# Nutrition Support for the ELBW Infant: Implications for More than Just Growth

Josef Neu, MD

Professor of Pediatrics

University of Florida

# AGA 27 week : How do we Nourish this Baby?

# Parenteral Nutrition: Common Practice

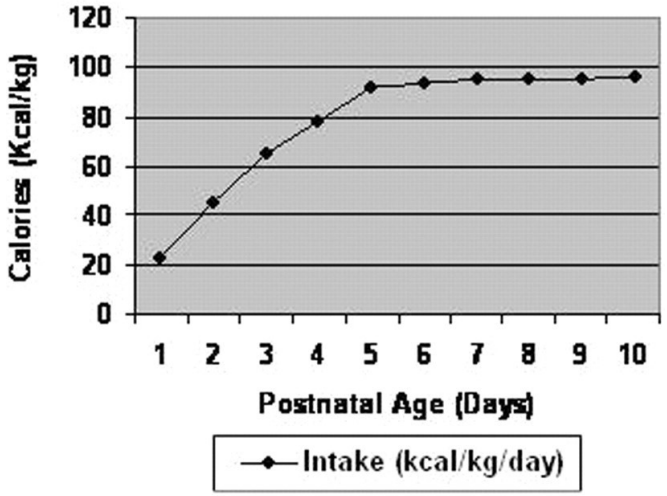
- Amino acids started in first week of life and advanced slowly in increments.
- Lipid infusions started in first week of life and advanced incrementally.
- Amino acids and lipids frequently delayed or interrupted.

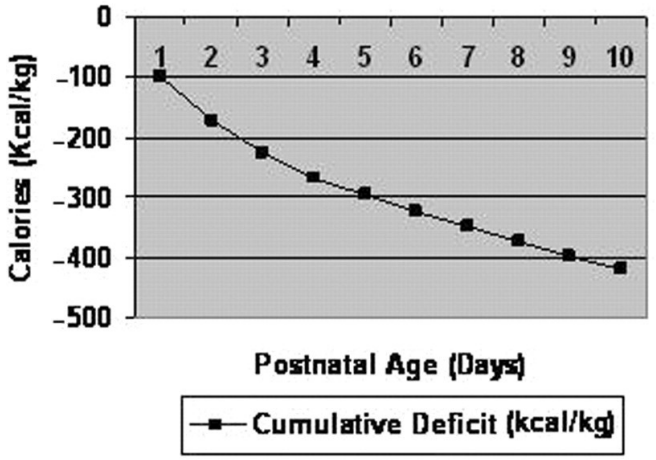
# Excuses To Withhold ENTERAL "Feedings"

- Low APGAR scores.
- Umbilical catheters.
- Apnea and Bradycardia.
- Mechanical ventilation.
- CPAP.
- Vasoactive drugs.
- TPN is available.

None of these are evidence based!!

# Calorie intake and cumulative deficit over the first 10 days: 50 British NICUs



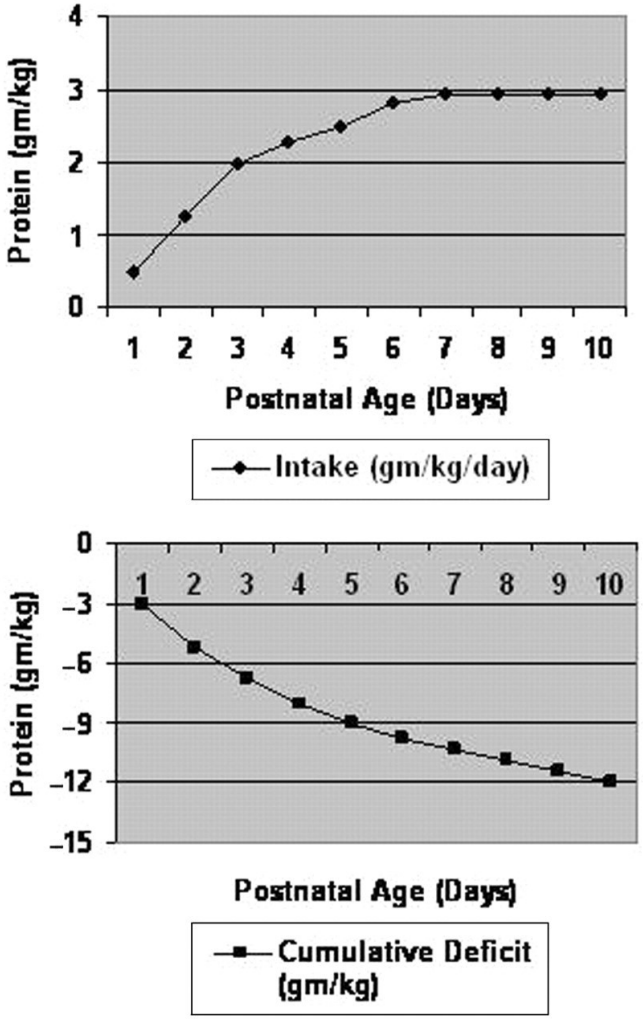




Grover A et al. JPEN J Parenter Enteral Nutr 2008;32:140-144



JPEN JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

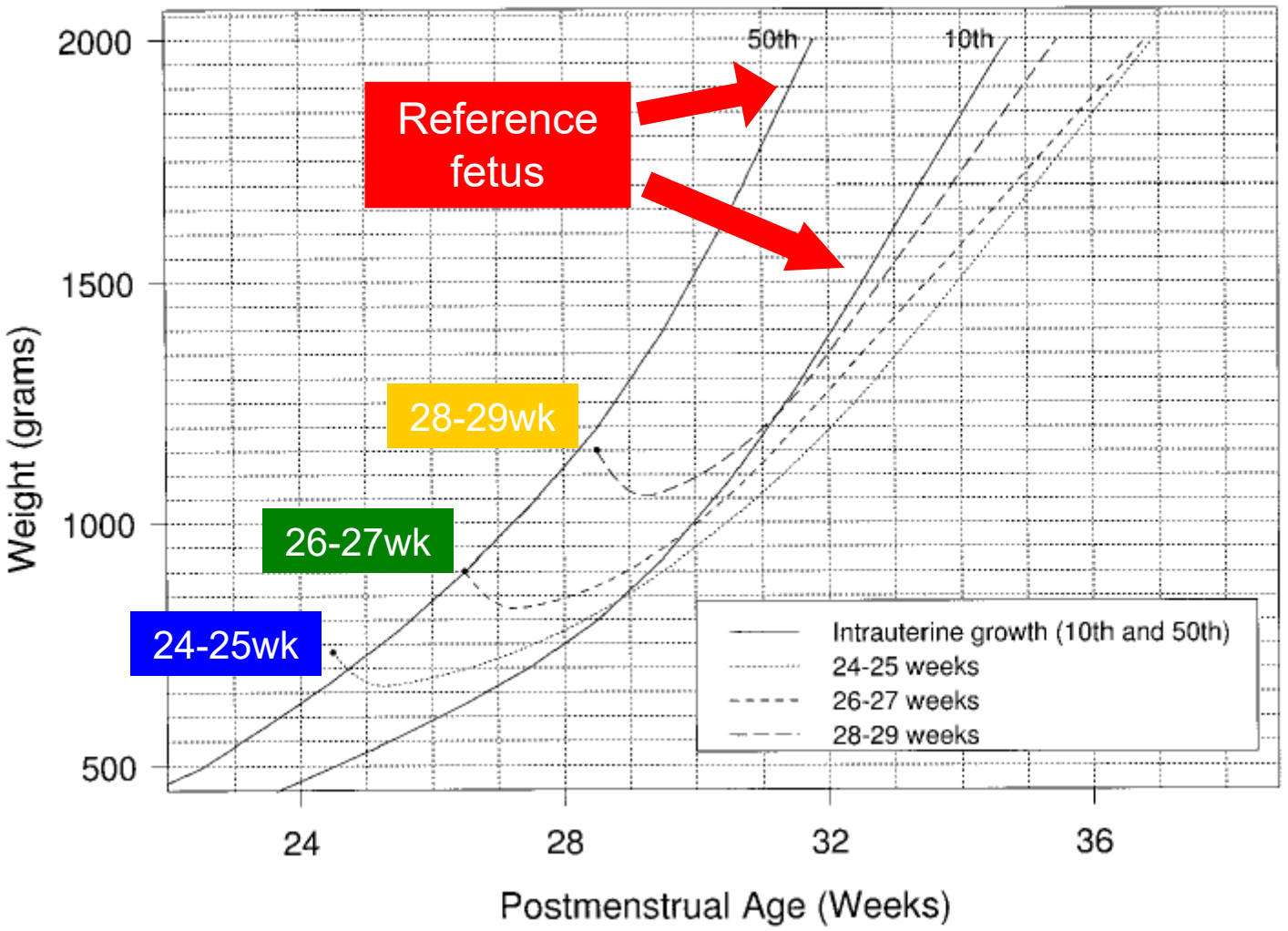
# Protein intake and cumulative deficit over the first 10 days: 50 British NICUs




