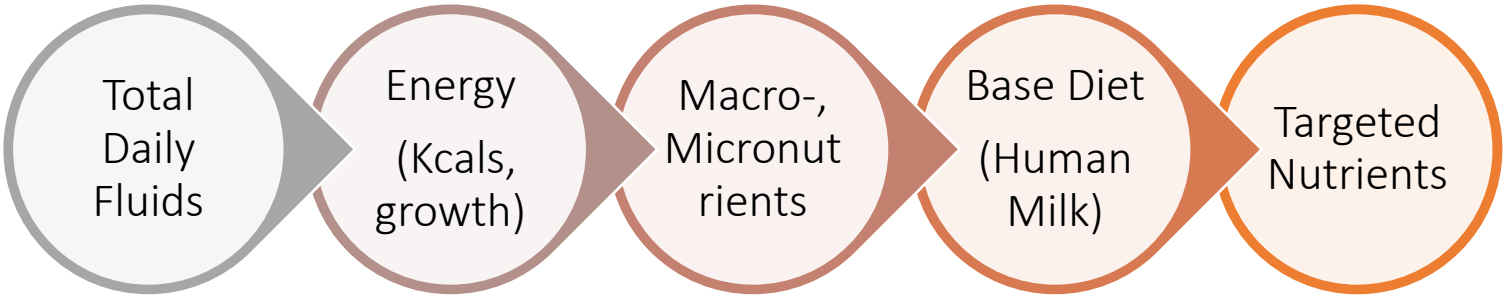
Ehrenkranz, et al. Pediatrics 2006

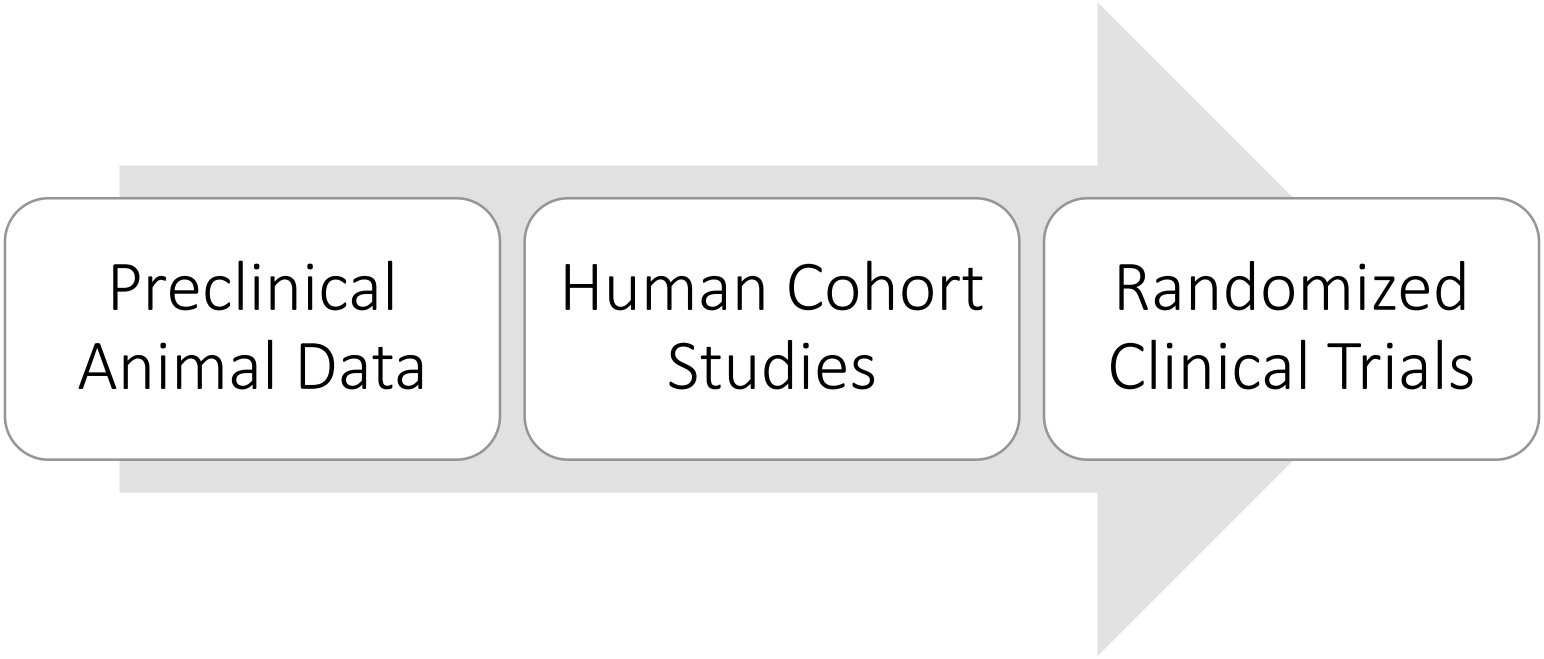
Nutrition & BPD: Mechanisms?

