Protein: Requirements and Measuring its Impact in the NICU

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Disclosure Statement

- **Employee**
  - Spouse: Johnson & Johnson

- **Consultant**
  - Mead Johnson Nutrition- clinical area: Growth and growth assessment of preterm infants

- **Speakers Bureau**
  - Mead Johnson Nutrition- clinical area: Dietary protein and impact on growth

- I have no conflicts of interest to resolve.

- I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.
Protein: Requirements and Measuring Its Impact in the NICU

Learning Objectives

1. Review evidence for protein requirements of preterm infants
2. Discuss nutrition, growth and health outcomes research in preterm infants
3. Examine growth assessment tools and outcomes used to measure impact in the NICU
Protein: Requirements and Measuring Its Impact in the NICU

Why is this important?
Impact on health outcomes

Nutritional intake → Growth
Impact on health outcomes

Nutritional intake → Growth

Other health outcomes, (Neurodevelopment)
What causes postnatal growth restriction?

“Although it is possible that nonnutritional causes occasionally play a role, for all intents and purposes, growth failure is caused by inadequate nutrition. More specifically, it is most commonly inadequate intake of protein that is responsible, with deficiencies of other nutrients possible but not well documented.”

Ziegler EE, Carlson SJ. *Nutrition Today* 2016;51;228
Nutritional intake and growth

• Inadequate nutritional intake leads to poor growth = well documented; e.g.,

Carlson *JPerinatol* 1998
Embleton *Pediatrics* 2001
Olsen *Pediatrics* 2002
Clark *JPerinatol* 2003
Ziegler *Nutrition Today* 2016

Poindexter *JPediatr* 2006
Ziegler *Ann Nutr Metab* 2011
Senterre *Acta Paediatr* 2012
Iacobelli *BMC Pediatrics* 2015

• “Growth” usually defined as weight growth; head circumference and especially length measurements often not included as growth outcomes
Growth of VLBW preterm infants

Based on retrospective review of n=62 AGA VLBW preterm infants ≤30wks born between 2003 – 2007 with follow up data

Poor postnatal growth: L > WT > HC

Adapted from: Ramel SE et al. Neonatology 2012;102:19
Growth of VLBW preterm infants

Based on retrospective review of n=62 AGA VLBW preterm infants ≤30wks born between 2003 – 2007 with follow up data

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Fig. 1. Growth of VLBW preterm infants from birth to 24 months CA. p values refer to statistical significance of the difference between the mean growth Z-score at each time point compared to the mean Z-score at birth.

Poor postnatal growth: L > WT > HC
Nutritional intake and growth

• “Aggressive nutrition” practices, including earlier and higher protein, improves growth (randomized clinical trials)
  – Moya F et al. *Pediatrics* 2012;130:e928
  – Morgan C et al. *Pediatrics* 2014;133:e120 (Head only)

• Implementation of “optimized” or “best” nutrition practices improves growth
  – Bloom BT et al. *Pediatrics* 2003:112:8 (WT only)
What causes postnatal growth restriction?

“Although it is possible that nonnutritional causes occasionally play a role, for all intents and purposes, growth failure is caused by inadequate nutrition. More specifically, it is most commonly inadequate intake of protein that is responsible, with deficiencies of other nutrients possible but not well documented.”

Ziegler EE, Carlson SJ. *Nutrition Today* 2016;51;228
Nutritional intake and growth

- **Protein** not kilocalories is the rate-limiting nutrient to **growth** in preterm infants
  
  - Kashyap *AJCN* 1990
  - Carlson *JPerinatol* 1998
  - Olsen *Pediatrics* 2001
  - Arslanoglu *JPerinatol* 2006
  - Senterre *Acta Paediatrica* 2012
  - Iacobelli BMC *Pediatrics* 2015

  *~ Bolded articles reported weight growth only ~*

- Our understanding of optimal nutrition, optimal growth (in all growth measures) and the impact on other outcomes in preterm infants continues to evolve...
Growth and neurodevelopment