Grover A et al. JPEN J Parenter Enteral Nutr 2008;32:140-144

JPEN JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

# NICU vs. Fetal Weight Gain



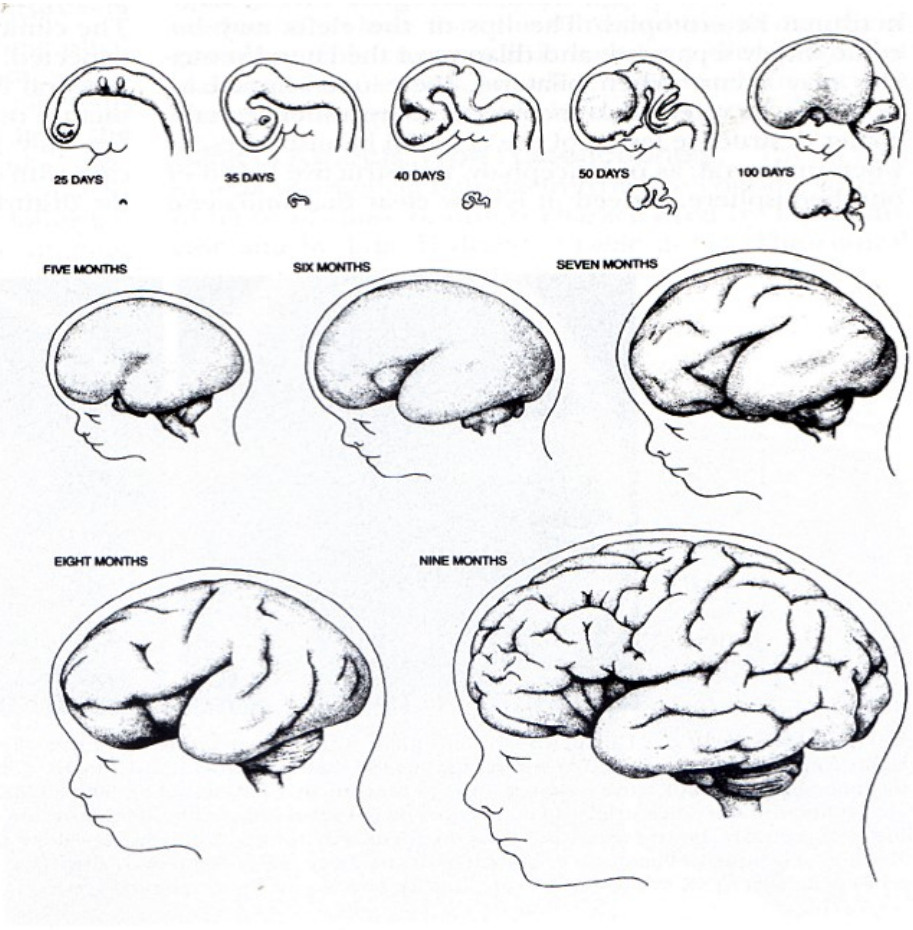

Ehrenkranz et al Pediatrics 1999

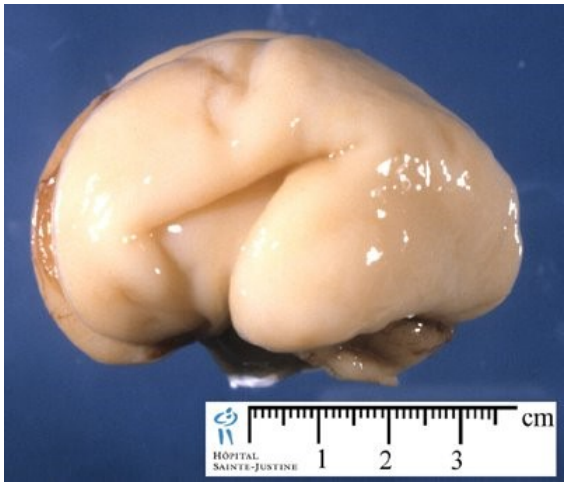
# Energy Stores in the Fetus and Newborn

| Weeks | Wt (g) | Water (%) | Protein (%) | Lipid (%) | Energy (kcal) |
|---|---|---|---|---|---|
| 24 | 690 | 86.6 | 8.8 | 0.1 | 19.5 |
| 26 | 880 | 86.8 | 9.2 | 1.5 | 123.6 |
| 28 | 1160 | 84.6 | 9.6 | 5 | 326.2 |
| 40 | 3450 | 74.0 | 12 | 15.3 | 3152.4 |
| 2 months | 5450 | 71.4 | 11.4 | 25 | 9866 |

Ziegler, E. Growth, 1976

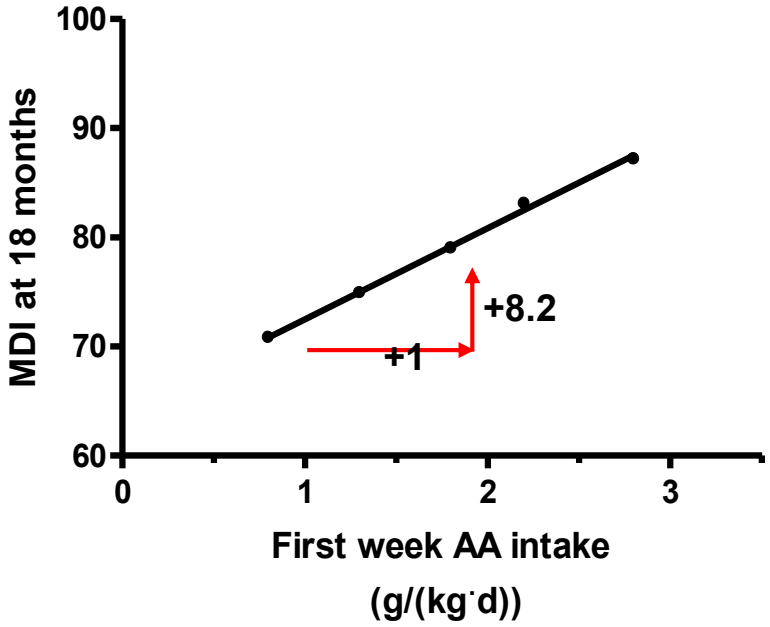
# Brain Development through Term Gestation

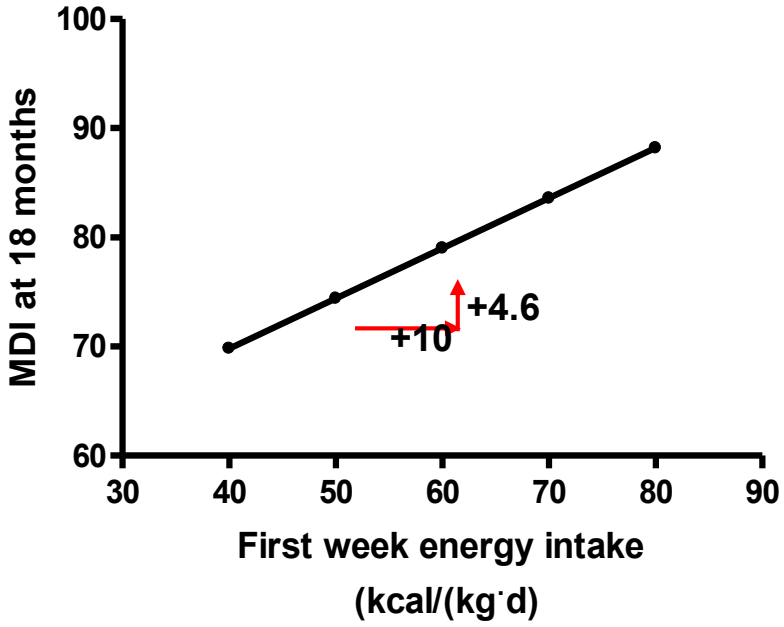



# First week protein and energy intake and neurodevelopmental outcome @18 months

- Retrospective study of 124 ELBW infants at 18 months CA




Stephens, B.E. Pediat. *2009*;123:1337-1341.

