New Ideas in the Nutrition of the ELBW Infant
Reese H Clark, MD

Disclosures
- I have no relevant financial relationships to disclose or conflicts of interest to disclose.
- I will not discuss unapproved or off label experimental or investigational use of a product, drug or device.

Goals
- To challenge conventional thinking on nutrition in the NICU
- To encourage earlier use of enteral nutrition
- To show that exclusive use of human milk as a nutritional support can safely promote good growth of preterm infants

GROWTH IS IMPORTANT
Real Important! Effects Everyone

Outcomes of Small for Gestational Age Infants
Born at <27 Weeks' Gestation
Lilia C. De Jesus et al.
Journal of Pediatrics
DOI: 10.1016/j.jpeds.2012.12.097
Postnatal Growth Impacts Outcome

How growth is monitored and supported in the NICU matters

Methods

• Infants 501 to 1000 g birth weight were divided into quartiles of in-hospital growth velocity rates
• Variables considered for the logistic-regression models included gender, race, gestational age, small for gestational age, mother’s education, severe intraventricular hemorrhage, periventricular leukomalacia, age at regaining birth weight, necrotizing enterocolitis, late-onset infection, bronchopulmonary dysplasia, postnatal steroid therapy for pulmonary disease, and center


| Table IV. Model-estimated effects of SGA on primary outcome |
|-------------|----------|----------|-------|
| Primary outcomes | OR | 95% CI | P value |
| Death or neurodevelopmental impairment | 3.91 | 2.91-5.25 | <.001 |
| Death or neurodevelopmental impairment (early deaths excluded)* | 3.63 | 2.68-4.92 | <.001 |
| RDS III score < 70 | 2.08 | 1.12-3.85 | .018 |
| RDS III score < 80 | 2.38 | 1.49-3.81 | <.001 |
| Moderate or severe CP | 2.55 | 1.69-3.86 | <.001 |
| Hearing loss with or without amplification | 1.38 | 0.44-4.36 | .68 |
| Blindness (<20/200 vision bilaterally) | 16.9 | 2.15-505.8 | .003 |

*Early death defined as death at or before 17 hours of age.

Methods

• Infants 501 to 1000 g birth weight were divided into quartiles of in-hospital growth velocity rates
• Variables considered for the logistic-regression models included gender, race, gestational age, small for gestational age, mother’s education, severe intraventricular hemorrhage, periventricular leukomalacia, age at regaining birth weight, necrotizing enterocolitis, late-onset infection, bronchopulmonary dysplasia, postnatal steroid therapy for pulmonary disease, and center


| Table IV. Model-estimated effects of SGA on primary outcome |
|-------------|----------|----------|-------|
| Primary outcomes | OR | 95% CI | P value |
| Death or neurodevelopmental impairment | 3.91 | 2.91-5.25 | <.001 |
| Death or neurodevelopmental impairment (early deaths excluded)* | 3.63 | 2.68-4.92 | <.001 |
| RDS III score < 70 | 2.08 | 1.12-3.85 | .018 |
| RDS III score < 80 | 2.38 | 1.49-3.81 | <.001 |
| Moderate or severe CP | 2.55 | 1.69-3.86 | <.001 |
| Hearing loss with or without amplification | 1.38 | 0.44-4.36 | .68 |
| Blindness (<20/200 vision bilaterally) | 16.9 | 2.15-505.8 | .003 |

*Early death defined as death at or before 17 hours of age.

Head Growth

| Table IV. Model-estimated effects of SGA on primary outcome |
|-------------|----------|----------|-------|
| Primary outcomes | OR | 95% CI | P value |
| Death or neurodevelopmental impairment | 3.91 | 2.91-5.25 | <.001 |
| Death or neurodevelopmental impairment (early deaths excluded)* | 3.63 | 2.68-4.92 | <.001 |
| RDS III score < 70 | 2.08 | 1.12-3.85 | .018 |
| RDS III score < 80 | 2.38 | 1.49-3.81 | <.001 |
| Moderate or severe CP | 2.55 | 1.69-3.86 | <.001 |
| Hearing loss with or without amplification | 1.38 | 0.44-4.36 | .68 |
| Blindness (<20/200 vision bilaterally) | 16.9 | 2.15-505.8 | .003 |

*Early death defined as death at or before 17 hours of age.

Head Growth
How were growth velocities calculated?