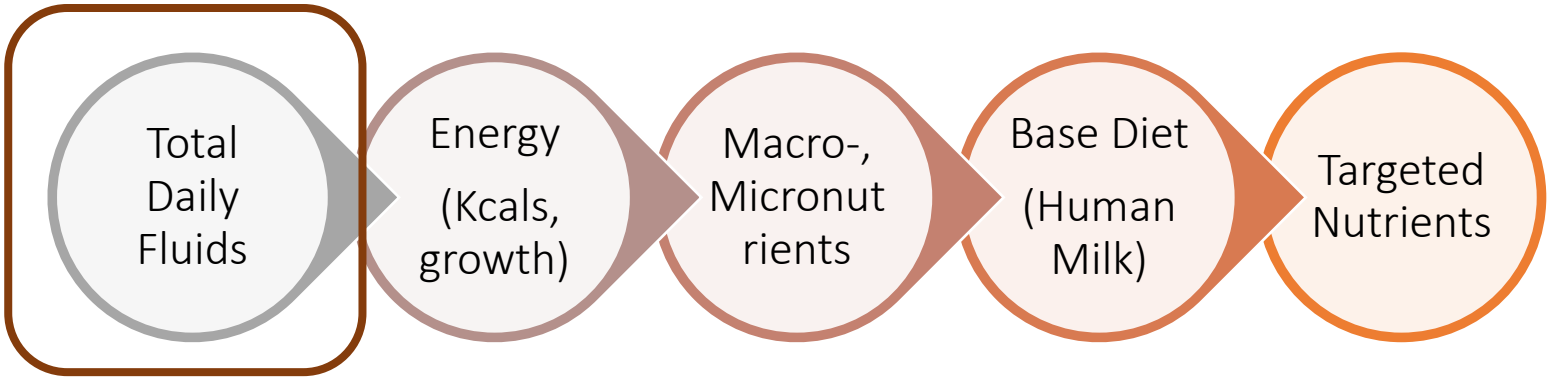


- **Is nutrition driving the lung disease** (A), or **is the lung disease driving the nutritional intake** (B)
- Role of nutrition:
  - Primary – direct evidence of that a specific nutritional parameter or nutrient is in the pathway of lung injury or repair
  - Secondary – a proxy to our practices around lung disease (fluid restriction, diuretics, steroids)

Approach to Understand Role of Nutrition in the Prevention and Management of BPD



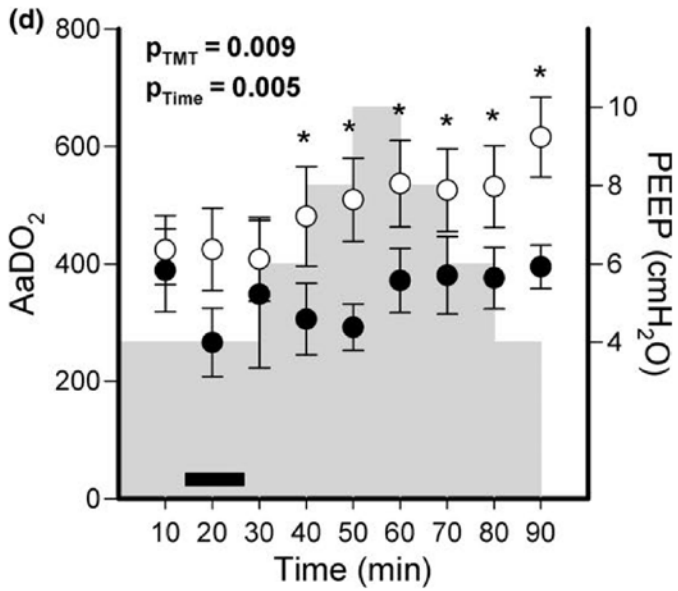



Total Daily Fluids
Energy (Kcals, growth)
Macro-, Micronutrients
Base Diet (Human Milk)
Targeted Nutrients

Preclinical Animal Data

Total Daily Fluids

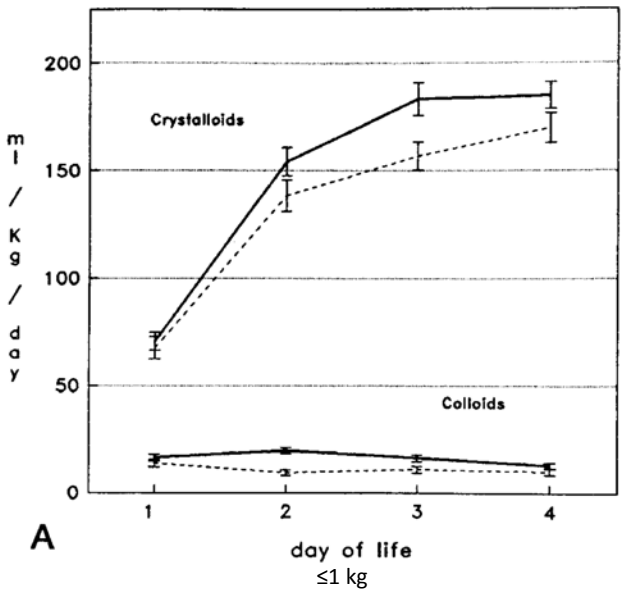
Study	Protocol	Findings
Cardiopulmonary hemodynamics in lambs during induced capillary leakage immediately after preterm birth. Poglase et al. Clin & Exp Pharm & Phys,2011	Preterm lambs, C v Vol Load (50 mL/k), then PEEP challenge	- Increased protein in BAL fluid - Interstitial fluid retention - Decreased PBF, P/SBP, oxygenation - Increased pulm hemorrhage

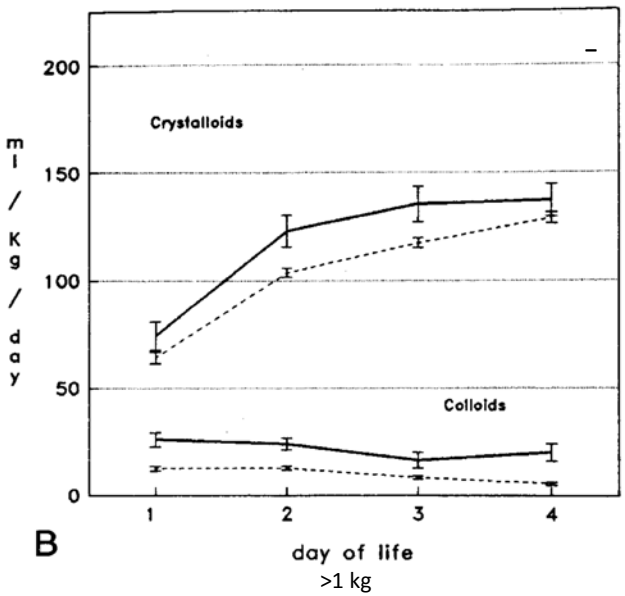


Human Cohort Studies

Total Daily Fluids

Study	Protocol	Findings
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*	Case-Control n=76/147	- 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