# ENERGY REQUIREMENTS

- **120 CAL/KG/D FOR GROWTH IF FED ENTERALLY.**
- **IF ON TPN, POSITIVE NITROGEN BALANCE CAN BE ATTAINED WITH 60 CAL/KG/D WITH ABOUT 2.5 G/KG/D OF PROTEIN.**
- **MINIMAL CALORIC INTAKE FOR WEIGHT GAIN IS ABOUT 80 CAL/KG/D IF ON TPN.**

# High Glucose Infusions and the Micropremie

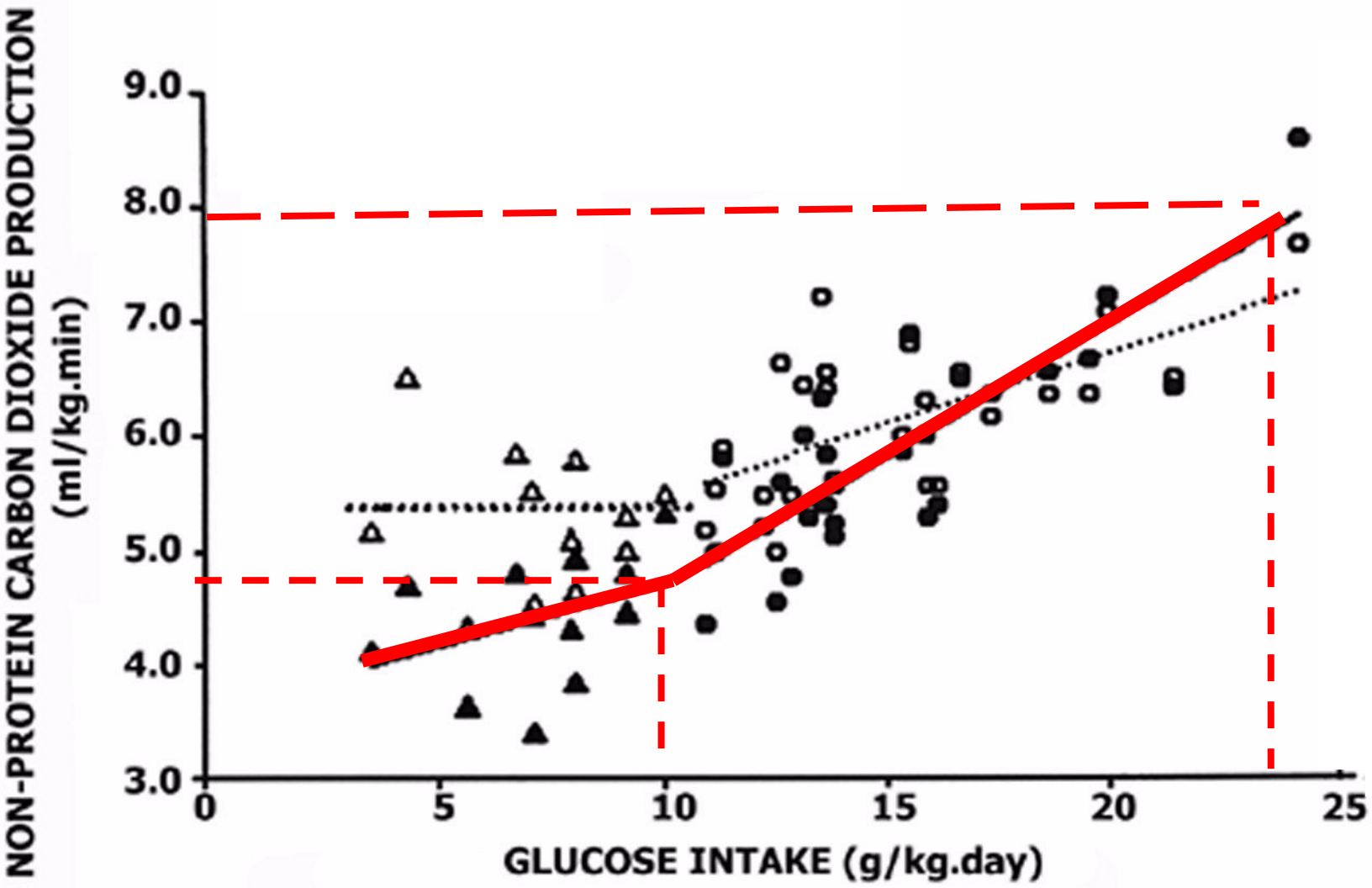
- Maximum Oxidation of Glucose is about 12 mg/kg/min.
- Infusion rates of glucose greater than 12 mg/kg/min may exceed capacity for infants with lung disease to eliminate $CO_{2.}$.

$C_6H_{12}0_6 + 6\ 0_2$----------->$6\ CO_2 + 6H_20$
glucose

$$RQ = \frac{6CO_2}{60_2} = 1.0$$

$C_{15}H_{31}\ COOH + 23O_2$ --------> $16\ CO_2 + 16\ H_20$
Palmitic acid

$$RQ = \frac{16CO_2}{23O_2} = 0.70$$




**Carbon dioxide production almost doubled from 4.7 to 7.9 mL/kg/min when the glucose intake ⇑ from 10 to 24 g/kg/day** Van Aerde, 2003

# Early Insulin Therapy in Very Low Birthweight Infants

- Done because studies in adults suggested that tight control of hyperglycemia in adults decreased mortality.
- International Randomized trial: 0.06 U per Kg insulin per hour versus standard neonatal care.
- Early Insulin group had lower glucose levels.
- Intention to treat insulin group showed higher mortality at 28 days.

**Beardsall K. Early insulin therapy in very-low-birth-weight infants.**
N Engl J Med. 2008 Oct 30;359(18):1873-84. doi: 10.1056/NEJMoa0803725.

# How much lipid do you provide the ELBW from Day 0? What do Others Do?

IV nutrition introduced early, but lipid introduced slowly and incrementally.

**Hans DM, et al. Pediatrics. 2009 Jan;123(1):51-7.2007-3644. Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey.**

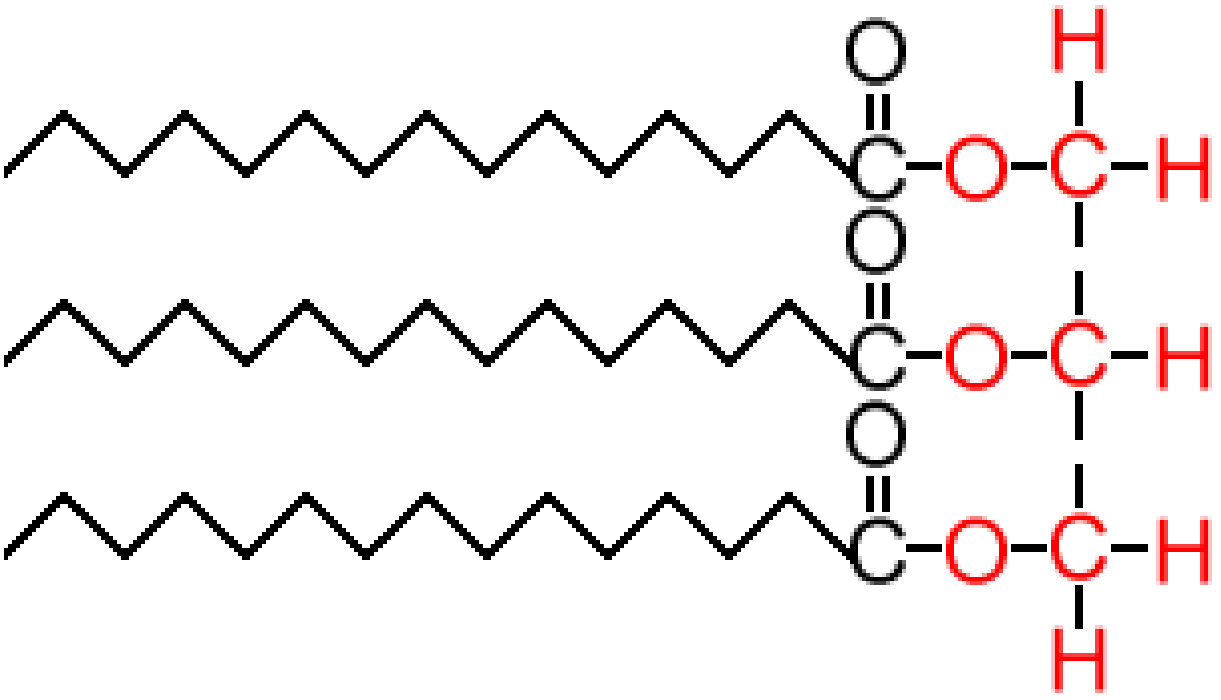
# Dogmas to Withhold Lipids

- Hyperbilirubinemia
- Sepsis
- PPHN
- Lung Disease
- Liver Disease
- Thrombocytopenia

# Rationale for Providing Lipids Early

- In utero lipid supply is approximately 2.5-3.0 grams/kg/d
- Essential Fatty Acid (EFA) status in early infancy is low and is rapidly exacerbated with lipid free nutrition.
- Long Chain Polyunstaturated Fatty Acid (LCPUFA) derivatives from EFAs are important in brain and retinal development.
- Prevention of catabolism and protein sparing.

