Nutrition Strategy for Premature Infants

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AGA 27 week : How do we Nourish this Baby?

Parenteral Nutrition: Common Practice

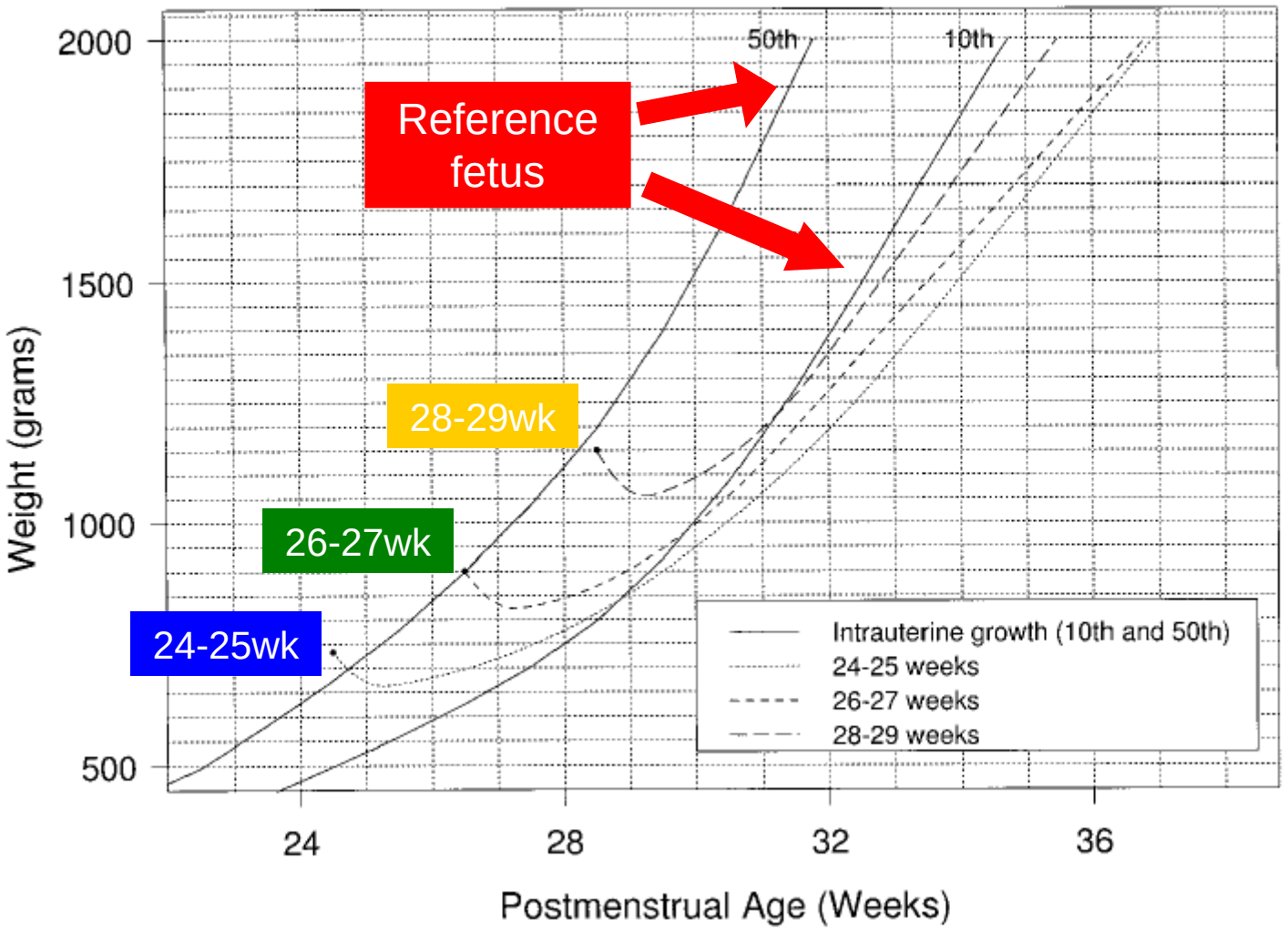
- Amino acids started in first week of life and advanced slowly in increments.
- Lipid infusions started in first week of life and advanced incrementally.
- Amino acids and lipids frequently delayed or interrupted.