Human Cohort Studies

Total Daily Fluids

Study	Protocol	Findings
Association between fluid intake and weight loss during the first *10* days of life and risk of BPD in ELBW infants. *Oh et al (Neonatal Network), JPeds 2005*	Retrospective cohort n=1382	- higher fluid intake and less weight loss during the first 10 days of life associated with an increased risk of BPD

Randomized Clinical Trials

Total Daily Fluids

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

Study or subgroup		Restricted n/N		Liberal n/N		Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bell 1980	751-2000	5/85	122	8/85	169		11.9 %	0.63 [0.21, 1.83]
Kavvadia 2000	<1500	21/84	-11 %	22/84			32.8 %	0.95 [0.57, 1.60]
Lorenz 1982	750-1500	10/44	65-80	12/44	80-140		17.9 %	0.83 [0.40, 1.73]
Tammela 1992	<1751	21/50	50-120,150	25/50	80-150, 200		37.3 %	0.84 [0.55, 1.29]
Total (95% CI)		**263**		**263**			**100.0 %**	**0.85 [0.63, 1.14]**

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

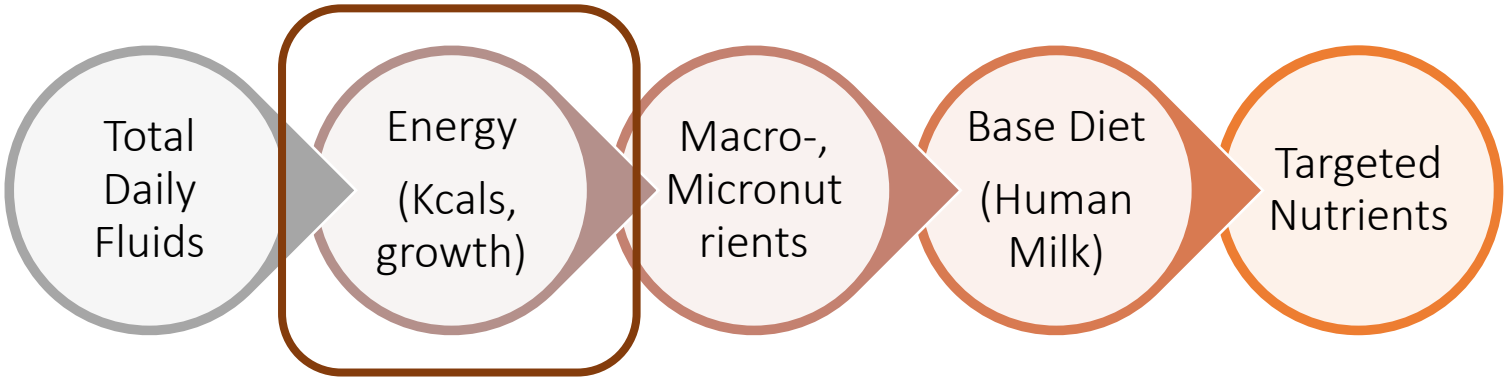
Heterogeneity: $Chi^2 = 0.51$, df = 3 (P = 0.92); I^2 =0.0%

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

Test for subgroup differences: Not applicable

Bell EF, Acarregui MJ: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2008;1: CD000503

Barrington KJ, Fortin-Pellerin E, Pennaforte T. Fluid restriction for treatment of preterm infants with chronic lung disease. Cochrane Database Syst Rev 2017;2:CD005389.

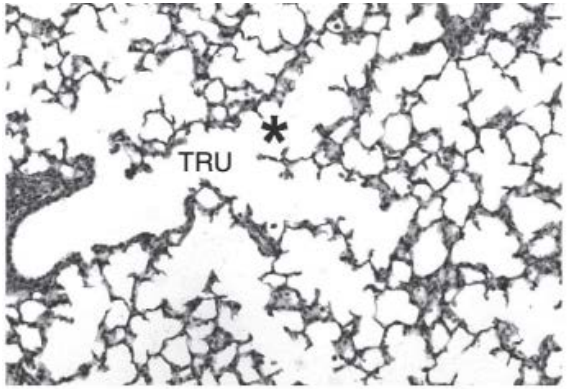

Total Daily Fluids
Energy (Kcals, growth)
Macro-, Micronutrients
Base Diet (Human Milk)
Targeted Nutrients