- Growth velocity was calculated for the period between the time that the infant regained birth weight and discharge, transfer, age 120 days, or until a body weight of 2000 g was reached, a time point that is referred to as “status.”
- *Not clear to me what weight was used to calculate per kg values*
- Infants within each 100-g birth weight interval from 501 to 1000 g were then divided into quartiles of in-hospital growth velocity rates

Have We Caught Up? Growth and Neurodevelopmental Outcomes in Extremely Premature Infants (GA<27 wks). Brenda Poindexter et al. SPR May 2013

- Of the 1616 infants (GA 23-26 wks) who survived to discharge, 1396 (86%) were evaluated at 18-22 months CA
- Growth failure (weight <10th %tile) was present in 79% at 36 wks PMA and in 40% at FU
- As the rate of weight gain increased between quartile 1 and 4 (12 to 18 g/kg/d; p<0.0001), the incidence of adverse outcomes decreased significantly
- Weight gain quartile (1 vs 4) was associated with increased likelihood of severe/profound NDI (AOR=7.3; 4-14)
Slopes of postnatal growth in the NICU
Inborn Infants Who Survived, 26 weeks EGA (n=1000)
Based On Data in the Pediatric Clinical Data Warehouse 2009-2010

EGA and birth weight remain the most important factors influencing postnatal growth


<table>
<thead>
<tr>
<th>Variable</th>
<th>Birth Mean</th>
<th>Birth SD</th>
<th>Discharge Mean</th>
<th>Discharge SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>2.2</td>
<td>1.0</td>
<td>1.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Length</td>
<td>24.5</td>
<td>1.5</td>
<td>22.5</td>
<td>1.5</td>
</tr>
<tr>
<td>BMI (Weight/Length²)</td>
<td>1.6</td>
<td>0.5</td>
<td>1.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Re did models on current data set. Protein use not a significant factor in influencing growth.
Head Circumference Z score
Birth vs Discharge

Growth Assessment

Nutrition

Parenteral Nutrition

Neonatal PN - "Starter PN"

- A standardized PN solution
  - Contains amino acids, electrolytes, and other nutrients
- May allow more convenient and cost-effective timely initiation of PN
- Can be used as a bridge until a more complete PN solution can be ordered
- These solutions are often started in the delivery room or upon admission to the NICU
- Usually run at a maximum of 60 - 80 mL/kg per day
- Additional intravenous fluids may be ordered separately to provide electrolytes when needed.
Glucose Infusion Rate

• A GIR of 5-8 mg/kg/min is typical
• Infants who are not feeding should not be allowed a rate less than 5 mg/kg/min for any significant period of time
• The GIR needed to optimize nutrition in neonates is 10-16 mg/kg/min

Median Glucose Infusion (Zero if not on Fluids) (grams/kg/day)

Which of our patients is most at risk for poor growth in the NICU?

Complications

Interventions for prevention of neonatal hyperglycemia in very low birth weight infants.

- Four eligible trials
- Two trials compared lower vs. higher rates of glucose infusion in the early postnatal period. These trials were too small to assess effects on mortality or major morbidities.
- Two trials, one a moderately large multicentre trial (NIRTURE, Beardsall 2008), compared insulin infusion with standard care.
- Insulin infusion reduced hyperglycemia but increased death before 28 days and hypoglycemia
- Reduction in hyperglycemia was not accompanied by significant effects on major morbidities; effects on neurodevelopment are awaited


---

Amino Acids

Clark RH, Chua DH, Spitzer AK. Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal intensive care unit: a randomized, controlled trial. Pediatrics. 2007;120:1286-1296.

- Randomly allocated premature (23-29 weeks and 6 days of gestation) neonates to
  - amino acid supplementation started at 1.0 g/kg per day and advanced by 0.5 g/kg per day to a maximum of 2.5 g/kg per day (2.5 g/kg per day group).
  - Other group received amino acids starting at 1.5 g/kg per day and advancing by 1.0 g/kg per day to a maximum of 3.5 g/kg per day (3.5 g/kg per day group)
- Enrolled 122 neonates
- Higher doses of amino acid supplementation did not improve neonatal growth and were associated with increased blood amino acid and urea nitrogen levels


- OBJECTIVE: To examine the effects of early and high intravenous (IV) amino acid (AA) supplementation on growth, health, and neurodevelopment of extremely-low-birth-weight (ELBW) infants throughout their first 2 years of life
- Infants were prospectively randomized in a double-masked fashion and treated for 7 days with either IV AA starting at:
  - 0.5 g/kg/day and increased by 0.5 g/kg every day to 3 g/kg/day
  - 2 g/kg/day and advanced by 1 g/kg every day to 4 g/kg/day
- Forty-three of 51 survivors were studied
  - the early and high AA group had a lower MDI at 18 months. This difference disappeared at 2 years of age
  - The early and high AA group z score means for weight, length, and head circumferences were significantly lower than the standard AA group at most visits
  - Cumulative and single plasma AA concentrations correlated negatively with MDI and postnatal growth
Factors that Influence Amino Acid and Acylcarnitine Profiles in Premature Infants From The Pediatrix-Obstetrix Center for Research, Education and Quality

