Impact of an Exclusive Human Milk Diet in Neonates with Congenital Gastrointestinal Disorders: Initial Clinical Results

Heidi E. Karpen, M.D.
Associate Professor of Pediatrics
Associate Director Neonatal-Perinatal Medicine Fellowship Training Program
Division of Neonatology
Emory University/Children’s Healthcare of Atlanta

Disclosures

Dr. Karpen has the following to disclose:

• Prolacta Bioscience, Research grant recipient
• Progeny Health, Medical Advisory Board

Objectives

• Describe the characteristics of three common types of congenital intestinal disorders (CGDs): gastroschisis, omphalocele and intestinal atresias
• Discuss the unique nutritional needs of and feeding difficulties encountered by these patients
• Characterize the risks of prolonged parenteral nutrition and formula feeding in these patient groups
• Expand on the role of human milk in intestinal rehabilitation in these patients
• Review the preliminary results from the first trial of an exclusive human milk diet in neonates with CGDs.

Background

• Surgical intestinal disorders in neonates are associated with significant morbidity and mortality

Some of these conditions can co-exist, such as gastroschisis and intestinal atresias, and are associated with significant loss of bowel length or function, leading to intestinal failure (IF).
Gastroschisis (cGS)

- Abdominal contents (bowel loops, other organs such as stomach, liver and gonads) are not covered and are exposed to amniotic fluid in utero.
- Associated with intestinal atresia (70%), necrosis or perforation (27%), volvulus, and vanishing gastroschisis (8%).
- 60% of infants delivered before 37 weeks.
- Often IUGR/SGA infants.
- Many infants fall below the 10th percentile for birthweight.
- Carries a higher risk of mortality (28%), NEC (10%), short bowel syndrome/IF, prolonged PN, liver disease, transplantation and death.
- Mortality 7.6 fold higher with cGS.

Clinical Case

Baby Macie is a 34 week preterm infant with simple gastroschisis requiring silo x 5 days prior to skin closure. She had a protracted period (4 weeks) before return of bowel function. She was started on trophic MOM feeds at DOL # 32 and advanced by 10-20mL/kg/d. Her growth was faltering as she reached 110mL/kg/d and PN was weaned. Enfacare fortifier was added to her MOM to a concentration of 24kcal/oz and she was advanced to a total of 160mL/kg/d and ~130kcal/kg/d. Five days later she developed abdominal distention, apnea, bradycardia and shock and was found to have extensive NEC of her small bowel and after resection had ~40cm of jejun-ileum, no ICV and transverse colon to rectum remaining.

NEC occurs in ~10% of infants with gastroschisis - that’s a higher rate than in ELBW preterm infants!

Feeding Challenges and Growth Failure in GS Infants

- Altered bowel motility, repeated episodes of feeding intolerance/feeding interruptions and increased risk of NEC (~10%).
- Unfortified, exclusive MOM diets appear to decrease central line days, days on PN, LOS and days from first feed to discharge but does not alter growth.
- Growth failure is worsened as PN is weaned off and persists after achievement of full feeds.

Omphalocele

- Midline defect typically in the base of the cord, abdominal contents covered by sac.
- Giant:
  - Stomach, colon, other organs may be in sac.
  - Associated pulmonary hypoplasia, respiratory insufficiency.
- Associated with other abnormalities in ~54% of cases.
  - Cardiac(7-47%), Gastrointestinal (3-20%) and genitourinary (6-20%).
  - Karyotype abnormalities (Trisomy 13 and 18).
  - Beckwith-Wiedemann Syndrome.
Nutritional Challenges in Omphaloceles

• Early work of breathing, impact of neonatal surgery and prolonged hospitalization, causes growth faltering which persists for the first several years of life
• At twelve, and again at twenty-four months, height and weight z-scores in children with giant and minor omphaloceles are significantly lower than the corresponding normative median z-score values
• Many need the assistance of feeding tubes (NG or GT)
• Those with a small defects achieved full feeds significantly faster and required fewer days of TPN.
• Infants fed primarily human milk during the first three months of life achieved full enteral feeds significantly faster.