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!!

NICU vs. Fetal Weight Gain



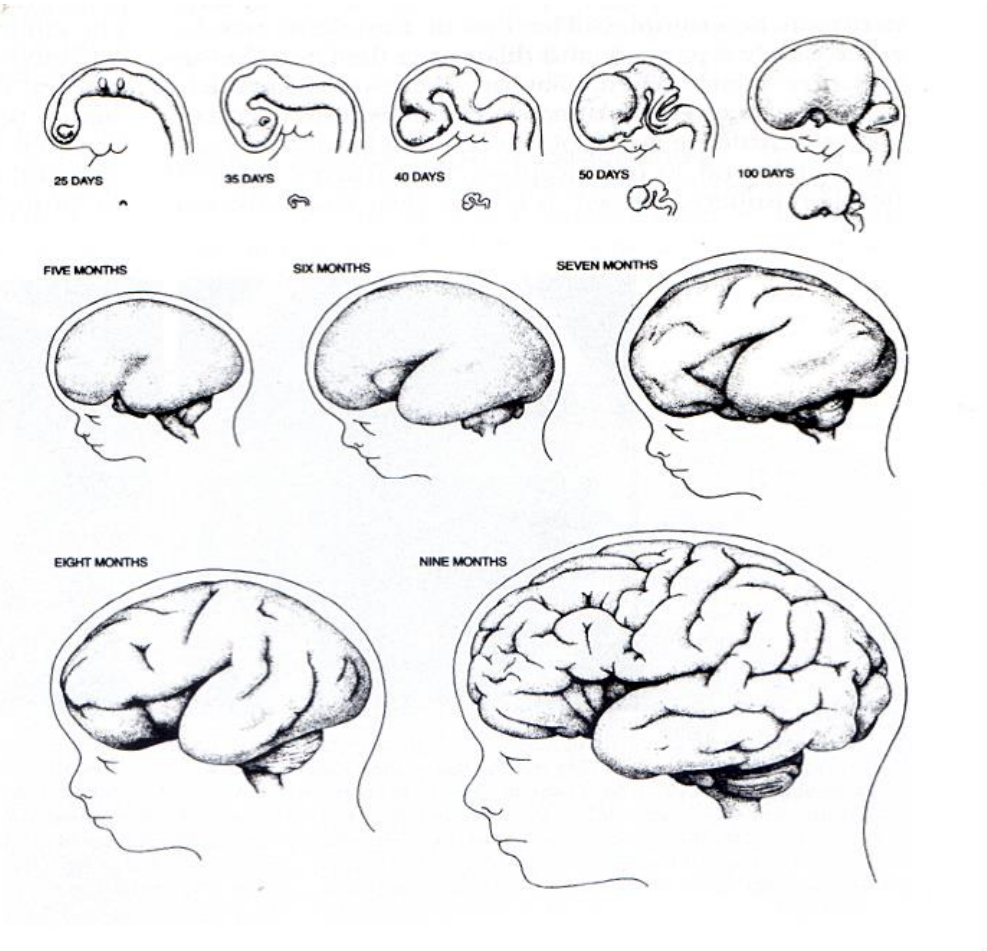
Ehrenkranz et al Pediatrics 1999

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

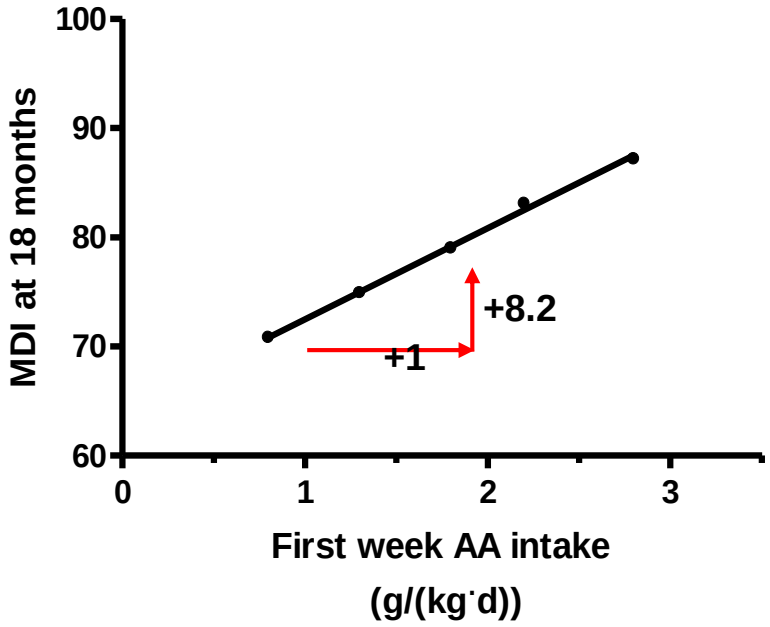
Ziegler, E. Growth, 1976

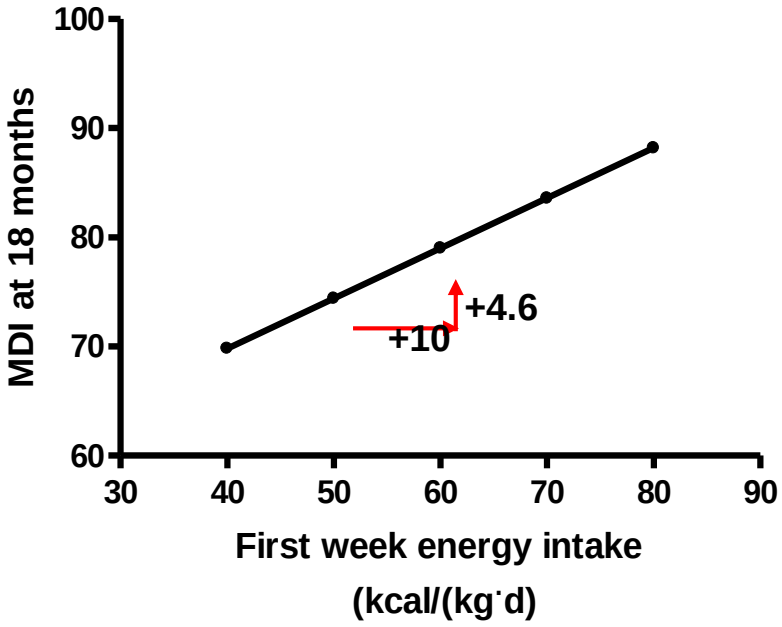
Brain Development through Term Gestation



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

- **110-120 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.**

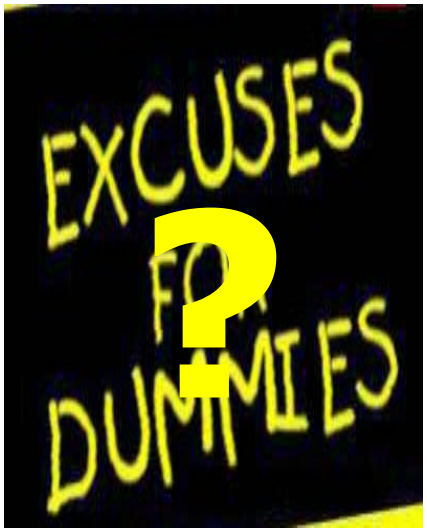
How much lipid do you provide the ELBW from Day 0? What do Others Do?

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.

