NICU Nutrition in 2018

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Associate Professor

Disclose that I serve as a consultant for Alcresta Therapeutics.

What Issues Persists in Optimizing VLBW Infant Nutrition?

Best Methods to Give Protein

- The Importance of Energy
  - A Culture of Feeding

Issues with Fortification

Sustaining Human Milk through Hospitalization
Protein

Tennessee Best Practice: Provide with 12 hours of birth

Recommendations for Parenteral Delivery
- As soon as possible
- First fluid if possible
- 3-3.5 g/kg/day parenteral protein
- Avoid < 1 g/kg/day actual intake (and potentially < 2 g/kg/day)

Trivedi et al Cochrane 2013

How Much Protein for VLBW Infants

- Fetal Body Composition “Reference fetus”
  - 3.5 g/kg/day
  - 2.5 g/kg/day accretion
  - 1 g/kg/day protein loss

- Weight gain and nitrogen retention studies
  - 1 g/kg/day to avoid negative nitrogen balance
  - ≥ 3 g/kg/day to promote positive nitrogen balance
  - 3.5-4.5 g/kg/day to achieve growth equivalent to fetal growth

Randomized Controlled Trials of Early Protein Concentrations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Comparison</th>
<th>Effect on Outcomes</th>
<th>Safety Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivedi et al 2013</td>
<td>28 ELBW infants</td>
<td>1 g/kg/d versus 3 g/kg/d with glucose and lipid</td>
<td>Higher positive protein balance with 3 g/kg/d</td>
<td>No difference in acidosis or BUN, amino acid levels</td>
</tr>
<tr>
<td>Thureen et al 2003</td>
<td>32 VLBW infants</td>
<td>2 g/kg/d initiated at 48 hours of age versus 3.5 g/kg/d initiated at Day 1 with glucose and lipid</td>
<td>Greater nitrogen balance with 3.5 g/kg/d</td>
<td>No difference in fluid, creatinine, and pH</td>
</tr>
<tr>
<td>Clark et al 2007</td>
<td>&lt;30 weeks gestation</td>
<td>1 g/kg/d and increased by 0.5 g/kg/d to 2.5 g/kg/d versus 1.5 g/kg/d and increased by 1 g/kg/d to 3.5 g/kg/d</td>
<td>No difference in growth</td>
<td>No difference in BUN, amino acid levels</td>
</tr>
<tr>
<td>Vlaardingerbroek et al 2013</td>
<td>144 VLBW infants</td>
<td>2.4 g/kg/d versus 2.4 g/kg/d plus lipids versus 3.6 g/kg/d plus lipids</td>
<td>Nitrogen balance improved in both interventions compared to control</td>
<td>Higher urea</td>
</tr>
</tbody>
</table>
### Randomized Controlled Trials of Early Protein Concentrations

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<th>Comparison</th>
<th>Efficacy Outcomes</th>
<th>Safety Outcomes</th>
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<tr>
<td>Blanco et al. 2012</td>
<td>43 ELBW infants</td>
<td>0.5 g/kg/d and increased by 0.5 g/kg/d to 3 g/kg/d versus 2 g/kg/d and increased by 1 g/kg/d to 4 g/kg/d</td>
<td>Better recovery, outcomes at 2 yrs</td>
<td>No difference in growth or respiratory events at 2 yrs</td>
</tr>
<tr>
<td>Burattini et al. 2013</td>
<td>114 ELBW infants</td>
<td>2.5 g/kg/d versus 4 g/kg/d</td>
<td>No difference in growth or neurodevelopment at 2 yrs</td>
<td>Higher BUN, lower hyperglycemia</td>
</tr>
<tr>
<td>Morgan et al. 2014</td>
<td>148 &lt;29 week infants</td>
<td>Control PN at 2.8 g/kg/d versus added SCAMP with glucose and 3.8 g/kg/d protein/lipid</td>
<td>Greater head growth</td>
<td></td>
</tr>
<tr>
<td>Balasubramanian et al. 2013</td>
<td>150 VLBW infants</td>
<td>1 g/kg/d versus 3 g/kg/d increased by 1 g/kg/d to 4 g/kg/d (with glucose, sodium, and potassium only, no lipids)</td>
<td>Higher growth velocity with 1 g/kg/d</td>
<td>No significant difference in other outcomes</td>
</tr>
<tr>
<td>Uthaya et al. 2016</td>
<td>133 infants born &lt;31 weeks gestation</td>
<td>1.7 g/kg/day increased to 2.1 g/kg/day increased to max of 2.7 g/kg/day versus 3.6 g/kg/day from Day 1 (also compared lipid infusions in a 2x2 factorial trial)</td>
<td>Smaller head circumference at term in higher amino acid group, no other difference in growth parameters including no difference in non-adipose mass at term</td>
<td>Higher BUN in higher amino acid group</td>
</tr>
</tbody>
</table>