Intestinal Atresia

• Jejuno and ileal atresias (JIA) most common type of intestinal atresia: 1 in 5000 to 1 in 14,000 live births respectively
• Prognosis generally related to length of remaining intestine and the presence of an intact ileocecal valve.
• LOS and time to full feeds is longest in jejunal and ileal atresia, shortest in colonic/rectal atresia
• Over 1/3 of infants with atresia are preterm

Benefits of Human Milk

• Human milk (HM) is considered the ideal source of nutrition for all infants and is recommended as the exclusive diet for infants less than 6 months of age
• HM diets in preterm infants have been associated with a decreased the incidence of necrotizing enterocolitis, late-onset sepsis, increased intestinal motility and gastric emptying, improved feeding tolerance and general anti-inflammatory effects.
• HM diets in neonates with intestinal failure are associated with a decreased duration of PN, time to full feeds and DFI, up to 50% in some recent studies
• HM has been found to stimulate the development of healthy intestinal flora, modulate inflammatory processes, and encourage bowel maturity, repair, and function.
• These studies have been confounded to some degree, however, by the use of cow-milk based fortifiers in infants that required caloric concentration for growth.

CGD Study-Retrospective Cohort
Exclusive Human Milk Diet Improves Outcomes in Neonates with CGD

Conclusions

- Neonates with surgical GI disorders who received a 100% BM diet were found to have:
  - Earlier time to full enteral feeds
  - Shorter courses of PN
  - Shorter length of stay (LOS)
- Data suggest a potential for benefit conferred through a diet of ≥50% BM
- May be a titration effect as has been reported before
- Patel et al reported that each increase of 10 mL/kg/day of BM that an infant consumed, the odds of subsequently developing sepsis were reduced by 10%
- This was a novel study as no others have looked at the effects of an exclusive HM diet in this larger, surgical population
Human Milk for CGD Prospective Trial

Hypothesis

Use of an exclusive human milk diet (EHMD) comprised of Mother’s Own Milk (MOM), pasteurized donor human milk (PDHM), and donor milk-based fortifier (DMBF), when compared to formula or HM supplemented and/or fortified with cow-milk based fortifiers, will decrease the amount of time neonates with CGD are on PN and decrease the time needed to achieve full enteral feedings while in the Newborn Intensive Care Unit (NICU).

Specific Aims

• To compare the time to full enteral feeds and days on PN in neonates with CGD who receive an EHMD, compared with those receiving partial and non-human milk diets, while hospitalized in the NICU.

• To compare peak conjugated bilirubin levels, episodes of sepsis, feeding tolerance, feeding interruptions, episodes of NEC, LOS, and death between CGD neonates who receive EHMD versus partial and formula feeding, while hospitalized in the NICU.

Study Design

• Case-control, comparative effectiveness trial using a prospectively enrolled treatment cohort and a recent retrospective cohort as the controls. The retrospective cohort was comprised of babies from the same NICUs participating in the study over the period from 2010-2020.

• Data extracted includes, but not limited to, primary diagnosis, gestational age, birth weight, estimated residual small bowel length, presence of an ileocecal valve, length of colon, days on TPN, days to full enteral feedings, length of stay, death, episodes of sepsis, maximum direct bilirubin level, days with direct bilirubin >2mg and >4mg, lipid dose, liver biopsy results, and CMV status.