Essential Fatty Acids

Linoleic Acid-C18:2ω-6

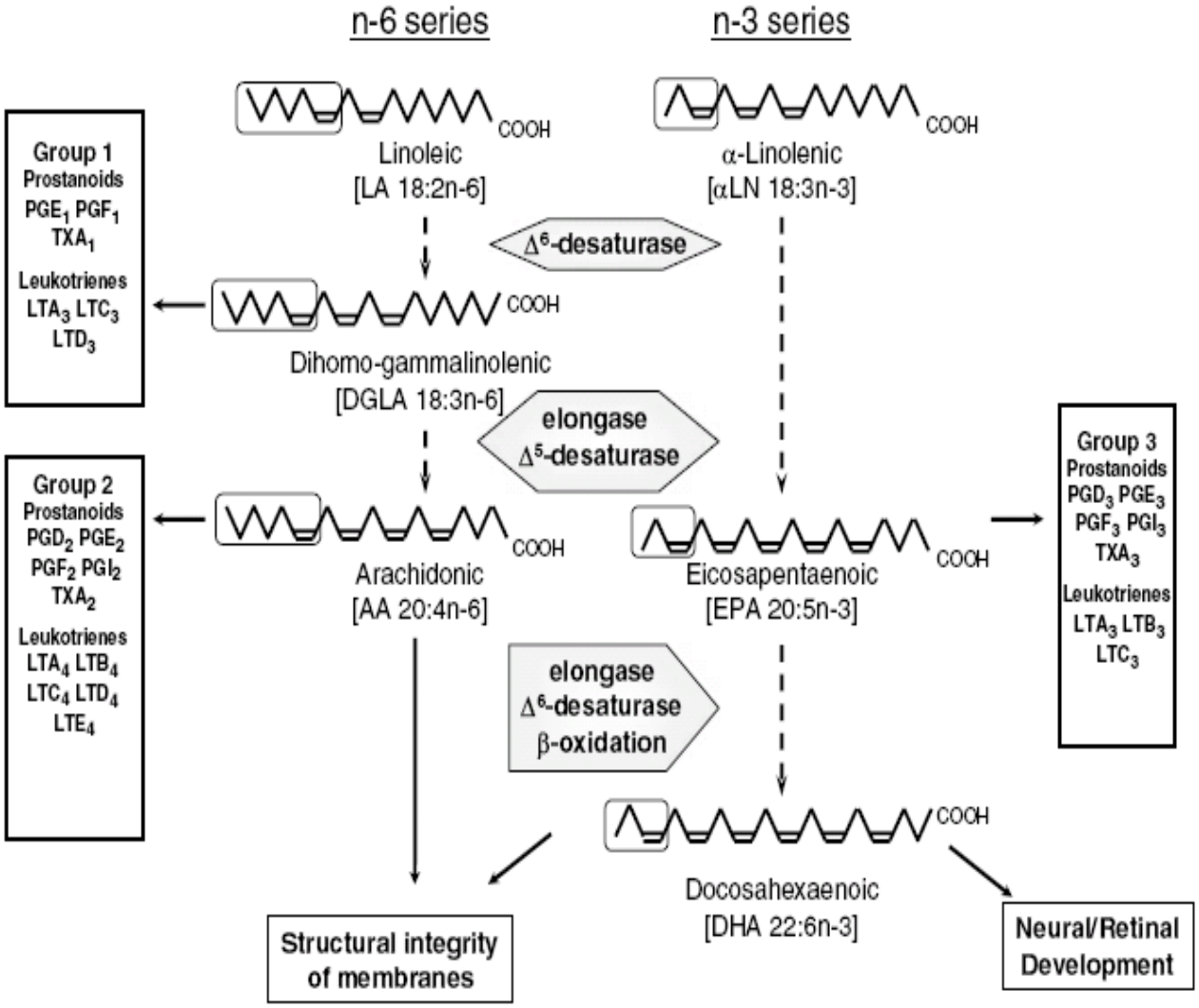
Linolenic Acid-C18:3ω-3

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

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

Safety and Efficacy of Early Parenteral Lipid and High-Dose Amino Acid Administration to Very Low Birth Weight Infants

Hester Vlaardingerbroek, MD, PhD[1], Marijn J. Vermeulen, MD, PhD[1], Denise Rook, MD, PhD[1], Chris H. P. van den Akker, MD, PhD[1], Kristien Dorst[1], Josias L. Wattimena[2], Andras Vermes, PharmD, PhD[3], Henk Schierbeek, PhD[1,4,5], and Johannes B. van Goudoever, MD, PhD[1,4,5]

Objective To assess the efficacy and safety of early parenteral lipid and high-dose amino acid (AA) administration from birth onwards in very low birth weight (VLBW, birth weight <1500 g) infants.