### Parenteral Protein Summary

- 3-3.5 g/kg/day has most consistent positive results
- Order 3.5 g/kg/day to ensure 3 g/kg/day given
- Monitor literature for further safety data
- Recognize
  - Higher protein associated with better in-hospital growth
  - Better in-hospital growth associated with better neurodevelopment
  - No association directly between higher protein and better neurodevelopment
Energy

• Likely need 70 kcal/kg/day to avoid using protein as energy source
• Minimum of 90 kcal/kg/day needed to avoid weight loss
• Protein enthusiasts teach “only 100 kcal/kg/day energy needed”
  • True for parenteral nutrition but NOT for enteral nutrition

*Stepwise regression analysis indicated that ~52% of the variation in (weight) z-scores could be explained by the cumulative energy deficits (~45%) and gestational age (~7%), cumulative protein deficit had no significant effect.

Embleton et al 2001

VLBW Infant Nutrition at MUSC

• 89 infants 2010-2012
• In the first postnatal week
• Average daily intake
  • Protein intake was 2.96 (2.24, 3.63) g/kg/day
  • Energy intake was 60 (46.8, 74.9) kcal/kg/day
• Nutrition delivery
  • Protein: 87% parenteral and 13% enteral
  • Energy: 90% parenteral and 10% enteral

Response: Start at 3 g/kg/day protein but increase to 3.5 g/kg/day D2
Concentrate every day on increasing energy
Lipid Infusion

Tennessee Best Practice: Initiate within 24 hours

Example of Evidence-Based Guidelines (MUSC 2016)

<table>
<thead>
<tr>
<th>Infants &lt; 26 weeks</th>
<th>Infants &gt; 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begin with 0.5 g/kg/day in PN</td>
<td>Begin with 1 g/kg/day in PN</td>
</tr>
<tr>
<td>Advance by 0.5 g/kg/day to a goal of 3 g/kg/day</td>
<td>Advance by 1 g/kg/day to a goal of 3 g/kg/day</td>
</tr>
</tbody>
</table>

*Exception:
1. Total caloric value meeting exchange levels (hold lipids at 1.5 g/kg/day).

Note: In the presence of sepsis or PPIN, there is currently no clinical evidence that limiting lipids in these patients is beneficial.

Adjusting lipids for TG > 200:
- TG level 200-250: Decrease lipids by 1 g/kg and recheck TG within 24 hours.
- Enterent nutrition is added to PN (10 mg/kg).
- TG level 250-275: Decrease lipids by 1.5 g/kg and recheck TG within 24 hours.
- Enterent nutrition is added to PN (10 mg/kg).
- TG level > 275: Stop lipids and recheck TG within 24 hours. If > 200, restart at 1 g/kg.
- Enterent nutrition is added to PN (10 mg/kg).

Lipid Infusion References

References:

Enteral Nutrition

Culture of Feeding
Not “Prove to me why it is safe to feed this baby”
Instead “Prove to me why we have to stop feeding this baby”

Fetus has 200 ml/kg/day of amniotic fluid moving through the gut
15% of fetal nutrition from amniotic fluid

When to Start Feeding Evidence

- Is NPO safer than feeding?
  - Early feeding (≤4 days) versus delay progressive feeds (4-7 days)
  - Delayed associated with 2-4 days larger to full feeds
  - No difference NEC or mortality for all and for SGA alone
- Longer to full feeds means longer need for parenteral nutrition and central line


ELBW infants
MM and DM only
Intervention:
- education regarding safety to feed in first 24 hours
How Much and How Quickly

- Slow (15 to 24 ml/kg/day) versus Fast (30-40 ml/kg/day)
  - No differences
  - NEC
  - All-cause mortality
- Slow
  - Delayed full feeds by 1-5 days
  - Increased invasive infection risk [1.46 (95% CI 1.03-2.06)]
    - Number needed to treat: 14

Morgan J et al. Cochrane Database 2015

Trophic Feeds First?