Retrospective Comparison Cohort

• The retrospective cohort was comprised of babies from each participating center NICU admitted between 2010-2020. Patients in the retrospective met the following criteria:

  • Must have a qualifying CGD diagnosis (gastroschisis, omphalocele, intestinal atresia)
  • Must have been >32 weeks gestational age and >1,250g at birth
  • Must have received formula as part of their diet.
Prospective Cohort

- Approximately 150 patients with CGD admitted to the NICU who met inclusion criteria and provided informed consent were enrolled in the prospective cohort of the study.
- These patients were fed an EHMD comprised of mother’s own milk (MoM) and/or pasteurized donor human milk (PDHM- Prolacta Biosciences, Inc).
- Fortification was provided with one of two human milk-based fortifiers (HMBFs):
  - Prolact+ H2MF®, (Prolacta Bioscience Inc.) for infants born at <37 weeks or <2,200g
  - PBCLN-002 (Prolacta Bioscience Inc.), formulated for infants ≥37 weeks and ≥2,200g.
- All management decisions, laboratory and radiologic studies were at the discretion of the treating physicians and dietician caring for the patient.

Inclusion Criteria

- Admission to participating NICU at ≤14 days of age
- Birthweight >1250g and gestational age at birth ≥32 weeks
- Less than 7 days of enteral feedings and at ≤60ml/kg/day of MOM or PDHM
- No formula feedings after diagnosis of CGD has been made*
- Diagnosis of eligible primary “Congenital Gastrointestinal Disorders” defined as: gastroscisis, omphalocele and intestinal atresias
- Consent to the use of PDHM products, including fortifiers
- Consent to participate in this study

* Infants with intestinal atresias often receive formula feeds before the diagnosis is made.

Exclusion Criteria

- Admission to participating NICU at >14 days of age
- Birthweight <1250g or gestational age <32 weeks
- Diagnosis of non-eligible gastrointestinal disorders: congenital diaphragmatic hernia, midgut volvulus, Hirschsprung’s disease, esophageal atresia, imperforate anus
- Evidence of short bowel syndrome at the time of enrollment that is a) not expected to be survivable or b) not expected to wean from TPN
- Evidence of significant liver dysfunction at time of enrollment (direct bilirubin >4 and transaminases elevated more than ±2SD above upper limit of normal for age)
- Known liver malformations such as biliary atresia and choledochal cyst
- Major congenital or chromosomal abnormalities that could significantly affect survival
- Refusal of consent

Feeding Progression

**Intake**

- Feeding initiation:
  - Soft, non-distended abdomen, + bowel sounds, stooling.
  - After consensus with surgical team
    - MOM or DM at 10-20mL/kg/d, PO or NG bolus
    - Continue for 3-5 days, depending on length of time of bowel rest after surgery.
    - If does not tolerate, back down or stop until exam improves and stooling well.

**Volume Advancement:**

- 10-20mL/kg/d Q24hrs, as tolerated
  - If does not tolerate, back down to previously tolerated volume or stop feeds if serious clinical concerns.
  - Consider continuous NG/NJ feeds.

**Fortification:**

- At 60mL/kg/day, fortification as follows:
  - Prolact+ H2MF® if <37 weeks GA or <2,200g at birth
  - PBCLN-002 +6 if >37 weeks and >2,200g at birth
  - Not tolerated, stop fortification or back down on caloric density.
  - If growth continues to be sluggish, increase fortification to +8 or +10 as tolerated.

**Discontinue TPN**

- Stop TPN when infant is tolerating 120-140mL/kg/d feeds.
  - Minimum goal feeds of 160mL/kg/d or 120kcal/kg/d
  - Not tolerated, back down to previously tolerated volume (or rate if continuous).
  - Resume TPN as needed.
Study Endpoints

- The infants were maintained on an EHMD until they reached one of the following endpoints:
  - Achieved full enteral feedings, defined as 120kcal/kg/day or 160mL/kg/d, for 7 days with bowel in continuity
  - Were imminently preparing for discharge home or
  - Reached 6 months PMA and the benefits of human milk were unlikely to affect outcome.