- Metabolic profiles were obtained using standard newborn screening techniques on inborn infants between gestational ages of 23 weeks and 31 weeks. Metabolic profiles were collected within the first 24 hours after birth, on approximately day 7, on day 28, and on day 42 of life or at discharge, whichever came first. A single, central, contract laboratory analyzed and managed the samples.
- We studied 995 patients; none was subsequently diagnosed with an inborn error of metabolism. Of the 3579 samples, there were 257 (7.2%) amino acid or acylcarnitine alerts reported in 214 infants (21.4% of infants studied). Both gestational age and post-birth chronological age significantly influenced the metabolic profile.
- Twenty nine percent of infants at 23 to 26 weeks' gestational age had an abnormal metabolic profile compared to 17 percent of infants at 29 to 31 weeks' gestational age (p<0.01). On the day of birth, 12 percent of the profiles were abnormal compared to 2 percent on day 28 (p<0.01). The highest rate of abnormal values occurred on day 7 in the infants 23 to 26 weeks' gestational age (21%).

Median Amino-Acid Infusion (Zero if not on Fluids) (grams/kg/day)

Factors that Influence Amino Acid and Acylcarnitine Profiles in Premature Infants From The Pediatrix-Obstetrix Center for Research, Education and Quality
Acylcarnitines

There was a direct correlation between the dose of intralipids and the valine/acylcarnitine (C18:2) that was independent of gestational age and age at sample.

Note Differences in Slope

First 28 days vs Discharge

Table 1: Geometric slope during hospital admission

<table>
<thead>
<tr>
<th>Group</th>
<th>First 28</th>
<th>Discharge</th>
<th>Maternal</th>
<th>Birth</th>
<th>Postnatal</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low AA, high FA</td>
<td>-0.01</td>
<td>0.59</td>
<td>0.01</td>
<td>0.49</td>
<td>0.01</td>
<td>0.59</td>
</tr>
<tr>
<td>High AA, low FA</td>
<td>-0.02</td>
<td>0.56</td>
<td>0.01</td>
<td>0.48</td>
<td>0.02</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Nutritional Interactions

- Nutrition is a dynamic interaction between what is provided (calories, glucose/carbohydrates, protein/amino-acids, lipids/fatty-acids/carnitine, electrolytes, and trace elements)
  - how it is provided (intravenous and/or enteral),
  - how it is used for energy and growth,
  - and how each nutritional component is metabolized
- Just as there are adverse events associated with drug-drug interactions that relate to metabolism, the potential for adverse side effects related to nutritional-nutritional interactions is real...
Nutritional Interactions

- We believe our data show precisely this type of problem in the most immature infants (23-26 EGA group).
- Both leucine-isoleucine (primary component of intravenous amino-acid solutions) and linoleoylcarnitine (linoleic and linolenic acids are key components of intralipids) are elevated on day 7 when the doses of amino-acids and intralipids are highest.
- At the same time, isovalerylcarnitine+methylbutyrylcarnitine (CS) and octanoylcarnitine (C8) are elevated.
- The accumulation of these carnitines may lead to the formation of toxic organic acid metabolites and/or liver injury.

To compare the values obtained for each analyte, we calculated a z-score for each patient using the mean and standard deviation values from a normal term infant population. The z-score for each value was calculated: observed value minus the mean value of a normal term infant divided by the standard deviation from the normal term infant sample. A z-score of greater than 1 or less than -1 means that 68% of the patients had a value that was more than 1 standard deviation away from the mean value seen in term infants.
Slopes of postnatal growth in the NICU
Inborn Infants Who Survived, 26 weeks EGA (n=1000)
Based On Data in the Pediatric Clinical Data Warehouse 2009-2010

Do not forget proportionality of growth

Enteral Nutrition

Median Total Calories (cal/kg/day)

Factors that Influence Amino Acid and Acylcarnitine Profiles in Premature Infants
From The Pediatric-Obstetrics Center for Research, Education and Quality

Total Enteral Feedings (cc/kg/day)

Factors that Influence Amino Acid and Acylcarnitine Profiles in Premature Infants
From The Pediatric-Obstetrics Center for Research, Education and Quality


- A multicenter randomized trial in extremely preterm infants compared a feeding regimen based exclusively on human milk (donor breast milk with fortifier derived from human milk) to one using preterm formula and fortifier derived from cow’s milk.
- Infants were eligible if their mothers did not provide their own breast milk.
- Infants fed with the human milk regimen had a shorter duration of parenteral nutrition and a lower rate of surgical NEC, but the rate of NEC overall was not statistically different in the two groups.
- The incidence of NEC in the group fed formula was very high (21%), much higher than the usual rate of NEC.