# Triglyceride Structure



# Fatty Acids

**CHAIN LENGTH**

**-Short-chain fatty acids (≤6 carbons)**

**-Medium-chain fatty acids (8-12 carbons)**

**-Long-chain fatty acids (≥14carbons)**

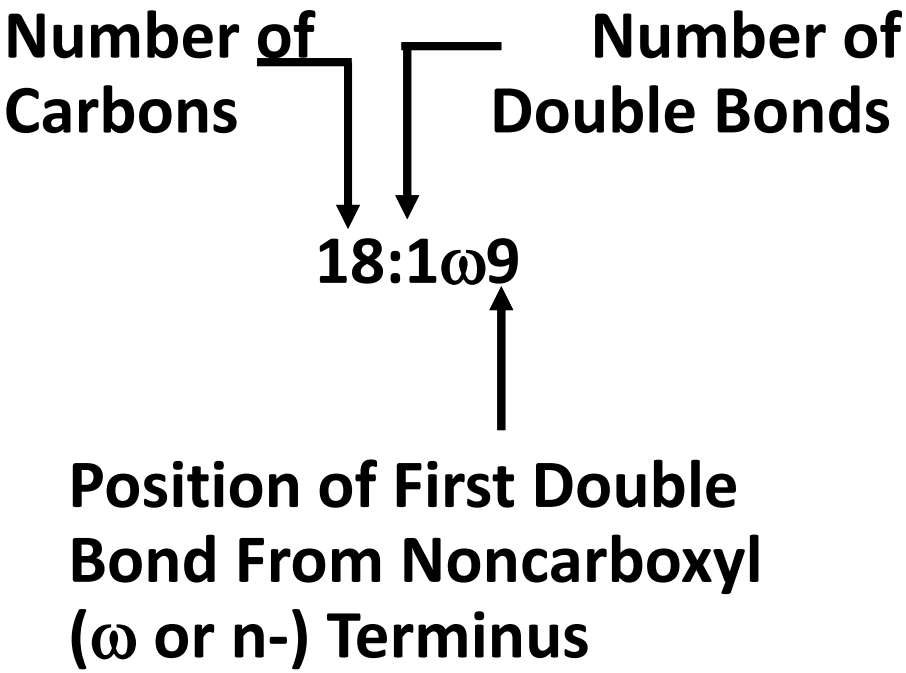
**NUMBER OF DOUBLE BONDS**

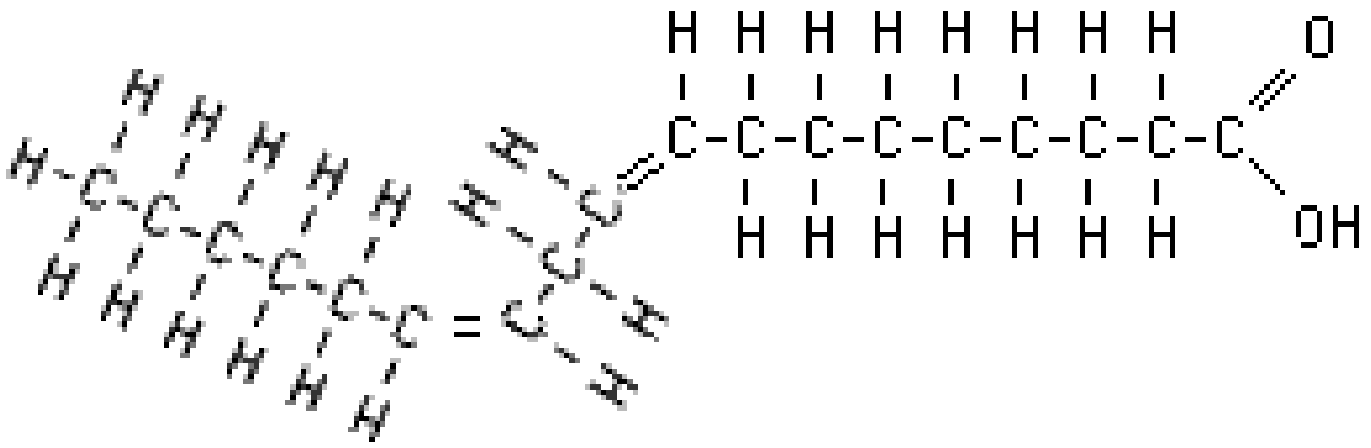
**-Saturated fatty acids (none)**

**-Monounsaturated fatty acids (1)**

**-Polyunsaturated fatty acids (2 or more)**

# Fatty Acid Nomenclature





Linoleic acid, a polyunsaturated fatty acid.
Both double bonds are *cis*.

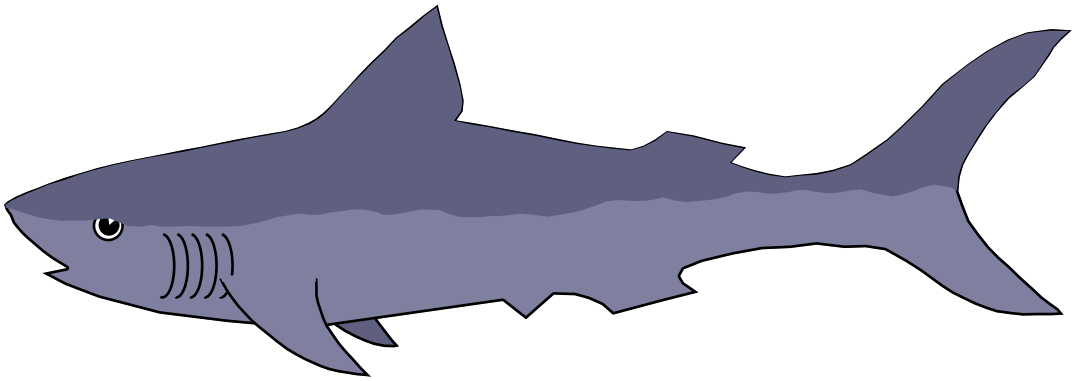
**18: 2 ω6**

# Essential Fatty Acids

**Linoleic Acid-C18:2ω-6**

**Linolenic Acid-C18:3ω-3**

- **Linoleic Acid-C18:2ω-6: 2-**
  **Prostaglandins (PGE2).**
- **Linolenic Acid-C18:3ω-3:D nd 2-series prostaglandins (PGE3)--less inflammatory and strongly inhibit platelet aggregation.**

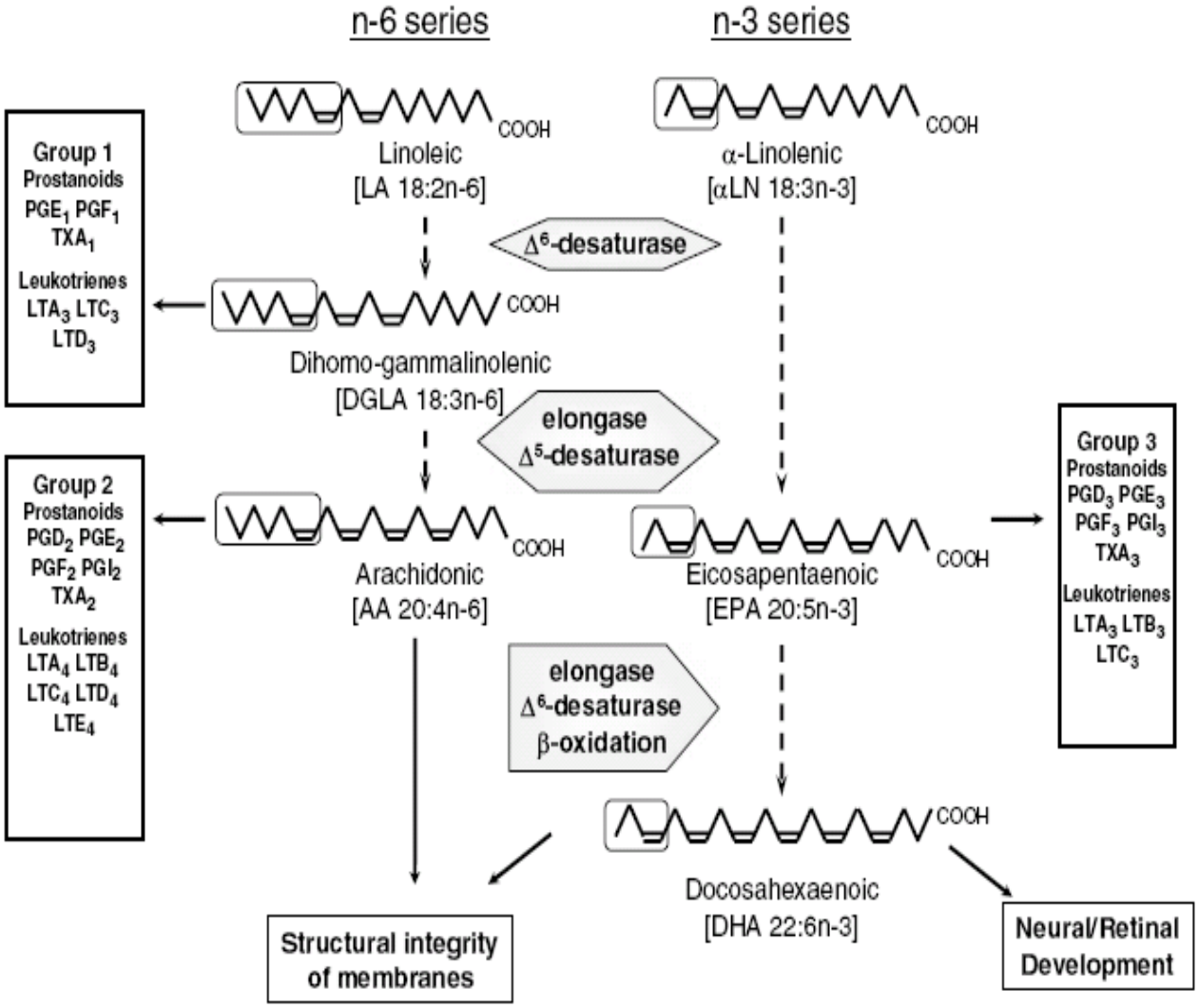


# Essential Fatty Acid Deficiency

FIG. 4. Flaky skin on the foot of patient SW who had received prolonged fat-free intravenous alimentation.