- Infants were transitioned directly to exclusive MOM or BF

- If an infant required addition of formula powder for caloric concentration or the use of formula if there was insufficient MOM, a specific transition protocol was followed in order to ensure a safe transition from the EHMD

Key Nutritional Differences

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>MOM (UOM)</th>
<th>Value</th>
<th>Proactiv6 (ratio)</th>
<th>Surgisof (ratio)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>g/dL</td>
<td>3.30</td>
<td>6.07</td>
<td>6.93</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>g/100kcal</td>
<td>8.3</td>
<td>9.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbs</td>
<td>g/dL</td>
<td>7.65</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cal</td>
<td>kcal/dL</td>
<td>59.11</td>
<td>59.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>mg/dL</td>
<td>26.52</td>
<td>138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>mg/dL</td>
<td>0.02</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe</td>
<td>mg/dL</td>
<td>0.03</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>mg/dL</td>
<td>2.09</td>
<td>3.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>mg/dL</td>
<td>12.22</td>
<td>15.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>mg/dL</td>
<td>30.60</td>
<td>52.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zn</td>
<td>mg/dL</td>
<td>0.14</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Propensity Matching: Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Propositive (n=151)</th>
<th>Retrospective (n=151)</th>
<th>p-value (unadjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>2555 ± 562</td>
<td>2541 ± 584</td>
<td>0.83</td>
</tr>
<tr>
<td>Maternal age (yrs)</td>
<td>26.3 ± 7.3</td>
<td>26.4 ± 7.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Apgar (5 min)</td>
<td>8.3 ± 1.3</td>
<td>8.0 ± 1.8</td>
<td>0.25</td>
</tr>
<tr>
<td>African American</td>
<td>15.9%</td>
<td>21.2%</td>
<td>0.24</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>37.8%</td>
<td>24.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroschisis</td>
<td>64.2%</td>
<td>64.2%</td>
<td>0.97</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>7.3%</td>
<td>6.0%</td>
<td>0.84</td>
</tr>
<tr>
<td>Intestinal atresia</td>
<td>28.5%</td>
<td>27.8%</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**Matching was based on gender, diagnosis, birthweight and gestational age**
Results - Entire CGD Cohort

| Outcome | Variable | Prospective (n=151) | Retrospective (n=151) | Unadjusted p-value | Adjusted p-value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital length of stay</td>
<td>NICU TPN days</td>
<td>29.9 ± 9.6</td>
<td>32.8 ± 9.2</td>
<td>0.003</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>NICU length of stay</td>
<td>6.8 ± 1.0</td>
<td>6.8 ± 1.0</td>
<td>0.95</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>Death</td>
<td>0.08 ± 0.71</td>
<td>0.14 ± 2.0</td>
<td>0.0007</td>
<td>0.26</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>Comparison (Kaplan-Meier survival)</td>
<td>0.52 ± 0.15</td>
<td>0.73 ± 0.17</td>
<td>0.011</td>
<td>0.85</td>
</tr>
<tr>
<td>NICU length of stay</td>
<td>Comparison (Kaplan-Meier survival)</td>
<td>0.52 ± 0.05</td>
<td>0.55 ± 0.02</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Adjusted p-value also includes Caucasian race and use of antenatal steroids besides group, gestational age, diagnosis, sex, and birthweight.

Growth Outcomes - Entire CGD Cohort

| Outcome | Variable | Prospective (n=151) | Retrospective (n=151) | Unadjusted p-value | Adjusted p-value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth length</td>
<td>Birth length</td>
<td>23.0 ± 0.5</td>
<td>23.0 ± 0.9</td>
<td>0.006</td>
<td>0.01</td>
</tr>
<tr>
<td>Birth length</td>
<td>Birth length (discharge)</td>
<td>0.48 ± 0.78</td>
<td>0.42 ± 0.72</td>
<td>0.83</td>
<td>0.037</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Birth weight</td>
<td>3.1 ± 0.0</td>
<td>3.1 ± 0.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Birth weight (discharge)</td>
<td>0.31 ± 0.32</td>
<td>0.31 ± 0.32</td>
<td>0.78</td>
<td>0.18</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Gestational age</td>
<td>-0.2 ± 0.25</td>
<td>0.18 ± 0.68</td>
<td>0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Gestational age (discharge)</td>
<td>0.2 ± 0.25</td>
<td>0.08 ± 0.68</td>
<td>0.03</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Adjusted p-value also includes Caucasian race and use of antenatal steroids besides group, gestational age, diagnosis, sex, and birthweight.