- Trophic versus increasing volume?
  - Early trophic versus feeding in first 96 hours
  - No benefit AND no harm
  - Growth rate, feed tolerance, NEC
- With new evidence that progressive feeds are tolerated day 1-2, do we need trophic feeds?


Current Pilot

VLBW Infants
All receiving mother’s milk or donor human milk
Entire feed initiation and advancement order at admission
Nursing-driven protocol with advancement in two steps daily
Hold feed volume advancement at day of fortification

Infants born <1 kg
3 days at 12 ml/kg/day
Then advance by 25 ml/kg/day daily
Will achieve 160 ml/kg/day fortified feeds by Day 10

Infants born 1-1.5 kg
Initiate at 12 ml/kg/day
Then advance by 30 ml/kg/day
Will achieve 160 ml/kg/day fortified feeds by Day 7
Fortification Initiation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Volume of Feedings at Time of Fortification (mL/kg/d)</th>
<th>Bovine or Human Milk-Derived Fortifier?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sullivan S et al 2010</td>
<td>40</td>
<td>Human milk-derived</td>
</tr>
<tr>
<td>Alhusein F et al 2013</td>
<td>≥ 80</td>
<td>Bovine</td>
</tr>
<tr>
<td>Carrasco et al 2010</td>
<td>90-100 (in 2 steps)</td>
<td>Bovine</td>
</tr>
<tr>
<td>Tikhonov et al 2012</td>
<td>At time of first feed</td>
<td>Bovine</td>
</tr>
<tr>
<td>Sarker et al 2013</td>
<td>40</td>
<td>Bovine</td>
</tr>
<tr>
<td>Carrasco ME 2014, Sherman K 2015</td>
<td>When feeds reached 5 mL per feed</td>
<td>Bovine</td>
</tr>
<tr>
<td>Sarker et al 2013</td>
<td>80</td>
<td>Bovine</td>
</tr>
<tr>
<td>Mota et al 2014</td>
<td>(in 2 steps)</td>
<td>Bovine</td>
</tr>
<tr>
<td>Kappeler-Kriet et al 2014</td>
<td>25</td>
<td>Bovine</td>
</tr>
<tr>
<td>Kim J et al 2015</td>
<td>100</td>
<td>Bovine</td>
</tr>
<tr>
<td>Shah S et al 2016</td>
<td>25</td>
<td>Bovine</td>
</tr>
<tr>
<td>Dutta S et al 2015</td>
<td>100 (in 2 steps)</td>
<td>Bovine</td>
</tr>
<tr>
<td>Loomis T et al 2014</td>
<td>50</td>
<td>Bovine</td>
</tr>
<tr>
<td>Lapointe M et al 2016</td>
<td>(in 2 steps)</td>
<td>Bovine</td>
</tr>
<tr>
<td>Butler et al 2013</td>
<td>80</td>
<td>Bovine</td>
</tr>
<tr>
<td>Cormack BE 2013; Cester EA 2015</td>
<td>When feeds reached 5 mL per feed</td>
<td>Bovine</td>
</tr>
</tbody>
</table>

Fortification

- Evaluate the energy and protein that your protocol delivers
- Fortify at a time to ensure energy and protein delivery
- If testing a new timing:
  - Follow tolerance (or your stops/starts)
  - Follow weight gain
  - Follow central line and PN days
- With our new protocol to advance feeds:
  - For infants born <1 kg, fortification will occur Day 8
  - For infants born 1-1.5 kg, fortification will occur Day 5
  - We are accepting of this timing at this moment