Nutritional intake → Growth

Other health outcomes, (Neurodevelopment)
Growth and neurodevelopment

Postnatal growth restriction has negative impact on health outcomes

– Evidence of impact of weight and head growth on neurodevelopment
  • Ehrenkranz RA et al. *Pediatrics* 2006;117:1253
  • Poindexter B et al. *PAS Abstract # [1395.2] 2013*
  • Franz AR et al. *Pediatrics* 2009;123:e101
  • Ong KK et al. (review) *Acta Paediatrica* 2015;104:974
  • Belfort MB et al. *Pediatrics* 2011;128:e899
Cerebral palsy by in-hospital weight gain quartile

Growth and neurodevelopment

Postnatal growth restriction has negative impact on health outcomes

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• Belfort MB et al. *Pediatrics* 2011;128:e899
Growth and neurodevelopment

Postnatal growth restriction has negative impact on health outcomes

– Now evidence of impact of BMI and length growth on neurodevelopment

• Belfort MB et al. *Pediatrics* 2011;128:e899
• Ramel SE et al. *Neonatology* 2012;103:19
Nutritional intake and neurodevelopment

Nutritional intake  →  Growth

Other health outcomes,
(Neurodevelopment)
Nutritional intake and neurodevelopment

Suboptimal postnatal nutritional intake has negative impact on neurodevelopment.

– Evidence of impact of nutritional intake, in particular protein, on neurodevelopment
  • Lucas A et al. BMJ 1998;317:1481
  • Isaacs EB et al. JPediatr 2009;155:229
Retrospective study of 1st 4 weeks of life
148 ELBW survivors in a single NICU
Collected total daily EN and PN kcalorie and protein intake, for weekly comparisons to outcomes
18 mo. corrected age outcomes
  – Neurodevelopment (Bayley MDI and PDI scores)
  – Growth (weight, length, head circumference)
Results:
  – Week 1 energy and protein intake independently related to improved neurodevelopment scores at 18mo.
  – Higher protein associated with lower rates of LN <10th%ile
  – Energy and protein intake unrelated to WT and HC
Protein: Requirements and Measuring Its Impact in the NICU

Protein requirements
Postnatal growth pattern: Not constant
Inborn Infants Who Survived, 26 weeks EGA (n=1000)
Based On Data in the Pediatrix Clinical Data Warehouse 2009-2010

Phases of Postnatal nutrition

Postnatal growth pattern: Not constant

Inborn Infants Who Survived, 26 weeks EGA (n=1000)
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Phases of Postnatal nutrition

Protein requirements

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<tr>
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<th>Koletzko et al. 2014*</th>
<th>ESPGHAN 2010**</th>
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<tbody>
<tr>
<td>Energy, kcal/kg/d</td>
<td>110-130</td>
<td>110-135</td>
</tr>
<tr>
<td>Protein, g/kg/d</td>
<td>3.5-4.5</td>
<td>3.5-4.5 (1-1.8kg) 4.0-4.5 (&lt;1.0kg)</td>
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</table>


In the NICU, are recommendations met?

- Suboptimal nutritional intake (kcalorie and protein) leads to deficits. eg.,
  - Carlson JPerinatol 1998
  - Embleton Pediatrics 2001 (figure)
  - Clark JPerinatol 2003
  - Ziegler Ann Nutr Metab 2011
  - Senterre Acta Paediatr 2012
  - Iacobelli BMC Pediatrics 2015

Fig 1. Nutrient intake and cumulative nutrient deficit during the first weeks of life. Data were analyzed using ANOVA. The asterisk indicates overall level of significant difference between infants at ≤30 weeks and ≥31 weeks as determined using ANOVA.
Individualized nutritional plans

Individualized fortification of human milk:

• Based on analysis of human milk
  – Creamatocrit, mid-infrared and near infrared spectrophotometry (Kim *Early Human Dev* 2013)

• Adjusted based on blood urea nitrogen (BUN)
  – Human milk fortifier and protein supplement added based on infant’s metabolic response (BUN 2x/wk)
    • Moro GE et al. *JPGN* 1995;20:162
    • Arslanoglu S et al. *JPerinatol* 2006;26:614 (RCT)
    • Arslanoglu S et al. *JPGN* 2015;61:s4
Enough protein to support growth?