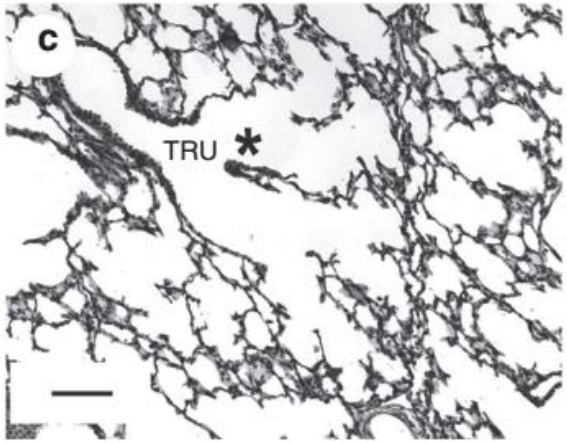
Energy - Overview

- 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

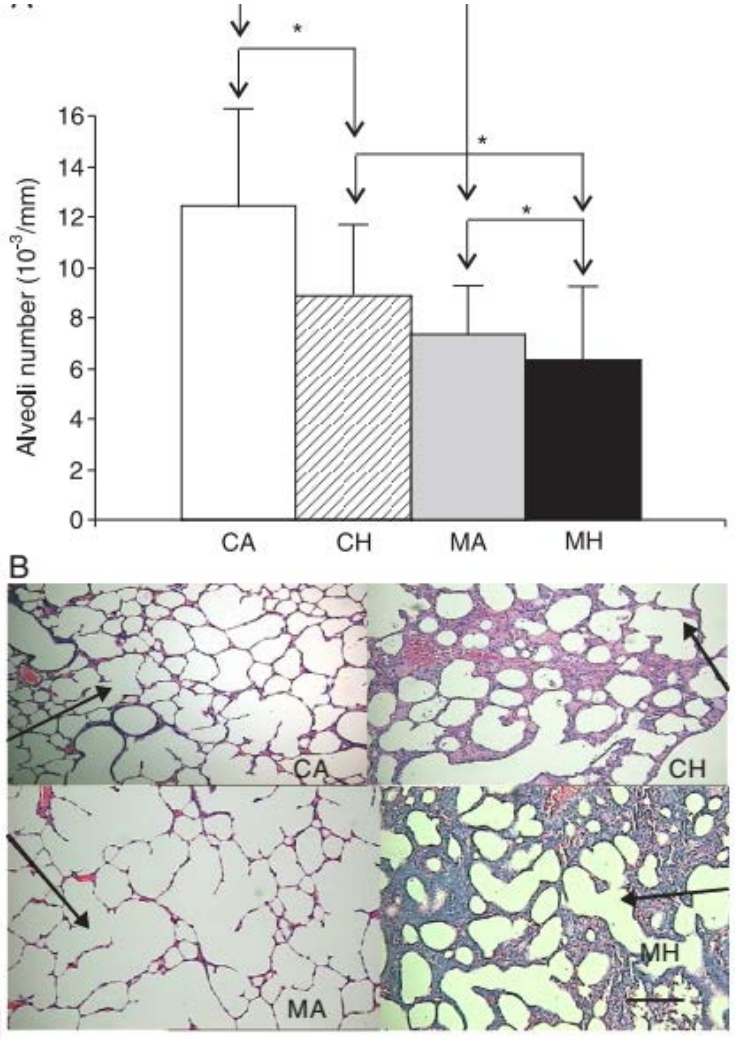
(Joss-Moore et al, Pediatric Research 2016)

- 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

- Effect of postnatal malnutrition on hyperoxia-induced newborn lung development (Mataloun et al, Braz J Med Biol Res 2009)
  - 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

Cardiac/Pulmonary Vascular Development

Table 1. Summary of similarities and differences between hyperoxia and PNGR in neonatal rat pups

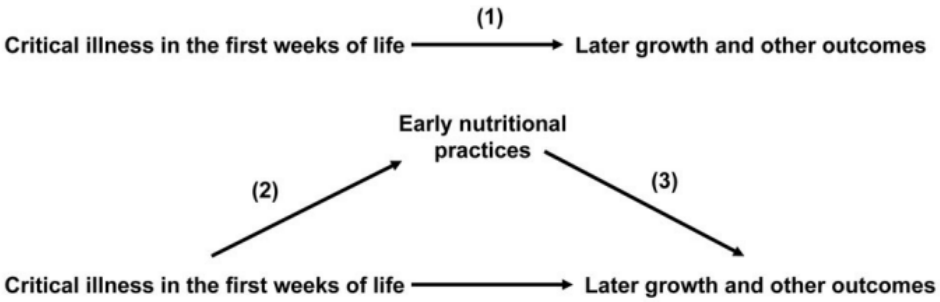
	Hyperoxia	PNGR	Hyperoxia + PNGR
Additive effects			
Fulton's index	↑	↑	↑↑
RV weight/body weight	↑	↑	↑↑
Medial wall thickness	↑	↑	↑↑
Vessels per HPF	↓	↓	↓↓
BCAA	↓	↓	↓↓
Effects unique to hyperoxia			
Mean alveolar area	↑	–	↑
Radial alveolar count	↓	–	↓
Effects similar but not additive			
VEGF/VEGFR2	↓	↓	↓
HIF1α/HIF2α	↓	↓	↓
P-4E-BP1	↓	↓	↓
eNOS	↓	↓	↓
Nitrate+nitrite	↓	↓	↓

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

- 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% O_2
  - 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