Paulsrud JR

# LCPUFA Synthesis




Haggarty P. EJCN 55:1563,2004

# Biochemical EFA Deficiency in Prematures: Holman Index

| | NO IV Lipid RDS + NO Feed | NO IV Lipid RDS + Feed + | IV Lipid + RDS + NO Feed | NO IV Lipid NO RDS Feed + |
|---|---|---|---|---|
| **Linoleic acid intake (g/kg/d)** | | | | |
| 1 | 0 | 0.02 | 0 | 0.2 |
| 3 | 0 | 0.20 | 0.80 | 1.0 |
| 7 | 0 | 0.50 | 1.1 | 1.7 |
| **Triene:Tetraene Ratio > 0.2** | | | | |
| 1 | 1 (5%) | 0 | 0 | 0 |
| 3 | 3 (15%) | 1 (3%) | 0 | 0 |
| 7 | 16 (80%) | 4 (13%) | 0 | 0 |

Birth weight 1.35 kg, gestational age 31 wk; **IV Lipid + = 1 - 3 g/kg/d**

*Gutcher, AJCN 1991; 54:1024*

# Early Initiation of Lipids: Meta Analyses

- NO differences in mortality, chronic lung disease or other morbidity in early versus late introduction of intravenous lipid.

1.Fox GF Pediatr Res 43:214A, 1998
2.Simmer K, Rao SC. Cochrane Database Syst Rev, 2005

# Calculation (assume 1kg baby)

- Need total of 80 Kcal/Kg/d for growth
- Glucose:
  - 8mg/kg/min~39 Kcal
- Amino Acids:
  - 3 gm/Kg/d=12 Kcal
- Lipids:
  - Still need ~30 Kcal for 80 total
  - 30 kcal X cc/2.2 KcalX0.2 gm/cc=2.7gm/d

# WHEN TO START LIPIDS

**ASAP—As Soon As Possible. No studies that show problems starting at 3.0 gm/kg/d.**

**USUALLY NOT MORE THAN 3.0 GM/KG/D NEED PROVIDED.**

**HYPERLIPIDEMIA TOUGH TO MONITOR**

**PROLONGED INFUSIONS USUALLY SAFE (<0.2 GM/KG/HR).**

# Monitoring Triglycerides

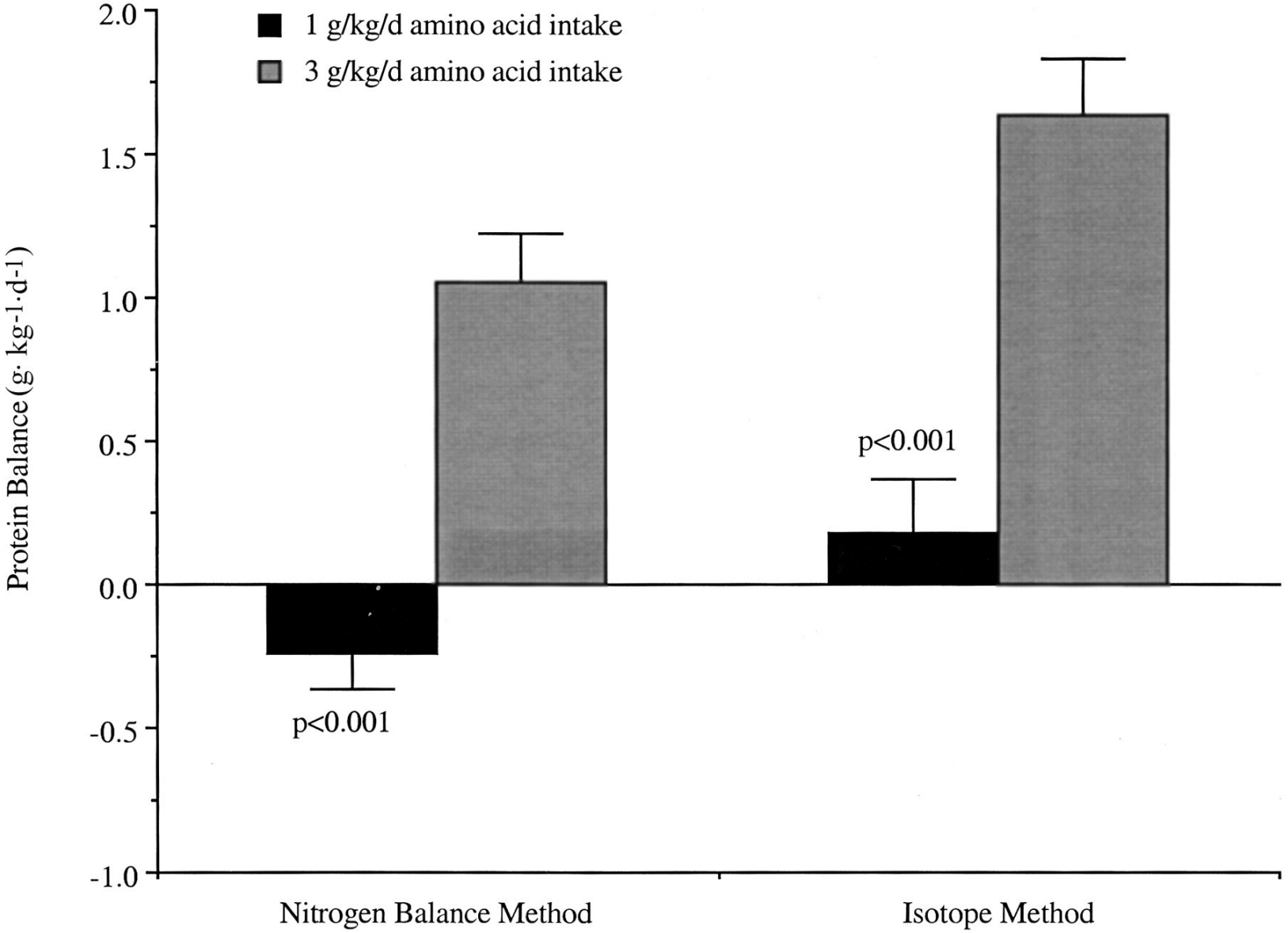
- Different norms are recommended by different authors (e.g. 100-150, <200 mg/dl, etc.)
- Is this efficacious and /or realistic?

# Amino Acids

- What day do you start?
- How much do you start with?