- Studies have tested protein intake at or slightly above protein recommendations with improved weight growth and adequate tolerance (Cooke Pediatr Res 2006; Arslanoglu JPerinatol 2006; Fanaro Early Hum Dev 2010; Miller AJCN 2012)

- Moya et al. (Pediatrics 2012) safety and efficacy trial of a high protein, liquid HMF vs older powder HMF - showed improved weight, length and head circumference growth with adequate tolerance
Enough protein to support growth?

- Olsen et al. *secondary analysis* of Moya data showed improved LN growth with higher cumulative protein intake over 28d study period.
- Warrants further research.

Modified from: Olsen IE et al. *JPGN* 2014;58:409
“Protein ceiling effect”? 

- Randomized clinical trial, single center (2012-14)
- 60 Preterm infants (<32wk, <1500g at birth)
- Intervention (intent-to-treat analysis), n=30 per group
  1. Lower protein group - +1g bovine pro/100ml HM via HMF
  2. Higher protein group, n=15 per group
    a. Standardized high protein w/ study fortifier (+1.8g bovine pro/100ml HM)
    b. Individualized high protein “based on pro and fat content of HM”
- Primary outcome: weight gain (g/kg/d) (birth to study end)
- Results: WT gain similar (16.3 vs 16.0g/kg/d, p=0.7); also HC and lower leg LN growth similar
- “Actual” pro intake: 3.7 vs 4.3g/kg/d by group (dif. 0.6g/kg/d)

Maas C et al. *JAMA Pediatrics* 2017;171:16
“Protein ceiling effect”?

Questions?

• “Actual” protein intake: 3.7 vs 4.3g/kg/d by group
  – Unfortified HM analyzed 2x/wk (mean of 3 measurements, 1 sample; mid-infrared spectroscopy)
  – Accurate assessment of “actual” protein intake?

• Primary outcome: Weight growth velocity (g/kg/d)
  – Ideal measures of growth outcome? (LN, HC, BMI, body comp)

• Is this a “protein ceiling effect” or suboptimal protein to support growth, in particular linear growth? Warrants further research.

Maas C et al. JAMA Pediatrics 2017;171:16
Growth assessment tools and Outcomes

How do we measure the impact of nutrition and growth in the NICU?
Nutrition and growth: Data and outcomes

What are ideal measures for preemies?

• Nutritional intake:
  – Actual vs assumed (estimated)

• Growth
  – Available, accurate growth measurements (WT, LN, HC; body composition, as possible)
  – Growth assessment tools
    • Growth velocity
    • Growth curves
    • Growth status (%iles, z-scores)
    • Body proportionality ratios (BMI)
Nutritional intake: Actual vs assumed

- 3-week study compared actual vs assumed (estimated) calorie and protein intake for each week
- **Actual** intake from HM analysis with feeding volumes, fortification, % Mom’s or donor milk (2/7 days, pooled)
- **Assumed** intake based on published data (HM, HMF, protein supplement content); recorded volumes
- **Results**:
  - **Protein**: Actual < Assumed – significant and consistent during each study week (dif range 0.5-0.8g/kg/d)
  - **Kcalories**: Small differences between study groups
- **Is “actual” intake always feasible? Should it be our standard?**

Nutrition and growth: Data and outcomes

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    • Growth velocity
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    • Growth status (%iles, z-scores)
    • Body proportionality ratios (BMI)
Growth measurements: Available, accurate

- **Weight**
  - Electronic scale; to nearest 10gm
  - Daily

- **Length**
  - Length board; to nearest 0.1cm
  - Weekly

- **Head circumference**
  - Non-stretch measuring tape; to nearest 0.1cm
  - Essential to move the measuring tape to find largest circumference
  - Weekly
Assessment tools: Growth velocity

• Common measure of growth in preterm infants

• Lacks generally accepted standard for calculation
  – Variation in calculation methods produce different estimates (vary by interval, formula)
  – In comparisons to published growth velocity estimates

• Single estimates overwrite growth because growth rate is not constant before or after birth
  – Appropriate rate of growth varies (gender, gestational age, postnatal age)

• Important to use in conjunction with growth curves
Pre and postnatal growth: Not constant