Human Cohort Studies

Energy Delivery



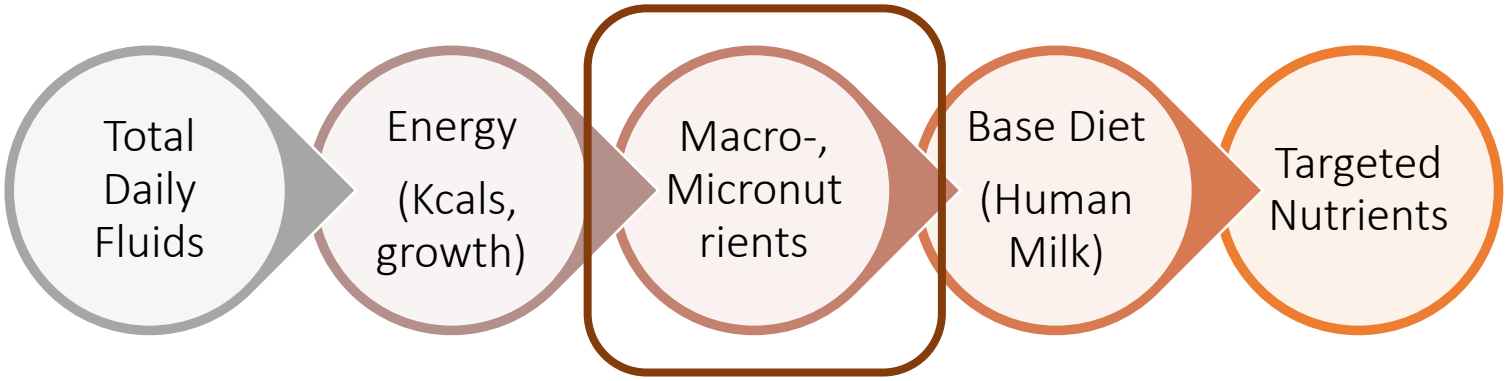
- **Early Nutrition Mediates the Influence of Severity of Illness on Extremely Low Birth Weight Infants**
  (Ehrenkranz et al, Pediatr Res 2011)
  - NICHD Neonatal Network
  - n=1366
  - During the first 7 days of life, the OR of NEC, late-onset sepsis, BPD, and NDI decreased by about 2% for each 1 kcal/ kg/d of total energy intake
  - Concept of early energy provision in reducing neonatal morbidities has been reinforced in other cohort studies, including ROP

Randomized Clinical Trials

Energy Delivery

- 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.

Lai NM, Rajadurai SV, Tan K. Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/chronic lung disease. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD005093.


Total Daily Fluids
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Base Diet (Human Milk)
Targeted Nutrients

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

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

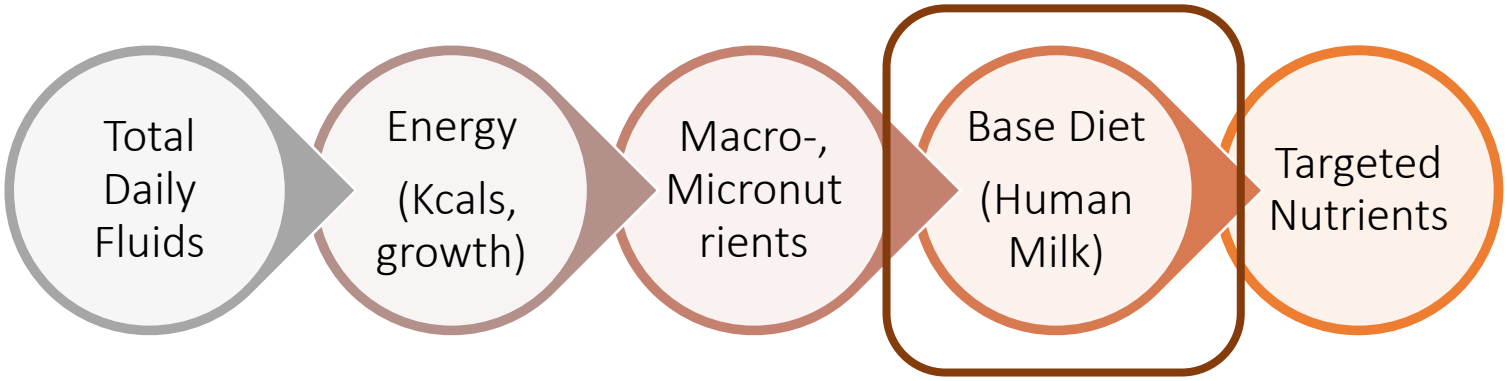
Uberos J, et al. Nutrition in extremely low birth weight infants: impact on bronchopulmonary dysplasia. Minerva Pediatr 2016;68:419–26.

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)

BCAA Enriched TPN resulted in:

- Increased dynamic compliance
- Decreased pulmonary resistance
- All values returned to baseline with resumption of the routine TPN


Total Daily Fluids
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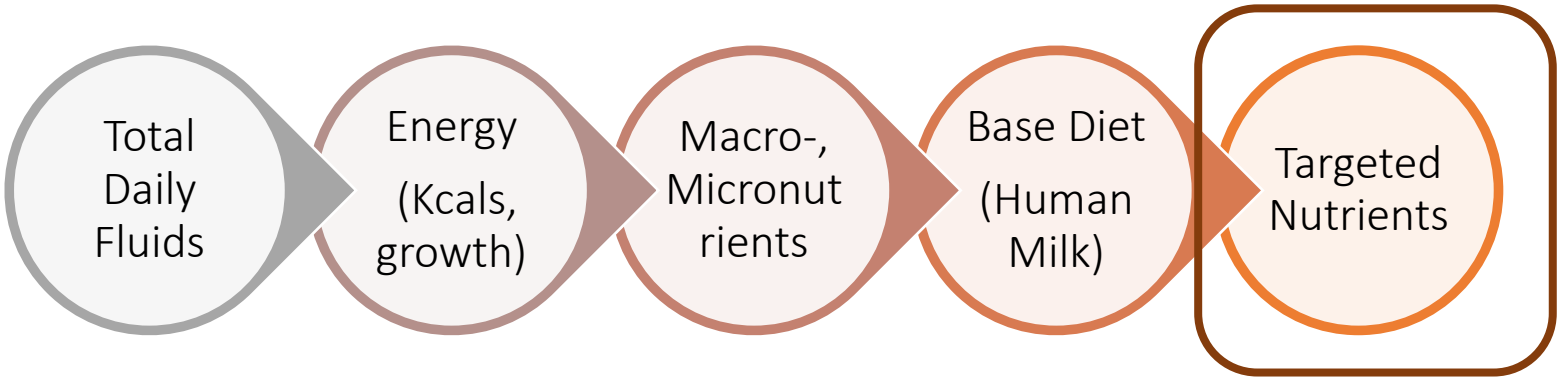
Targeted Nutrients