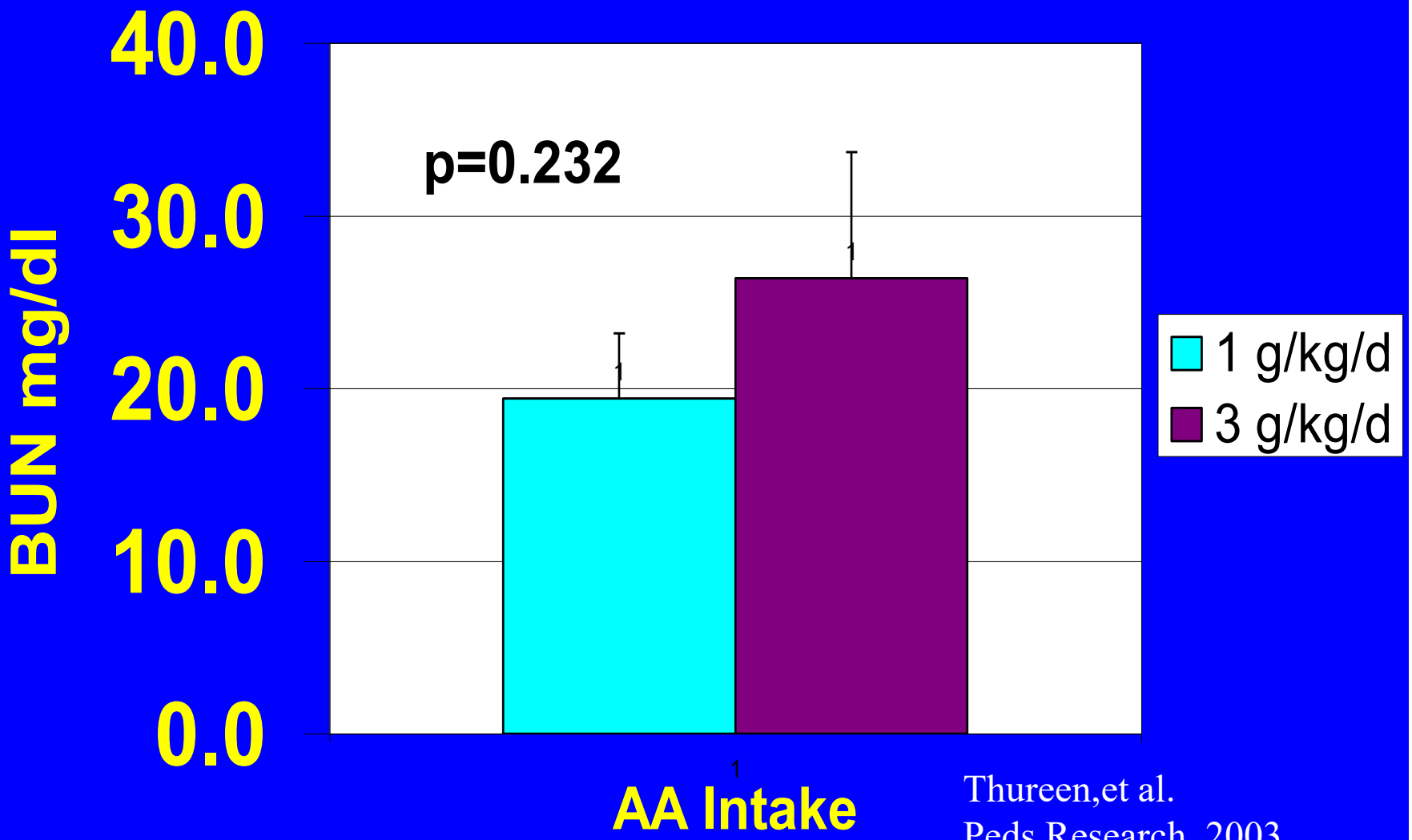
# PROTEIN DEFICITS

- Many NICUs delay TPN amino acids, then begin at 0.5 g/kg/d and advance slowly.
- Using this approach, may infants do not attain the intrauterine accretion (3.5-4.0 g/kg/d) until they are 7-14 days of age.
- This leads to a significant early protein deficit.




Thureen,et al. Peds Research, 2003

# Serum BUN




Thureen,et al.
Peds Research, 2003

# High vs. Low Amino Acid Intake and Glucose/Insulin

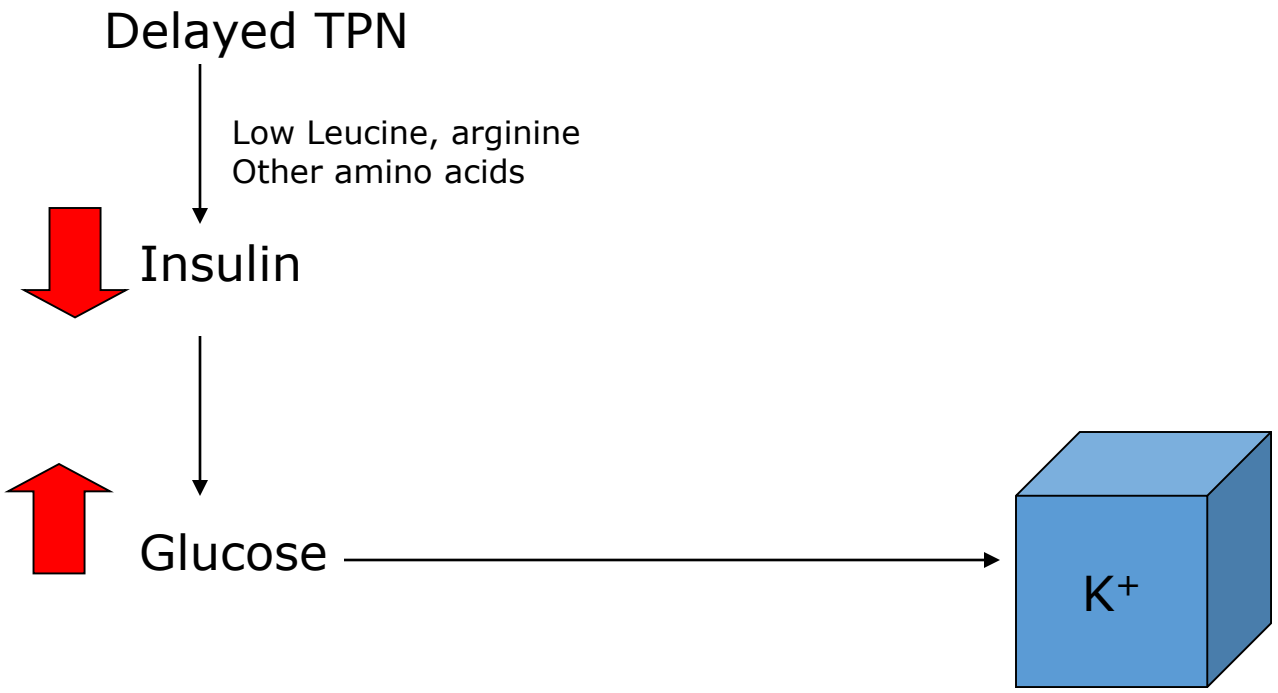
| | Low amino acids | High amino acids |
|---|---|---|
| **Glucose, mmol/L (mg/dL)** | **6.2 ± 0.7 (113 ± 13)** | **6.9 ± 0.8 (125 ± 14)** |
| **Insulin, pmol/L (μU/mL)** | **75 ± 13 (10.5 ± 1.9)** | **139 ± 23 (19.3 ± 3.1)*** |

Values expressed as mean ± SEM.

* Significant difference between groups, $p < 0.05$.

**Thureen, Peds. Rsch. , 2003**

# Delayed TPN, Hyperglycemia and Hyperkalemia



# Questions: AGA 27 week

APGARS 3 and 5,
UA and UV catheters in place,
On mechanical ventilation and prophylactic indomethacin

- Can we feed this baby using the GI tract?
- What are the consequences of not feeding this baby?
- How do we feed this baby?

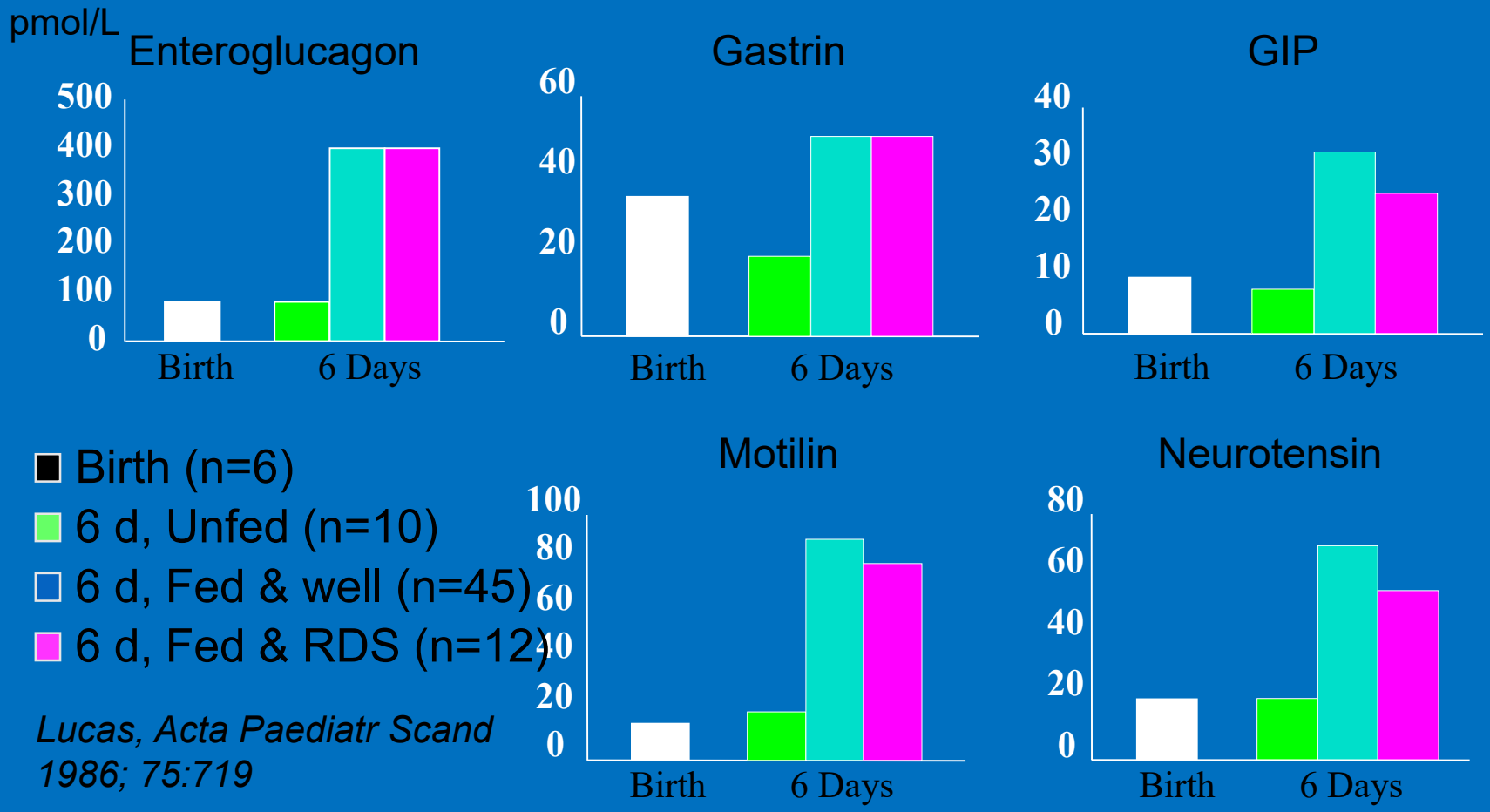
# Dr. Elsie Widdowson (1906-2000)

A formal photograph of Dr Widdowson sitting at her desk (which incidentally is untypically tidy). (Photograph taken by Mr David Reed for the National Portrait Gallery, reproduced courtesy of Mr David Reed and Dr Eva Crane.)