Study design VLBW infants (n = 144; birth weight 862 ± 218 g; gestational age 27.4 ± 2.2 weeks) were randomized to receive 2.4 g of AA $kg^{-1} \cdot d^{-1}$ (control group), or 2.4 g AA $kg^{-1} \cdot d^{-1}$ plus 2-3 g lipids $kg^{-1} \cdot d^{-1}$ (AA + lipid group), or 3.6 g AA $kg^{-1} \cdot d^{-1}$ plus 2-3 g lipids $kg^{-1} \cdot d^{-1}$ (high AA + lipid group) from birth onwards. The primary outcome was nitrogen balance. The secondary outcomes were biochemical variables, urea rate of appearance, growth rates, and clinical outcome.

Results The nitrogen balance on day 2 was significantly greater in both intervention groups compared with the control group. Greater amounts of AA administration did not further improve nitrogen balance compared with standard AA dose plus lipids and was associated with high plasma urea concentrations and high rates of urea appearance. No differences in other biochemical variables, growth, or clinical outcomes were observed.

Conclusions In VLBW infants, the administration of parenteral AA combined with lipids from birth onwards improved conditions for anabolism and growth, as shown by improved nitrogen balance. Greater levels of AA administration did not further improve the nitrogen balance but led to increased AA oxidation. Early lipid initiation and high-dose AA were well tolerated. *(J Pediatr 2013;163:638-44)*.

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

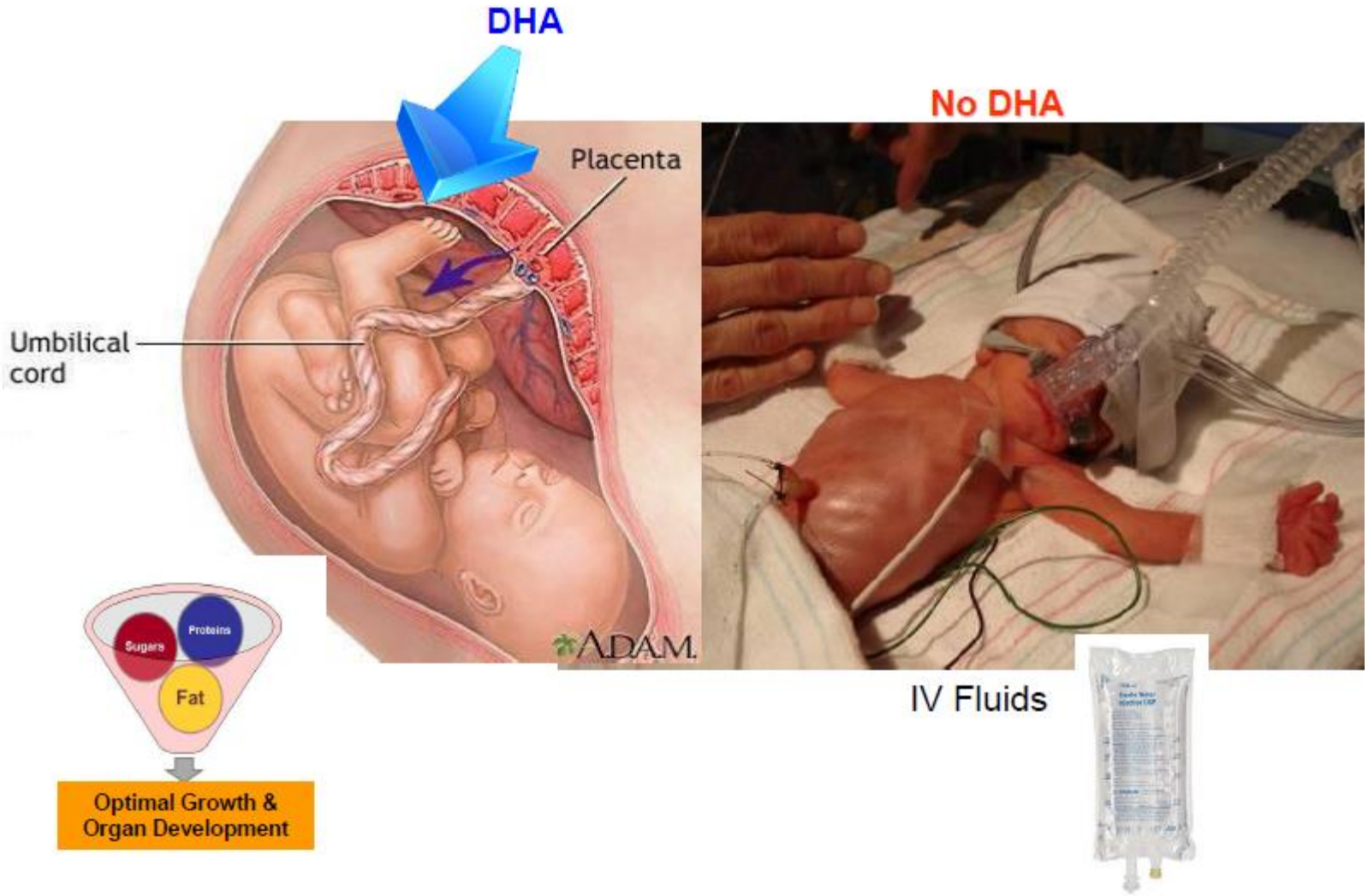
ASAP—As Soon As Possible. No studies that show problems starting at 3.0 gm/kg/d.