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)


Total Daily Fluids
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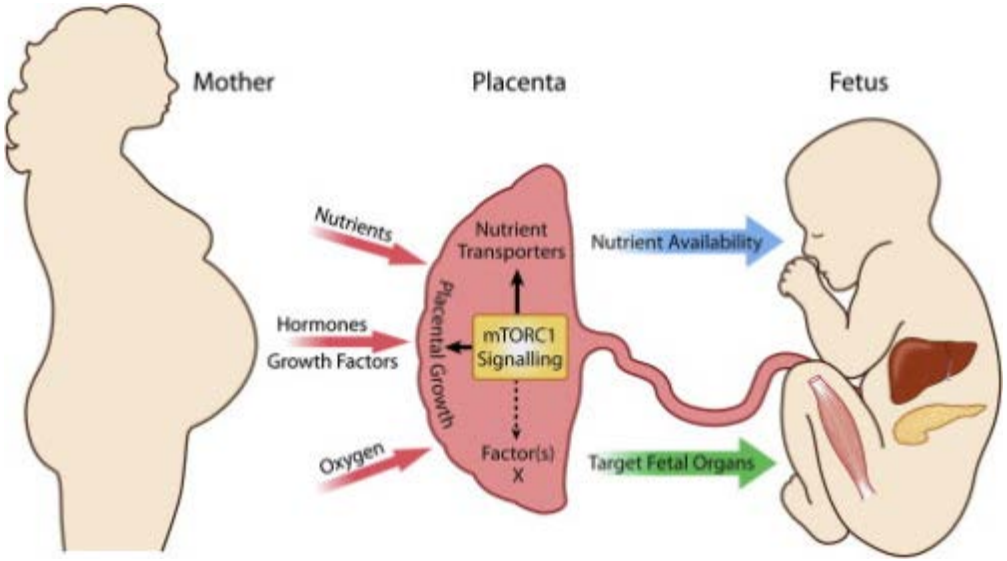
Targeted Nutrients

Abrupt cessation of in utero nutrient transfer and insufficient postnatal nutritional delivery results in accrued nutrient deficits

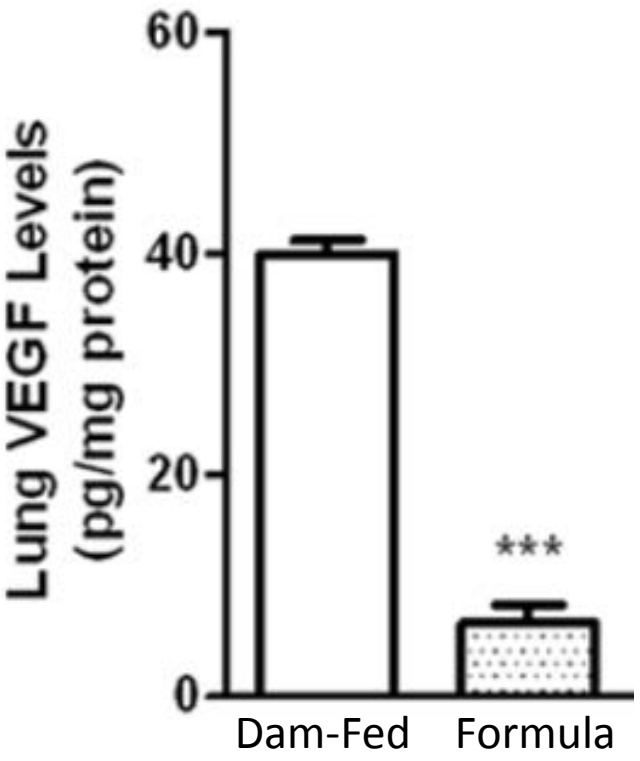


Can we identify nutrients important in lung development that can be candidates for targeted delivery in sufficient amounts during critical periods?

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.

Ahmad A, Cai CL, Kumar D, et al. Am J Transl Res 2014

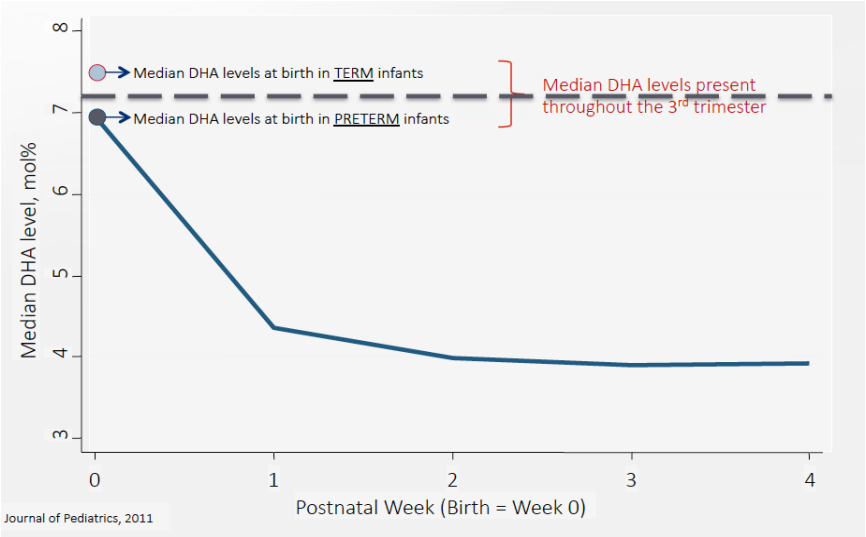
- Formula-fed groups were significantly growth suppressed with decreased lung weights
- Lung VEGF was decreased
- All genes involved in angiogenesis were downregulated in the formula-fed groups compared to maternally-fed.