The suckled pig's duodenum gains 42% of it's weight in the first 24 hours after birth.

*Ashwell M*
*Nature* **406**, 844 (24 August 200

# Plasma [GI Hormone] in Premature Infants



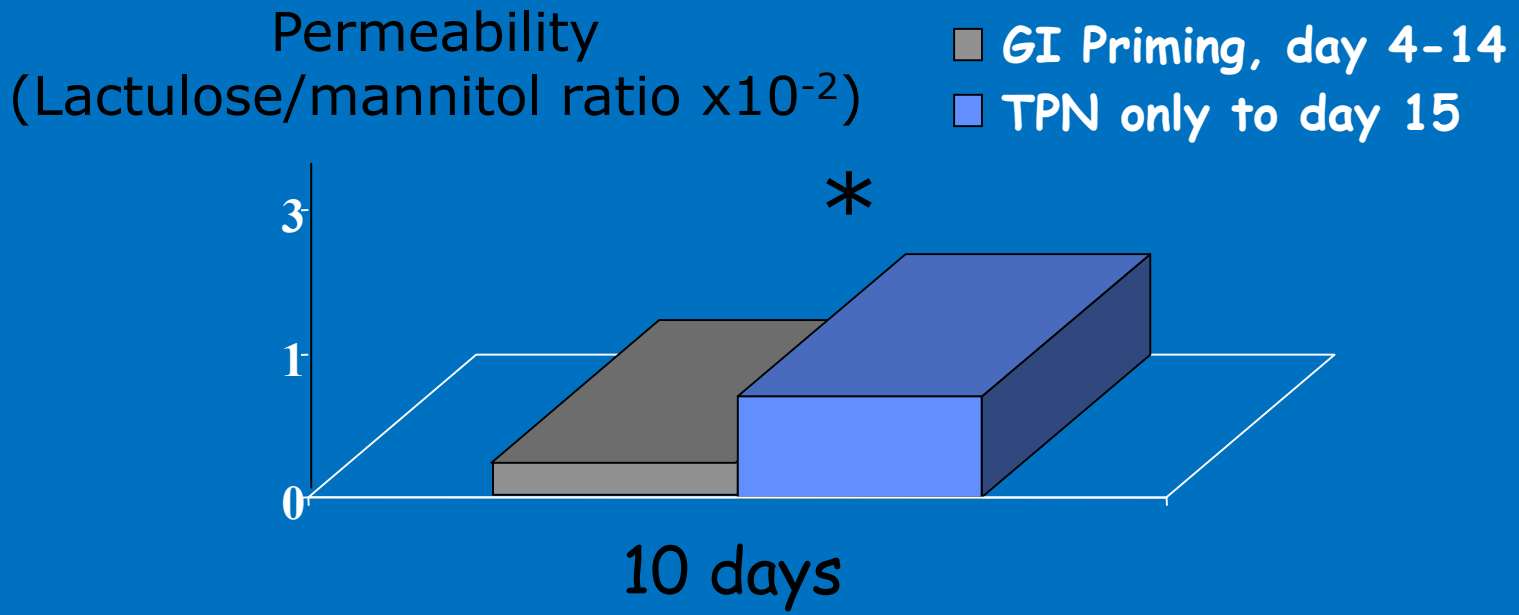

*Lucas, Acta Paediatr Scand 1986; 75:719*

# MINIMAL ENTERAL NUTRITION (12 Studies)

- Improved feeding tolerance and growth.
- Less need for phototherapy.
- Decreased cholestasis.
- Decreased osteopenia.
- Gastrointestinal trophic hormone surges.
- Improved motility.
- No increase in complications (e.g.-NEC).

# Effect of GI Priming on Intestinal Permeability

Birth weight 1 kg
Gestational age 28 wk




*Shulman et al, Pediatr Res 1998;44:519*

# Morbidities: Early vs. Late Feeding

**Table 3. Univariate Analysis of Neonatal Morbidities by Group.**

| Outcomes (%) | Early (n = 79) | Late (n = 51) |
|---|---|---|
| NEC | 6.3 | 10.0 |
| ROP | 16.7 | 52.1** |
| CLD | 21.5 | 69.4** |
| PVL | 0.0 | 6.0* |
| IVH | 24.1 | 24.0 |
| Comorbidities | 8.0 | 25.0** |

* Early vs. Late $p<0.05$;

** Early vs. Late $p<0.0001$

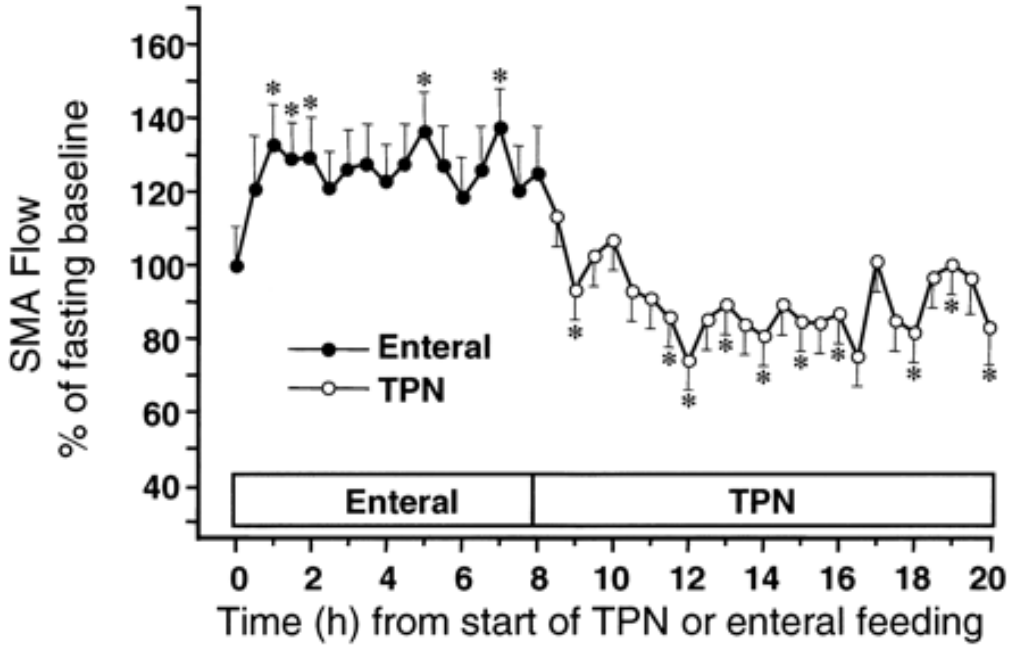
Necrotizing Enterocolitis (NEC); Retinopathy of Prematurity (ROP); Chronic Lung Disease (CLD); Periventricular Leukomalacia (PVL); Intraventricular Hemorrhage (IVH); Cormorbidities = The presence of 2 or more neonatal outcomes.

Konnikova, et al. PLOS One 2015

# Controversies: Do You Keep Feeding?

- Indomethacin for Ductus?
- Indomethacin for IVH Prophylaxis?
- Blood transfusions?
- During Hypothermia for HIE?

# Superior Mesenteric Artery Flow




**Niinikoshi, J. Nutrition, 2004**

# Enteral Feeding during Indomethacin and Ibuprofen Treatment of a Patent Ductus Arteriosus

Ronald Clyman, MD[1,2], Andrea Wickremasinghe, MD[1,2], Nami Jhaveri, MD[1,2], Denise C. Hassinger, MD[3], Joshua T. Attridge, MD[4], Ulana Sanocka, MD[5], Richard Polin, MD[5], Maria Gillam-Krakauer, MD[6], Jeff Reese, MD[6], Mark Mammel, MD[7], Robert Couser, MD[7], Neil Mulrooney, MD[7], Toby D. Yanowitz, MD[8], Matthew Derrick, MD[9], Priya Jegatheesan, MD[10], Michele Walsh, MD[11], Alan Fujii, MD[12], Nicolas Porta, MD[13], William A. Carey, MD[14], and Jonathan R. Swanson, MD[3], on behalf of the Ductus Arteriosus Feed or Fast with Indomethacin or Ibuprofen (DAFFII) Investigators*

**Objective** To test the hypothesis that infants who are just being introduced to enteral feedings will advance to full enteral nutrition at a faster rate if they receive "trophic" (15 mL/kg/d) enteral feedings while receiving indomethacin or ibuprofen treatment for patent ductus arteriosus.