Results - Gastrosciasis Cohort Only

| Outcome | Variable | Prospective (n=77) | Retrospective (n=77) | Unadjusted p-value | Adjusted p-value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>Birth weight</td>
<td>3.1 ± 0.0</td>
<td>3.1 ± 0.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Birth weight (discharge)</td>
<td>0.31 ± 0.32</td>
<td>0.31 ± 0.32</td>
<td>0.78</td>
<td>0.18</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Gestational age</td>
<td>-0.2 ± 0.25</td>
<td>0.18 ± 0.68</td>
<td>0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Gestational age (discharge)</td>
<td>0.2 ± 0.25</td>
<td>0.08 ± 0.68</td>
<td>0.03</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Growth Outcomes - Gastrosciasis Only

| Outcome | Variable | Prospective (n=77) | Retrospective (n=77) | Unadjusted p-value | Adjusted p-value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>Birth weight</td>
<td>3.1 ± 0.0</td>
<td>3.1 ± 0.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Birth weight (discharge)</td>
<td>0.31 ± 0.32</td>
<td>0.31 ± 0.32</td>
<td>0.78</td>
<td>0.18</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Gestational age</td>
<td>-0.2 ± 0.25</td>
<td>0.18 ± 0.68</td>
<td>0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Gestational age (discharge)</td>
<td>0.2 ± 0.25</td>
<td>0.08 ± 0.68</td>
<td>0.03</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Adjusted p-value also includes Caucasian race and use of antenatal steroids besides group, gestational age, diagnosis, sex, and birthweight.
### Feeding and Growth Outcomes by Diet

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prolact (n=70)</th>
<th>Surgifort (n=95)</th>
<th>Control (n=151)</th>
<th>Prolact vs. Control</th>
<th>Surgifort vs. Control</th>
<th>Prolact vs. Surgifort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEEDING OUTCOMES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to full enteral</td>
<td>31*</td>
<td>31*</td>
<td>44</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>COMORBIDITIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>1 (1.4)</td>
<td>2 (2.1)</td>
<td>1 (0.7)</td>
<td>0.11</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (2.9)</td>
<td>5 (5.3)</td>
<td>14 (9.3)</td>
<td>0.10</td>
<td>0.25</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>GROWTH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Weight Velocity (g/d)   | 21.2 ± 7.7      | 20.9 ± 10.2      | 17.2 ± 12.2     | 0.009               | 0.003                 | 0.047                 | 0.007

*Several babies received both Prolact and Surgifort

### Summary

- Congenital intestinal disorders such as gastroschisis, omphalocele and intestinal atresias result in significant feeding challenges, prolonged need for PN and a high rate of growth failure.
- Patients with these disorders can have significant bowel loss, resulting in intestinal failure (IF).
- Infants with these types of CGD and IF require significantly increased amounts of protein, non-protein calories and additional micronutrients for optimal growth and bowel adaptation.
- Human milk has been shown to aid in bowel adaptation and faster weaning from PN in these patients.