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

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.)
- For most preterms who are also being advanced on enteral feedings, this is a moving target.
- "Routine" monitoring is for all preterms is not efficacious and /or realistic!



Even if mothers are receiving fish oil or omega 3 supplements, ELBW babies do not receive much milk because of lack of enteral feedings.

Perhaps Improved DHA intake with Newer Parenteral Lipid Emulsions Containing Fish Oil

	Intralipid	**Omegaven**	**SMOF-lipid**	**Lipoplus**
Oil	soybean 100%	**Fish 100%**	Soy 30 Olive 25% Coconut 30% **Fish 15%**	Soy 40% Coconut 50% **Fish 10%**
Linoleic	**44 – 62**	**0.1 - 0.7**	**22**	**24.5**
Linolenic	4 – 11	0.2	2	3.5
Palmitic	7 – 14	0.25 - 1.0	10	6
Oleic	19 – 30	0.6 - 1.3	31	8
DHA	**0**	**1.4 - 3.1**	**2**	**2.5**
Alpha-Tocopherol	38 mg/dL	150-296 mg/dL	?	?
Phytosterols	**348 mg/L**	**0**	**?**	**?**

Kasmi E, et al. Phytosterols promote liver injury and Kupffer cell activation in parenteral nutrition-associated liver disease. Sci Transl Med 2013;5:206.

Original Communication

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Short-Term Use of Parenteral Nutrition With a Lipid Emulsion Containing a Mixture of Soybean Oil, Olive Oil, Medium-Chain Triglycerides, and Fish Oil: A Randomized Double-Blind Study in Preterm Infants

Maissa Rayyan, MD[1]; Hugo Devlieger, MD, PhD[1]; Frank Jochum, MD, PhD[2]; and Karel Allegaert, MD, PhD[1]