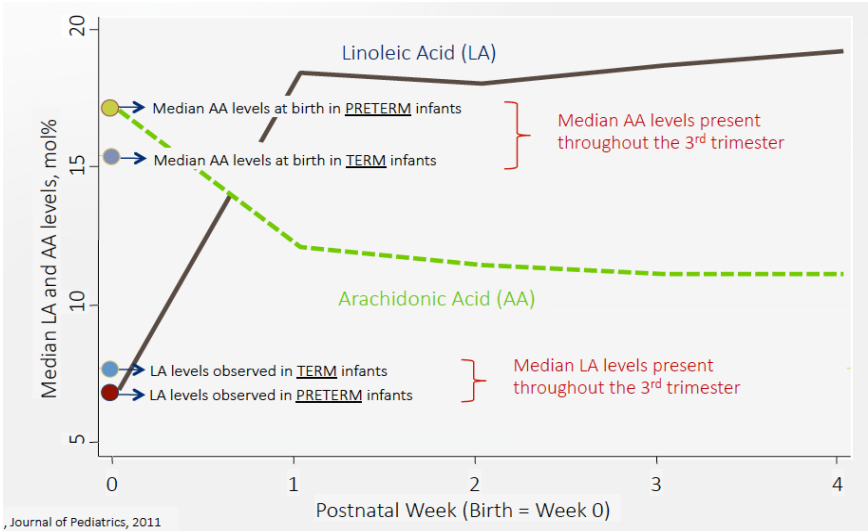
Same effect with delayed feedings!