### Acknowledgments

**Study Sites/Investigators:**

- Austin, TX: University of Texas Southwestern Medical Center
- Boston, MA: Boston Children’s Hospital
- Calgary, Canada: University of Calgary
- Calgary, Canada: Calgary Children’s Hospital
- Chicago, IL: Northwestern University Feinberg School of Medicine
- Columbus, OH: Nationwide Children’s Hospital
- Dallas, TX: University of Texas Southwestern Medical Center
- Denver, CO: Children’s Hospital Colorado
- Edmonds, WA: University of Washington Hospital
- El Paso, TX: Texas Tech University Health Sciences Center El Paso
- Houston, TX: University of Texas Medical School at Houston
- Jacksonville, FL: University of Florida College of Medicine
- Memphis, TN: University of Tennessee Health Science Center
- Miami, FL: University of Miami Miller School of Medicine
- New York, NY: Columbia University Irving Medical Center
- Oklahoma City, OK: Oklahoma University Medical Center
- Oklahoma City, OK: University of Oklahoma Health Sciences Center
- Orlando, FL: University of Central Florida
- Philadelphia, PA: University of Pennsylvania
- Portland, OR: Oregon Health & Science University
- Providence, RI: Brown University Alpert Medical School
- Santa Fe, NM: University of New Mexico School of Medicine
- Tulsa, OK: University of Oklahoma Health Science Center
- Washington, DC: George Washington University
- Wheaton, IL: Northwestern University-Federnet Children’s Hospital

**Prolacta Biosciences, Inc:**

- Martin Lee, PhD
- Amy Piacentino
- Karl Erickson
- Sarah Reyes
- Melinda J. Elliott, MD
- David Rechtman, MD

**Emory University:**

- Megan Durham, MD
- Shelly Connor

**Sarah Taylor, MD**

- Yale University
- New Haven, CT

**Abhay Bhatt, MD**

- University of Mississippi Medical Center
- Jackson, MS

**Ruffin Bronner, MD**

- Children’s Hospital Los Angeles
- Los Angeles, CA

**Marianne Garland, MD**

- Columbia University
- New York, NY

**Brian Scottoline, MD**

- Oregon Health and Science University
- Portland, OR

**Emory University:**

- Megan Durham, MD
- Shelly Connor
A Randomized Controlled Trial of Exclusive Human Milk Diet vs. Mixed Human/Bovine Diet in Neonates with Single Ventricle Physiology

Cynthia Blanco MD1, Amy Hair MD2, Lindsey B Justice DNP3, Dantin Roddy MD4, Krista Bonagurio RD4, Patricia K. Williams MD5, Desiree Machado MD6, Bradley B. Manni MD6, Annie Chi MD7, Cheryl Takao MD8, Erin Gordon DO9, Amir Ashrafi MD10, Nicole Cacho DO, MPH1, John M. Costello MD, MPH11 and David S. Cooper, MD, MPH1 for the Cardiac Neonate Nutrition Study Group

1. University of Texas Health Science Center, 2. Texas Children’s Hospital, Baylor College of Medicine, 3. The Heart Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 4. Oklahoma University, 5. University of Florida, 6. Lurie Children’s Hospital of Chicago, 7. Cook Children’s Medical Center, 8. Children’s Hospital of Los Angeles, 9. UT Southwestern Medical Center, 10. Children’s Hospital of Orange County, 11. Medical University of South Carolina

Email: blanco@uthscsa.edu

Cardiac Defects and Growth Failure

- Neonates with single ventricle physiology experience poor growth which translates into adverse short and long-term outcomes
  - Variable feeding advancement prior to surgical repair
  - Feeding after surgical repair is suboptimal due to fluid restriction and challenges with maximizing caloric concentration due to risk of NEC

- An exclusive human milk diet improves short term growth and feeding tolerance in other populations (premature infants)

Hypothesis

Infants with single ventricle physiology fed an exclusive human milk diet will have improved short-term growth compared to standard feeding
Objectives

**Primary:**
- Weight velocity (g/kg/day) at 30 days after the initiation of feeds post-surgery

**Secondary:**
- Other measures of growth (linear and head circumference growth)
- Clinical outcomes:
  - NEC
  - Feeding tolerance
  - Hospital and ICU stay
  - Developmental outcomes at 18-24 months

**Study Design**

- Prospective, randomized, blinded, controlled trial from Nov 2016-Dec 2020 conducted at 10 US centers (Investigator initiated; Industry sponsored)

**Inclusion criteria:**
- Term infants ≤ 7 days old thought to require surgical palliation within 30 days of life
- NPO or 100% human milk diet prior to enrollment