Table I. Characteristics of study infants

<table>
<thead>
<tr>
<th></th>
<th>BOV</th>
<th>HUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>903 ± 207</td>
<td>906 ± 152</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>26.5 ± 2.4</td>
<td>27.7 ± 1.5</td>
</tr>
<tr>
<td>Small-for-gestational age, n</td>
<td>2 (9%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Male sex, n</td>
<td>11 (46%)</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>Apgar score at 5 minutes &lt;6, n</td>
<td>3 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of hospital stay, d</td>
<td>52 (12, 742)</td>
<td>62 (12, 742)</td>
</tr>
<tr>
<td>Mean central intake, mL/kg/d</td>
<td>92 ± 32</td>
<td>99 ± 32</td>
</tr>
<tr>
<td>First feeding, d</td>
<td>8.0 ± 3.0</td>
<td>4.0 ± 2.1</td>
</tr>
<tr>
<td>Time to full enteral feed, d</td>
<td>29.3 ± 14.7</td>
<td>24.6 ± 11.7</td>
</tr>
<tr>
<td>Feeding intolerance events, n</td>
<td>1.7 ± 1.3</td>
<td>1.1 ± 1.3</td>
</tr>
<tr>
<td>Weight gain, g/d</td>
<td>17 ± 7.1</td>
<td>15 ± 5.8</td>
</tr>
<tr>
<td>Head growth, cm/vk²</td>
<td>0.68 ± 0.16</td>
<td>0.78 ± 0.26</td>
</tr>
<tr>
<td>Length gain, cm/vk¹</td>
<td>1.12 ± 0.20</td>
<td>0.04 ± 0.21</td>
</tr>
</tbody>
</table>


- Single center, prospective observational cohort study, preterm infants weighing ≤1250 g BW were fed an exclusive human milk-based diet until 34 wks postmenstrual age
- Evaluated 104 infants with mean EGA of 27.6 ± 2.0 wks and BW of 913 ± 181 gm
- Human milk fortification with donor human milk derived fortifier was started at 60 mL/kg/d and advanced to provide 6 to 8 additional kilocalories per ounce
- Weight gain was 24.8 ± 5.4 g/kg/day with length 0.99 ± 0.23 cm/week and head circumference 0.72 ± 0.14 cm/week.
- Weight velocity was affected by day of fortification and day of full feeds

Human Breast Milk- Donor

Meta-analysis showed risk of NEC increased by 2.5 if fed formula vs. DBM

<table>
<thead>
<tr>
<th></th>
<th>BOV</th>
<th>HUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral nutrition, n</td>
<td>36 (8, 77)</td>
<td>27 (14, 39)</td>
</tr>
<tr>
<td>LBW birth weight, n</td>
<td>19 (4, 50)</td>
<td>16 (3, 30)</td>
</tr>
<tr>
<td>NEC, n</td>
<td>5 (15)</td>
<td>1 (30)</td>
</tr>
<tr>
<td>NEC and/or death, n</td>
<td>5 (15)</td>
<td>1 (30)</td>
</tr>
<tr>
<td>Mechanical ventilation, d</td>
<td>24 (1975)</td>
<td>17 (2, 30)</td>
</tr>
<tr>
<td>Oxygen therapy, d</td>
<td>20 (1, 50)</td>
<td>20 (1, 50)</td>
</tr>
<tr>
<td>Respiratory age of prematurity, n</td>
<td>5 (21%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Death, n</td>
<td>2 (8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are median (25th, 75th percentile).

Donor BM likely has protective effect against NEC as well


Change in Reports of Medical or Surgical NEC in PDX or VON (Inborn, 401-1500 grams = VLBW All)

- For every 10 mL/kg per day increase in breast milk
  - Mental Developmental Index increased by 0.59 points,
  - Psychomotor Developmental Index by 0.56 points,
  - Behavior percentile score by 0.99 points
  - Risk of rehospitalization between discharge and 30 months decreased by 5%.


- Five randomized controlled trials in which a total of 588 infants participated.
- Few participants were extremely preterm, extremely low birth weight or growth restricted.
- The trials defined slow advancement as daily increments of 15 to 20 ml/kg and faster advancement as 30 to 35 ml/kg.
- Meta-analyses did not detect statistically significant effects on the risk of necrotizing enterocolitis (typical risk ratio (RR) 0.97, 95% confidence interval (CI) 0.54 to 1.74) or all-cause mortality (RR 1.41, 95% CI 0.81 to 2.74).
- Infants who had slow advancement took significantly longer to regain birth weight (reported median differences two to six days) and to establish full enteral feeding (two to five days).

Bloom et al. Improving Growth of Very Low Birth Weight Infants in the First 28 Days Pediatrics 2003;112;8-14

Conclusions

- Poor growth, growth failure and extrauterine growth restriction are common in prematurely born infants
- Nutrition matters -- Poor growth both intrauterine and extrauterine (postnatal growth) are associated with bad outcomes (more health problems, and neurodevelopmental impairment)
- Growth can be improved if it is made a high priority and growth is monitored