Martin et al. JPeds 2011
Martin et al. Plos One 2014

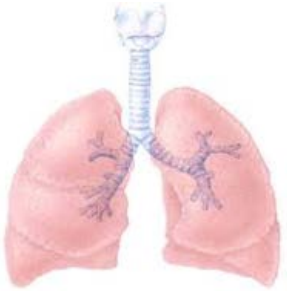
Preclinical Animal/Human Data

Scientific Rationale in Targeted Nutrient Delivery

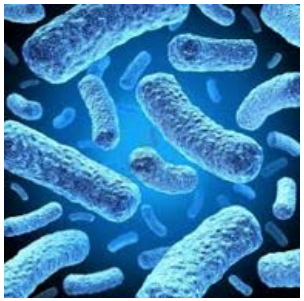




BPD

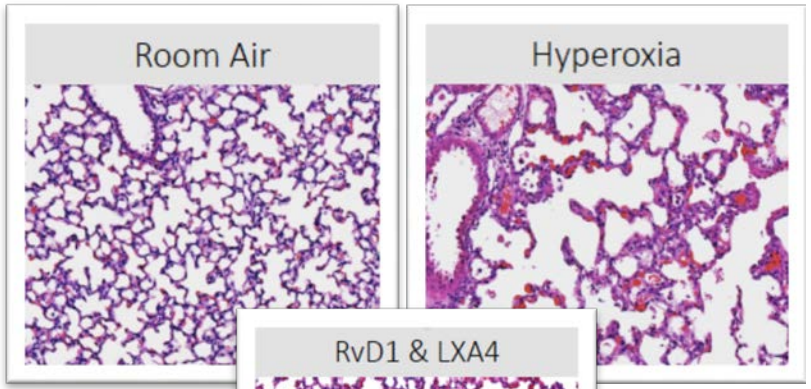


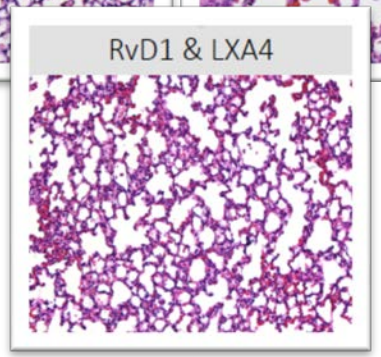
Late-Onset Sepsis



↑CLD 2.5x

↑LOS 40%

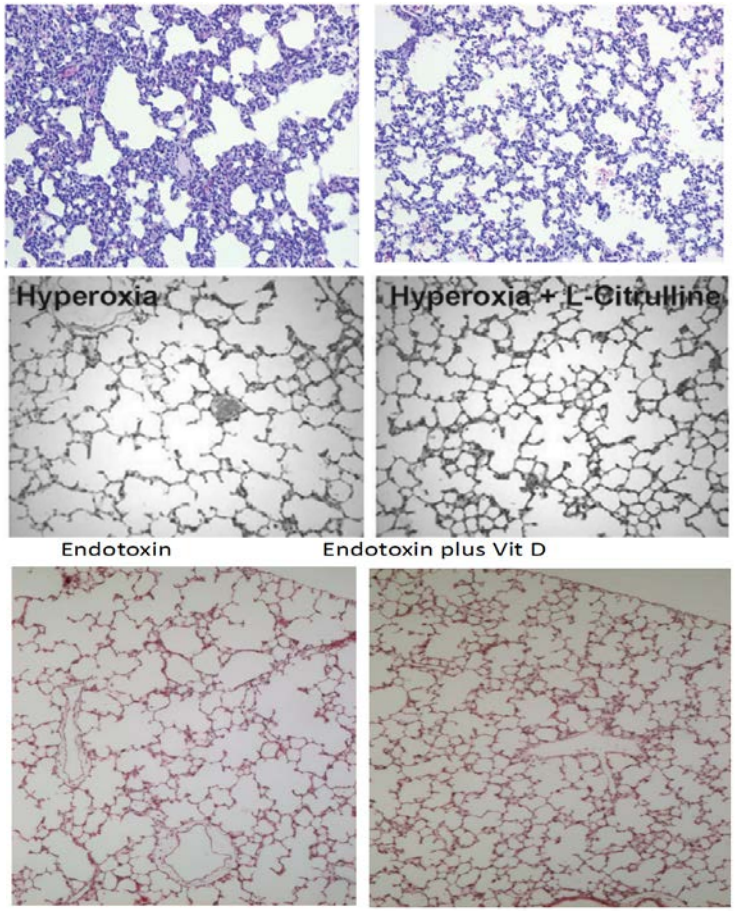




Mouse Model
RvD1 + LXA4

Preclinical Animal Data

Immunonutrients & CLD



Retinoids

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

Ozer et al., Pediatr Pulm. 2005, 39: 35-40

L-Citrulline

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

Vadevel et al., Pediatr Res. 2010 Dec;68(6):519-25.

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.

Mandell et al., Am J Physiol Lung Cell Mol Physiol. 2014 Mar 1;306(5):L420-8

Randomized Clinical Trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 1999;340:1962-8

VITAMIN A SUPPLEMENTATION FOR EXTREMELY-LOW-BIRTH-WEIGHT INFANTS

JON E. TYSON, M.D., M.P.H., LINDA L. WRIGHT, M.D., WILLIAM OH, M.D., KATHLEEN A. KENNEDY, M.D., LISA MELE, SC.M., RICHARD A. EHRENKRANZ, M.D., BARBARA J. STOLL, M.D., JAMES A. LEMONS, M.D., DAVID K. STEVENSON, M.D., CHARLES R. BAUER, M.D., SHELDON B. KORONES, M.D., AND AVROY A. FANAROFF, M.B., B.CH., FOR THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT NEONATAL RESEARCH NETWORK*

OUTCOME	VITAMIN A GROUP (N=405)	CONTROL GROUP (N=402)	RELATIVE RISK (95% CI)*	P VALUE
Chronic lung disease or death by 36 wk postmenstrual age — no. (%)	222 (55)	248 (62)	0.89 (0.80–0.99)	0.03†
Death by 36 wk postmenstrual age — no. (%)	59 (15)	55 (14)	1.07 (0.76–1.50)	0.72
Death before discharge — no. (%)	67 (17)	66 (16)	1.01 (0.74–1.38)	0.96
Survival with chronic lung disease at 36 wk postmenstrual age — no./total no. (%)	163/346 (47)	193/347 (56)	0.85 (0.73–0.98)	0.03

Randomized Clinical Trials

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2017;376:1245-55.

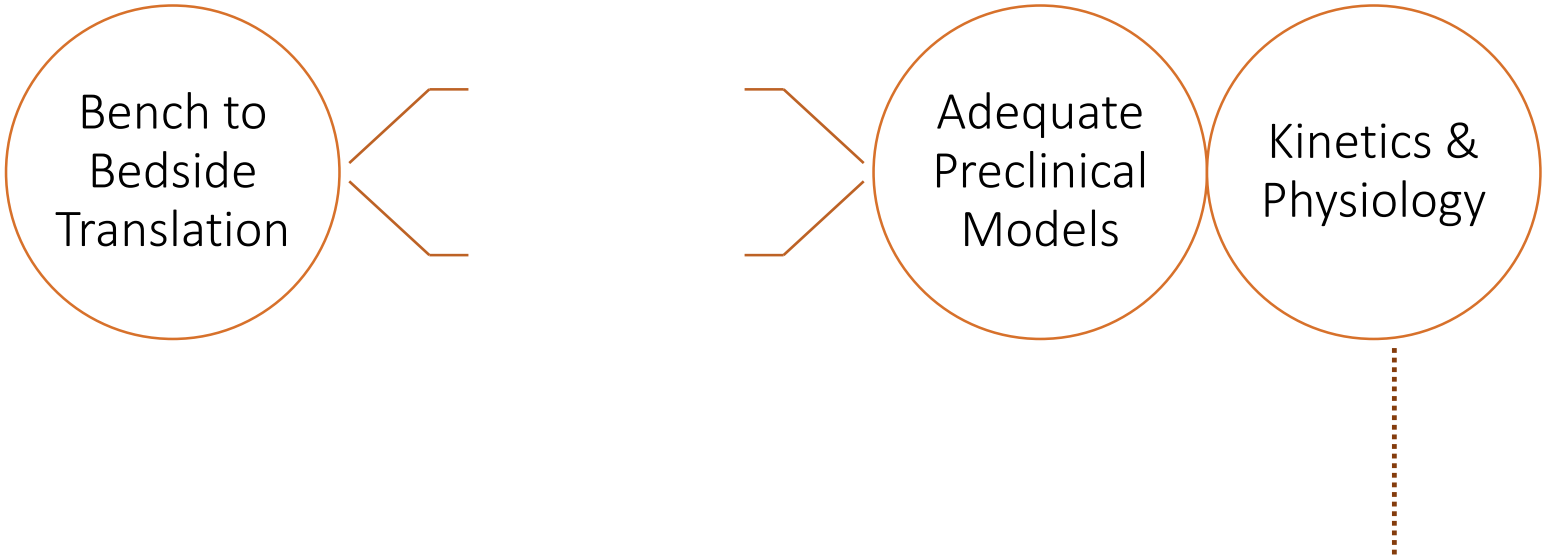
ORIGINAL ARTICLE

Docosahexaenoic Acid and Bronchopulmonary Dysplasia in Preterm Infants

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

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

Successful Bench to Bedside Translation for Targeted Nutrient Delivery



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!