**Exclusion criteria:**
- Infants who received formula prior to enrollment
- Major congenital anomalies affecting survival
- Genetic conditions affecting growth
- ECMO pre-operatively
- IVH ≥ 3

All clinical care team members were blinded except dietitians and dietary techs

---

### Study Design

**Post-Op Feeding Protocol**

@ 100mL/kg hold volume x24hrs and fortify to 26kcals/oz (PBCLN-002)

- After 24hrs of tolerating 26kcals/oz continue to increase volume by 0.5mL/kg/hr
- Once tolerating 130-140 mL/kg hold volume and fortify to 28kcals/oz (PBCLN-002)
- After 24hrs of tolerating 28 kcal/oz fortify to 30kcals/oz (PBCLN-002)

If patient has poor weight gain for 3-5 days on full fortification, may increase volume by 10-20mL/kg/d per physician order until adequate

If pt has poor weight gain for 3-5 days*

- After 24hrs of tolerating 24kcals/oz continue to increase volume by 0.5mL/kg/hr
- @130-140mL/kg hold volume x24hrs and fortify to 26kcals/oz with Standard Infant Formula
- Increase fortification to 28 kcals/oz

@ 60 mL/kg fortify to 24kcals/oz (PBCLN-002) and continue to advance volume

**STEP 2**

If pt has poor weight gain for 3-5 days*

- Increase fortification to 30 kcals/oz

**STEP 3**

Initiate feeds at 1mL/kg/hr and do not further advance for 24hrs

**Exclusively Human Milk (EHM) Control**

### Assessed for eligibility (n=310)

Enrolled (n=107)

**EHM** (n=45)

**CONTROL** (n=39)

Withdrawn from study prior to receiving intervention (n=2)

Excluded from growth analyses due to criteria set “a priori” (n=21)

Declined to participate (n=41)

Do not want formula, research, unknown

Other reasons (n=45)

Ineligible (n=117)

Prematurity, genetic conditions, severity of illness, early deaths, transfers
Demographic Characteristics- Intent to Treat

<table>
<thead>
<tr>
<th></th>
<th>CONTROL (n=52)</th>
<th>EHM (n=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age – weeks, mean (S.D.)</td>
<td>38.8 (0.8)</td>
<td>38.7 (0.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Gender - male, mean (S.D.)</td>
<td>33 (61)</td>
<td>36 (65)</td>
<td>0.8</td>
</tr>
<tr>
<td>Birth Length in cm, mean (S.D.)</td>
<td>49.6 (2.5)</td>
<td>49.5 (2.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Birth Head Circumference– cm, n (%)</td>
<td>33.9 (1.4)</td>
<td>33.9 (2.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Gestational Size (SGA) n (%)</td>
<td>4 (7.7)</td>
<td>10 (18.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>(AGA)</td>
<td>47 (90.4)</td>
<td>41 (74.5)</td>
<td></td>
</tr>
<tr>
<td>(LGA)</td>
<td>1 (1.9)</td>
<td>4 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Delivery (vaginal), n (%)</td>
<td>33 (63)</td>
<td>31 (56)</td>
<td>0.5</td>
</tr>
<tr>
<td>Chorioamnionitis, n (%)</td>
<td>1 (1.9)</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>Mechanical Ventilation at enrollment, n (%)</td>
<td>17 (32)</td>
<td>14 (25)</td>
<td>0.5</td>
</tr>
<tr>
<td>Prenatal Steroids, n (%)</td>
<td>3 (5.8)</td>
<td>3 (5.5)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Cardiac Disease- Intent to Treat