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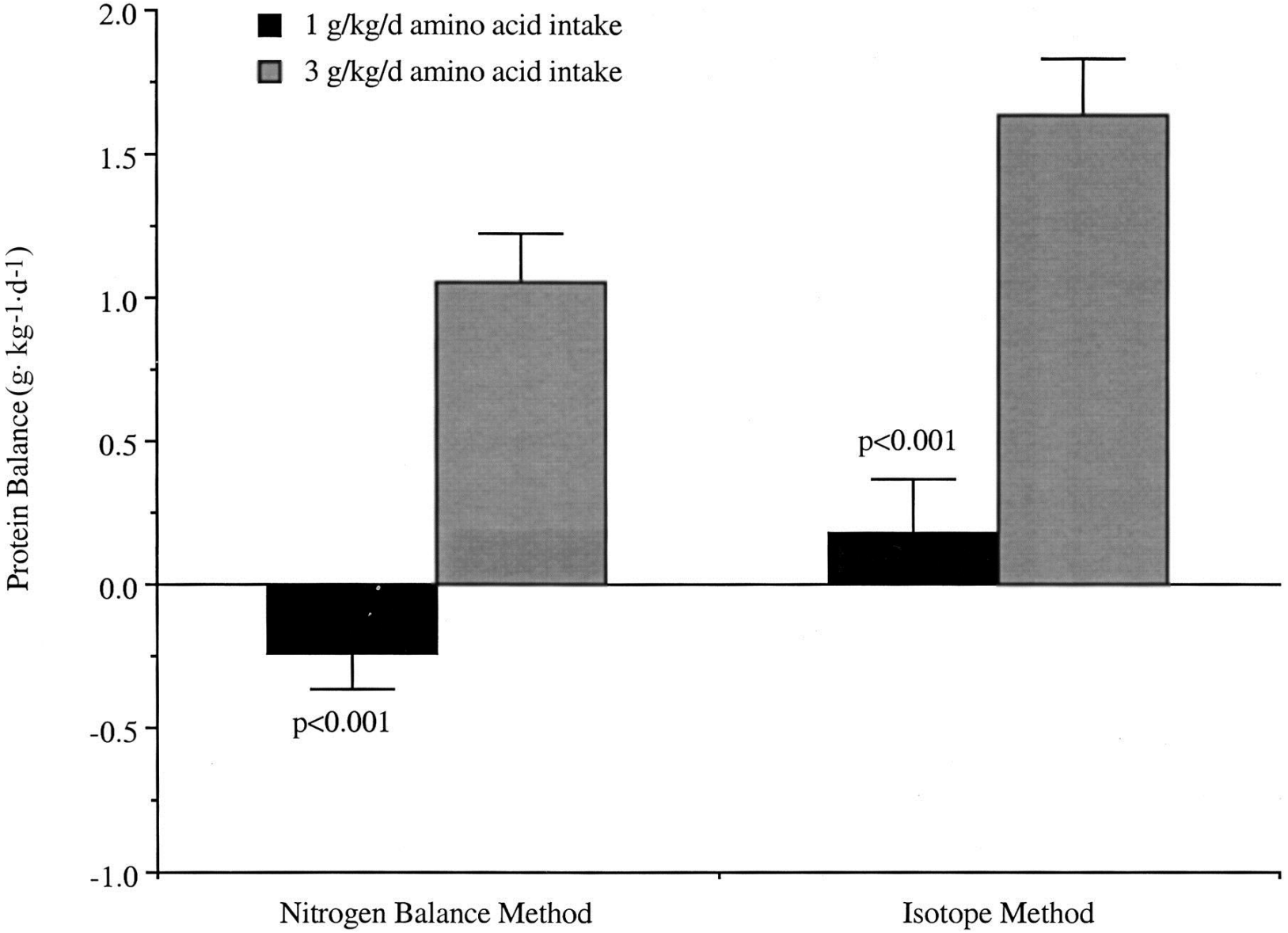
Background: For premature neonates needing parenteral nutrition (PN), a balanced lipid supply is crucial. The authors hypothesized that a lipid emulsion containing medium-chain triglycerides (MCTs) and soybean, olive, and fish oils would be as safe and well tolerated as a soybean emulsion while beneficially influencing the fatty acid profile. *Methods:* Double-blind, controlled study in 53 neonates (<34 weeks' gestation) randomized to receive at least 7 days of PN containing either an emulsion of MCTs and soybean, olive, and fish oils or a soybean oil emulsion. Target lipid dosage was 1.0 g fat/kg body weight [BW]/d on days 1–3, 2 g/kg BW/d on day 4, 3 g/kg BW/d on day 5, and 3.5 g/kg BW/d on days 6–14. *Results:* Test emulsion vs control, mean ± SD: baseline triglyceride concentrations were 0.52 ± 0.16 vs 0.54 ± 0.19 mmol/L and increased similarly in both groups to 0.69 ± 0.38 vs 0.67 ± 0.36 on day 8 of treatment ($P = .781$ for change). A significantly higher decrease in total and direct bilirubin vs baseline was seen in the test group compared with the control group ($P < .05$ between groups). In plasma and red blood cell phospholipids, eicosapentaenoic acid and docosahexaenoic acid were higher, and the n-6/n-3 fatty acid ratio was lower in the test group ($P < .05$ vs control). *Conclusions:* The lipid emulsion, based on a mixture of MCTs and soybean, olive, and fish oils, was safe and well tolerated by preterm infants while beneficially modulating the fatty acid profile. (*JPEN J Parenter Enteral Nutr.* 2012;36:81S-94S)

Keywords: parenteral nutrition; premature infant; fish oils; triglycerides; liver function; fatty acids

Amino Acids

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



Thureen,et al. Peds Research, 2003

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?