<table>
<thead>
<tr>
<th>Ingredient Values*</th>
<th>Hydrolyzed High Protein Bovinea</th>
<th>Hydrolyzed High Protein Human Milk-derived (6 kcal/oz)</th>
<th>Liquid Bovineb</th>
<th>Powdered Bovineb</th>
<th>Powdered Bovineb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipe</td>
<td>4 packets to 100 mL HM</td>
<td>4 packets to 100 mL HM</td>
<td>4 packets to 100 mL HM</td>
<td>4 packets to 100 mL HM</td>
<td>4 packets to 100 mL HM</td>
</tr>
<tr>
<td>kcal/kg/day</td>
<td>120</td>
<td>119</td>
<td>119</td>
<td>119</td>
<td>119</td>
</tr>
<tr>
<td>gm Protein/kg/day</td>
<td>4.5 (4)</td>
<td>4.3 (3.8)</td>
<td>4.2 (3.8)</td>
<td>3.5 (3)</td>
<td>3.6 (3)</td>
</tr>
<tr>
<td>kcal/kg/day</td>
<td>3.75 (3.5)</td>
<td>3.6 (3.2)</td>
<td>3.2 (2.9)</td>
<td>2.9 (2.5)</td>
<td>3 (2.5)</td>
</tr>
</tbody>
</table>

*At 150 mL/kg/day; estimates using mature, preterm HM values of 20 kcal/oz and 1.4 gm pro/oz; values in parenthesis estimate intakes using mature, term HM values of 20 kcal/oz and 1 gm pro/oz.

**Liquid Protein 6 mL= 1 gram protein**

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What is the evidence regarding higher enteral protein and outcomes

**Summary of Randomized-Controlled Trials**

- **High protein delivery:** 3.3-4.3 g/kg/day
- **Low protein comparison:** 2.8-3.7 g/kg/day

  - Association between high protein and significantly higher weight, length, head circumference in some studies
  - However, just as many studies with no significant difference in growth parameters
  - Do appear to demonstrate short-term tolerance (some studies show acidosis with acidified fortifier)


What if an infant continues to not grow?

**Add Calories? How?**

- **Medium Chain Triglyceride Oil**
- **Formula Powder**
- **Increased number of fortifier vials**

<table>
<thead>
<tr>
<th></th>
<th>Pre-exposure (n=11)</th>
<th>Post-exposure (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT oil</td>
<td>8.2</td>
<td>18.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>Formula powder</td>
<td>5.7</td>
<td>20.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Mean growth velocity: g/kg/day

Optimal Growth Velocity- We Think!

- For neurodevelopment
  - 18-21 g/kg/day
- Associated with ≥ z-score on growth curve
  - 20-30 g/kg/day
- To recover days lost while regaining birth weight
  - 19 g/kg/day [15 g/kg/d (fetal) + 4.3 g/kg/d]

<table>
<thead>
<tr>
<th>26 wks</th>
<th>811 g</th>
<th>22% lb</th>
<th>19.6 g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-27 wks</td>
<td>818 g</td>
<td>18% lb</td>
<td>20.3 g/d</td>
</tr>
<tr>
<td>32-37 wks</td>
<td>1800 g</td>
<td>36% lb</td>
<td>20.8 g/d</td>
</tr>
<tr>
<td>40 weeks</td>
<td>3400 g</td>
<td>37% lb</td>
<td>30.9 g/d</td>
</tr>
</tbody>
</table>

Double Check Method

Ehrenkrantz RA et al 2006; Martin CR et al 2008; Taylor unpublished
Sustaining Mother’s Milk Supply

Establish and Sustain Mother’s Milk Supply
- To sustain to >40 weeks gestation
  - Express by 6-hours post-delivery
  - Perform kangaroo care
  - Express milk ≥ 5 times per day
- To have adequate supply at discharge
  - Double pumping
  - 500 ml/day by day 10
  - Higher score for breast pump comfort
- NICU environment
  - Staffing, nurse level of education, nurse support of breastfeeding


Skin-to-Skin Care for Term and Preterm Infants in the Neonatal ICU

- Improved
  - Exclusive breastfeeding
  - Milk volume
  - Maternal attachment or bonding
  - Participation of parents in care
  - Less maternal stress
  - Parents’ response to infant cues
  - Potentially better sleep and neurobehavioral maturation
  - Potentially improved management of procedural pain
  - No increase in infections (decrease in developing countries)
  - Apparent physiologic stability

Pediatrics, September 2015
Take Home Points

Protein!
Parenteral 3-3.5 g/kg/day daily average
Enteral 3.3-4.3 g/kg/day

But do not forget about ENERGY!
Optimize daily
Parenteral 100-105 kcal/kg/day
Enteral >124 kcal/kg/day

Easiest to provide enteral nutrition
so feed whenever possible!

To sustain mother’s milk: express early, express at least 5 times/day,
hospital-grade double pump, educated/supportive NICU (and prenatal environment), KANGAROO CARE!