<table>
<thead>
<tr>
<th></th>
<th>CONTROL (n=52)</th>
<th>EHM (n=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLHS, n (%)</td>
<td>40 (76)</td>
<td>46 (83)</td>
<td>0.5</td>
</tr>
<tr>
<td>R Dominant AVSD, n (%)</td>
<td>1 (2)</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>DORV/Mitral Atresia, n (%)</td>
<td>7 (13)</td>
<td>4 (7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Double-inlet LV, n (%)</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>1.0</td>
</tr>
<tr>
<td>L Dominant AVSD, n (%)</td>
<td>0</td>
<td>1 (2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Tricuspid Atresia, n (%)</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Growth Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CONTROL (n=39)</th>
<th>EHM (n=45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to End of Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Velocity (g/kg/day)</td>
<td>2.79 [0.54, 4.16]</td>
<td>3.62 [0.33, 5.33]</td>
<td>0.04</td>
</tr>
<tr>
<td>Length Velocity (cm/week)</td>
<td>0.49 [0.33, 0.98]</td>
<td>0.56 [0.31, 0.85]</td>
<td>0.9</td>
</tr>
<tr>
<td>H.C Velocity (cm/week)</td>
<td>0.32 [0.07, 0.54]</td>
<td>0.21 [0.11, 0.39]</td>
<td>0.4</td>
</tr>
<tr>
<td>Birth to Discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Velocity (g/kg/day)</td>
<td>3.15 [2.31, 4.67]</td>
<td>4.32 [2.95, 5.46]</td>
<td>0.06</td>
</tr>
<tr>
<td>Length Velocity (cm/week)</td>
<td>0.48 [0.40, 0.76]</td>
<td>0.66 [0.47, 0.72]</td>
<td>0.5</td>
</tr>
<tr>
<td>H.C Velocity (cm/week)</td>
<td>0.28 [0.08, 0.35]</td>
<td>0.28 [0.19, 0.36]</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Protocol Compliance

Growth Outcomes
Growth velocity

Days from DOB

Weight (kg)

Infants Receiving an EHM Diet Tolerated Higher Caloric Concentration

Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CONTROL (n=39)</th>
<th>EHM (n=45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Stay (days)</td>
<td>33 (30, 44)</td>
<td>37 (33, 62)</td>
<td>0.64</td>
</tr>
<tr>
<td>Days from 1st Feed</td>
<td>21 (15, 29)</td>
<td>24 (19, 29)</td>
<td>0.67</td>
</tr>
<tr>
<td>TPN days</td>
<td>11 (9, 12)</td>
<td>11 (10, 16)</td>
<td>0.28</td>
</tr>
<tr>
<td>Length of Stay (days)</td>
<td>44 (35, 64)</td>
<td>59 (44, 81)</td>
<td>0.35</td>
</tr>
<tr>
<td>Surgery to End of Study (days)</td>
<td>24 (18, 32)</td>
<td>29 (26, 33)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

median (95% CI)

Safety Outcomes- Intent to Treat

<table>
<thead>
<tr>
<th></th>
<th>CONTROL (n=52)</th>
<th>EHM (n=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected NEC (Stage 1)</td>
<td>5 (9.6)</td>
<td>1 (1.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>NEC (Stage 2 or higher)</td>
<td>3 (5.8)</td>
<td>1 (1.8)</td>
<td>0.35</td>
</tr>
<tr>
<td>Surgical NEC (Stage 3)</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>NEC + Suspected NEC</td>
<td>8 (15.4)</td>
<td>2 (3.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (7.7)</td>
<td>2 (3.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>NEC or Sepsis</td>
<td>7 (13.5)</td>
<td>3 (5.5)</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Conclusion

- Neonates with single ventricle physiology receiving an exclusive human milk diet with early fortification following surgical repair had:
  - Improved short-term growth (increased growth velocity)
  - Increased caloric intake (≥ 26 cal/oz)
  - Potentially decreased risk of NEC
- Outpatient follow-up assessments at 18-24 months are ongoing (secondary aim)

Future Directions For EHMD Research

- Additional populations may benefit with an exclusive human milk nutrition
  - Other complex CHD at risk for growth failure or requiring optimization of growth prior to surgical correction
  - CHD infants at risk for intestinal disease such as preterm infants
  - Neonates with other high-acuity illnesses: CDH, ECMO, VACTERL, post-NEC feeding, SBS