Prenatal growth: Not constant
Based on Olsen female growth curves

Postnatal growth: Not constant
Inborn infants who survived, 26wk EGA (n=1000)
Based on data in the Pediatrix Clinical Data Warehouse 2009-10

Example: Growth velocity estimates

Olsen intrauterine curves (Olsen et al. *Pediatrics* 2010;125:e214)
(Weekly intervals based on medians, 23-36wk GA, genders combined)

- Weight  mean  ~18gm/kg/d (15-20gm/kg/d)
  » Using “Beginning WT” as end point

- Length  mean  ~1.4cm/wk (1.2-1.5cm/wk)

- Head circum.  mean  ~0.9cm/wk (0.8-1cm/wk)

Based on Clark et al. *Clin Perinatol* 2014;41:295
Growth velocity estimates: Not constant

- Weight GV estimate based on:
  - Weekly intervals, median weights, 23-36wk GA, “Beginning WT” as end point
  - Mean ~18gm/kg/d (15-20gm/kg/d) for females and males

Assessment tools: Growth curves

• **Why are growth curves important?**
  - Visualize and track growth over time (plotted weekly)
  - Identify high-risk infants
    • Small-for-gestational age (SGA) - <10th percentile
    • Large-for-gestational age (LGA) - >90th percentile

• **Growth curve choice matters**
  - High-risk categories vary based on the curve
  - Misclassification of infants to high risk

Intrauterine growth curves

• Based on cross-sectional data; fetal growth; comparison to “ideal” growth

• Examples of WT, L and HC-for-age curves:
  – Fenton (2003; 2013)
  – Olsen (2010)
  – Bertino (2010)
  – Niklasson (2008)
  – Babson/Benda (1976)
  – Lubchenco (1963, 1966)

Olsen IE et al. Pediatrics 2010;125:e214
Selection of growth curves

- For which parameters? (WT, L, HC and BMI?)
- Sample size, data source and how recent?
- Sample selection
  - “population” vs “reference” sample selected for “healthy” infants
- Gender (combined or gender-specific)
- Race/ethnicity (combined or separate)
- Gestational age
- “Smoothing” curves
- Validation
### Selection of growth curves: Data in 2013 Fenton curves - preterm only

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Fenton WT-for-Age curves

Fenton L-for-Age and HC-for-Age
Olsen curves: How did we do?

Sample:
- Dataset from Pediatrix Clinical Data Warehouse
- n= 391,861 infants
- 22 to 42 wk gestation at birth (1998-2006)
- 248 U.S. NICUs from 33 U.S. states

Birth data:
- Weight, length, head circum, gestational age, gender

Exclusions
- Missing growth measurements or gender
- Factors with negative impact on growth
- Physiologically improbable growth measurements (“extreme outliers” Tukey *Exploratory Data Analysis* 1977)

Validation
- Internally and externally *(De Jesus J Pediatr 2013)* validated
Female Intrauterine Growth Curves

Olsen IE et al. *Pediatrics* 2010;125:e214
Olsen intrauterine growth charts
(23 to 38 wk)
presented with
WHO growth charts
(39 to 50 wk)

- Curves not joined because independent sets of data
- WHO “fullterm”: 37-41 wk

Weblink to PDF:

Adapted from:
and
http://www.who.int/childgrowth/standards/en/
Boys meta-analysis weight curves (dotted) with the final smoothed growth chart curves (dashed).
Olsen intrauterine growth charts (23 to 38 wk) presented with WHO growth charts (39 to 50 wk)

- Curves not joined because independent sets of data
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Weblink to PDF:

Adapted from:
Olsen IE et al. Pediatrics 2010;125:e214-224 and
http://www.who.int/childgrowth/standards/en/
WHO Child Growth Standards Growth Chart for girls

WHO “fullterm”: 37 – 41 wk

http://www.who.int/childgrowth/standards/en/
Olsen intrauterine growth charts
(23 to 38 wk)
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• Growth
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  – Growth assessment tools
    • Growth velocity
    • Growth curves
    • Growth status (percentiles, z-scores)
    • Body proportionality ratios (BMI)
Growth status: Z-score vs Percentile