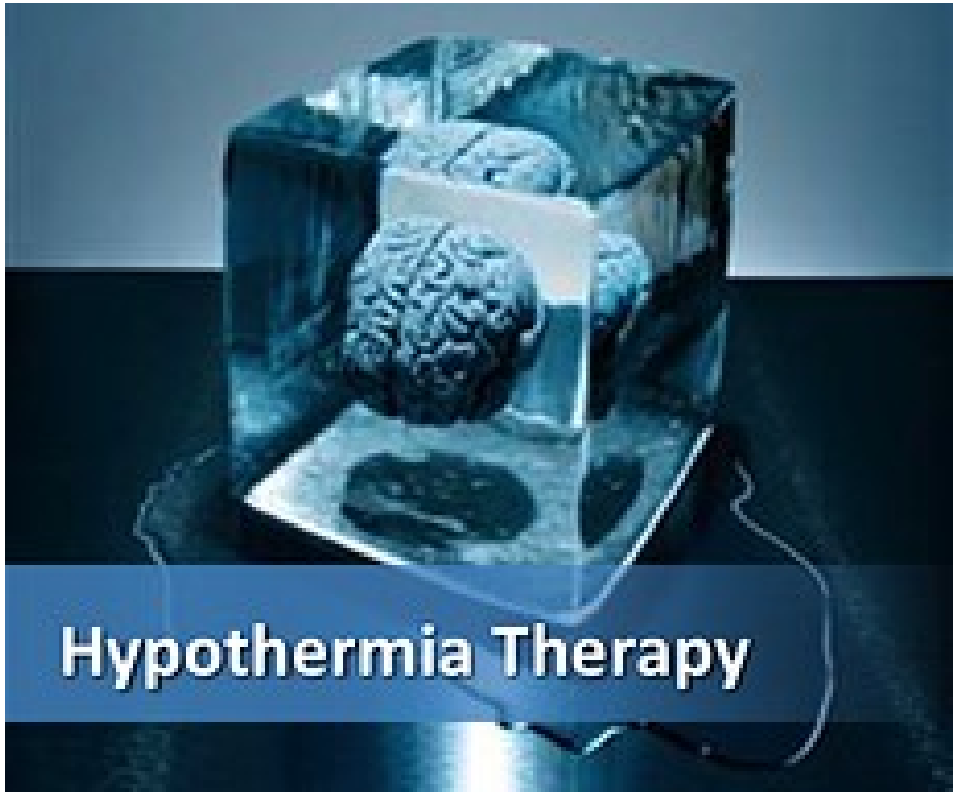
**Study design** Infants were eligible for the study if they were $23^{1/7}$-$30^{6/7}$ weeks' gestation, weighed 401-1250 g at birth, received maximum enteral volumes ≤60 mL/kg/d, and were about to be treated with indomethacin or ibuprofen. A standardized "feeding advance regimen" and guidelines for managing feeding intolerance were followed at each site (N = 13).

**Results** Infants (N = 177, 26.3 ± 1.9 weeks' mean ± SD gestation) were randomized at 6.5 ± 3.9 days to receive "trophic" feeds ("feeding" group, n = 81: indomethacin 80%, ibuprofen 20%) or no feeds ("fasting [*nil per os*]" group, n = 96: indomethacin 75%, ibuprofen 25%) during the drug administration period. Maximum daily enteral volumes before study entry were 14 ± 15 mL/kg/d. After drug treatment, infants randomized to the "feeding" arm required fewer days to reach the study's feeding volume end point (120 mL/kg/d). Although the enteral feeding end point was reached at an earlier postnatal age, the age at which central venous lines were removed did not differ between the 2 groups. There were no differences between the 2 groups in the incidence of infection, necrotizing enterocolitis, spontaneous intestinal perforation, or other neonatal morbidities.

**Conclusion** Infants required less time to reach the feeding volume end point if they were given "trophic" enteral feedings when they received indomethacin or ibuprofen treatments. *(J Pediatr 2013; ■:■-■).*

# Specific Circumstances: Hypothermia for HIE

- Why not?
- History of major advantages (decreased mortality, inflammatory responses, etc.) to feeding under high stress conditions (burns, trauma, etc.)
- Enteral feeding in Scandinavia—"safe". Thyagarajan B. Acta Paediatr. 2015 Feb;104(2):146-51
- Minimal Enteral Nutrition during hypothermia was associated with a reduced length of stay and time to full feeds, but did not increase feeding complications or systemic inflammation( Chang, L. et al. Neonatology, 2018).



Original Paper

Neonatology

Neonatology 2018;113:347–352
DOI: 10.1159/000487848

Received: January 22, 2018
Accepted after revision: February 17, 2
Published online: March 6, 2018

# Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy

Lilly L. Chang[a] James L. Wynn[a] Marisa J. Pacella[a] Candace C. Rossignol[a]
Felix Banadera[d] Neil Alviedo[d] Alfonso Vargas[e] Jeffrey Bennett[b]
Melissa Huene[a] Nicole Copenhaver[a] Livia Sura[a] Kimberly Barnette[d]
Jayne Solomon[e] Nikolay A. Bliznyuk[c] Josef Neu[a] Michael D. Weiss[a]

[a]Department of Pediatrics, University of Florida, Gainesville, FL, USA; [b]Department of Radiology, University of Florida, Gainesville, FL, USA; [c]Department of Agricultural and Biological Engineering, Biostatistics and Statistics,

**Question :You are on call at 2am. Nurse reports that this baby who is being fed 2 ml breast milk every 3 hours is having 2 cc gastric residuals. What do you do?**

- **Tell the nurse not to bother you at 2am?**
- **Stop all feedings?**
- **Ask about the physical exam and perhaps examine baby yourself?**

# Checking or Not Checking Gastric Residuals

| Table 2. Specific Outcomes Measured. (Mean ± SD) | | | |
|---|---|---|---|
| **Outcomes** | Check GR (N=30) | No Check GR (N=31) | P-value |
| **Enteral intake 2 weeks after birth** | 106.73±53.74 | 112.20±42.81 | 0.66 |
| **Enteral intake 3 weeks after birth** | 134.20±39.44 | 141.00±29.29 | 0.41 |
| **Day of life of full enteral intake at 120 ml/kg/d** | 16.8±12.4 | 14.3±12.5 | 0.29 |
| **Day of life of full enteral intake at 150 ml/kg/d** | 28.1±3.9 | 22.3±11.7 | 0.19 |
| | | | |
| **Percentage of Change of Growth Parameters:** | | | |
| **Weight at 3 weeks** | 23.8±19 | 23.6±21 | 0.98 |
| **Length at 3 weeks** | 7.1±5 | 6.4±5.5 | 0.58 |
| **Head circumference at 3 weeks** | 8.6±5.9 | 7.8±3.9 | 0.51 |
| | | | |
| **Day of life when PN was discontinued** | 15.1±11 | 13.8±5.9 | 0.57 |
| **Day of life when central access was discontinued** | **21.3±20.7** | **15.6±5.9** | **0.17** |

Murgas Torrazzo, R., J. Perinatology, 2014

# Checking or Not Checking Gastric Residuals

| Table 2. Clinical Complications Measured. (%) | | | |
|---|---|---|---|
| **Outcomes** | Check GR (N=30) | No Check GR (N=31) | P-value |
| **PNALD** | 4/30 (13.3) | 4/31 (12.9) | 1.00 |
| **SEPSIS** | 11/30 (36.7) | 9/31 (29) | 0.59 |
| **NEC** | 3/30 (10) | 1/30 (3.2) | 0.35 |

Murgas Torrazzo, R., et al. J. Perinatology, 2014

# Medications and Additives: Osmolality

- AAP recommended limit is 400mOsm/Kg
- Adding 3 or 4 of the following to human milk may markedly increase osmolality to near or over 1000mOsm/Kg.
  - Multivitamins
  - Spironolactone and Chlorthiazide
  - Dexamethasone
  - Caffeine Citrate

Radmacher and Adamkin, JPGN 201

# Question: Do you have feeding guidelines in your NICU?

- Yes
- No

# Take Home Messages

- **Early nutrition in premature babies can be safe and efficacious and may prevent significant morbidity.**
- **Growth is important but we also need to consider long term neurodevelopment and other health consequences.**
- **Many of the dogmas that have prevented rapid incorporation of early nutrition have either been disproved, not based on fact or weak.**
- **Not all preterm infants are the same and the future will need to focus on a more personalized approach that accounts for specific gestational age and degree of illness and "omic" considerations.**