Modified from: https://lexile.com/about-lexile/grade-equivalent/performance-standards/
By Derek Cox of Project Grow Baby Grow, Kennesaw State University – Statistics Dept.
Growth outcomes: Z-score

For data that is not normally distributed

$Z\text{-score} = \left[\frac{X}{M}\right]^L - 1$ 

Where

X: Measured value (Weight, kg; Length, cm; Head circum, cm)
M: Median
L: Box-Cox power transformation of skewness
S: Coefficient of variation

*Gender and GA-specific values from Olsen et al. growth curves data (Pediatrics 2010)
Growth outcomes: Z-score

\[
Z\text{-score} = \frac{\left(\frac{X}{M}\right)^L - 1}{LS}
\]

- **X**: Measured value (WT, kg; LN, cm; HC; cm)
- **M**: Median
- **L**: Box-Cox power transformation of skewness
- **S**: Coefficient of variation
Change in Z-score

- Accounts for initial size in addition to gender and GA specific

- Changes:
  - Positive (+) change in z-score
    - Improvement in growth status
  - Negative (-) change in z-score
    - Decline in growth status
  - No (0) change in z-score
    - Growth status stable or unchanged
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    • Body proportionality ratios (BMI)
Assessment tools: Body proportionality


- Preterm infants at corrected term have higher percent body fat than term infants (Johnson Pediatrics 2012; 130:e640; Gianni Pediatric Research 2016;79:710)


- Impact of rapid postnatal weight gain on later metabolic outcomes in preterm infants less clear (Embleton et al. Arch Dis Child 2016; Ong et al. (review) Acta Paediatrica 2015)
What is the “ideal” measure of body proportionality for preterm infants?

- We used gender-specific samples from our WT, L and HC-for-age curves (Males n = 74,375; Females n = 55,708) (Olsen et al. Pediatrics 2010;125:e214)


- We tested several Weight/Length ratios

- BMI ($WT/L^2$): Best candidate overall across gender and GAs

- Curves created and validated (methods paper pending) (Olsen IE et al. Pediatrics 2015)
Figure 2 from: Olsen IE et al. *Pediatrics* 2015;135:e572.

BMI-for-age intrauterine growth curves. A, Girls; B, Boys. ©2014 Olsen IE, Lawson ML, Ferguson AN, Cantrell R, Grabich SC, Zemel BS, Clark RH. All rights reserved. Reprinted with permission. The authors specifically grant to any health care provider or related entity a perpetual, royalty-free license to use and reproduce Fig 2 as part of a treatment and care protocol.
BMI limitations

• BMI does not distinguish between body fat mass and fat-free mass
  – Need to evaluate with body comp data as available

• Since BMI quantifies asymmetry between weight and length growth, symmetric growth stunting, excess or appropriate growth will not be identified

• Thus, BMI-for-age curves to be used along with size-for-age curves (WT, L, HC-for-age) not in place of them
Asymmetrical or Disproportionate growth status
WFA: WT-for-Age
LFA: L-for-Age

Symmetrical or Proportionate growth status
WFA: WT-for-Age
LFA: L-for-Age

Body proportionality: BMI-for-age curves

- Recommend BMI curves as adjunct to WT, LN, HC-for-age intrauterine curves
- Provides more individualized growth assessment to inform nutrition and clinical decisions
- Balance between adequate and excess growth?
  - Belfort MB et al. *JPediatr* 2013
  - Brown and Hay. (edit.) *JPediatr* 2013
  - Singhal A. “Optimizing Early Protein Intake for Long-Term Health of Preterm Infants”. In *Nestle Nutr Inst Workshop Ser*, vol 86, pp 129-137, 2016
Overall Summary and Conclusions

• Still more work to be done in determining (or confirming) optimal protein recommendations to support optimal outcomes in preterm infants

• Standardization of nutrition and growth data and outcomes used in clinical and research settings would help comparisons and making clinical decisions and policies (Cormack et al. Pedi Res 2015)

• Growth outcomes (at minimum): Weight, length, head circumference and BMI z-scores and change in z-scores; body composition, as possible
Thanks and Questions?