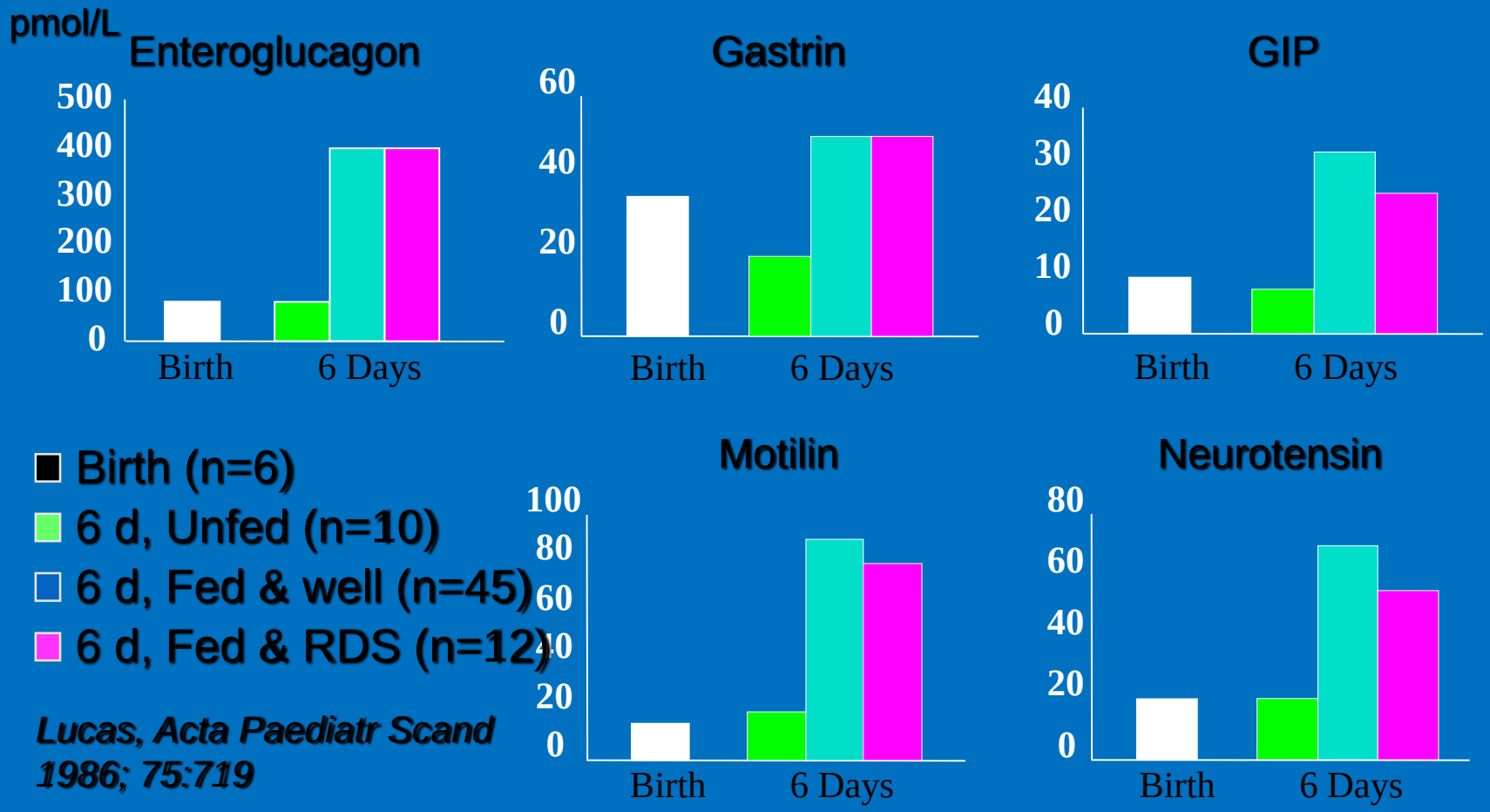
Dr. Elsie Widdowson (1906-2000)

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

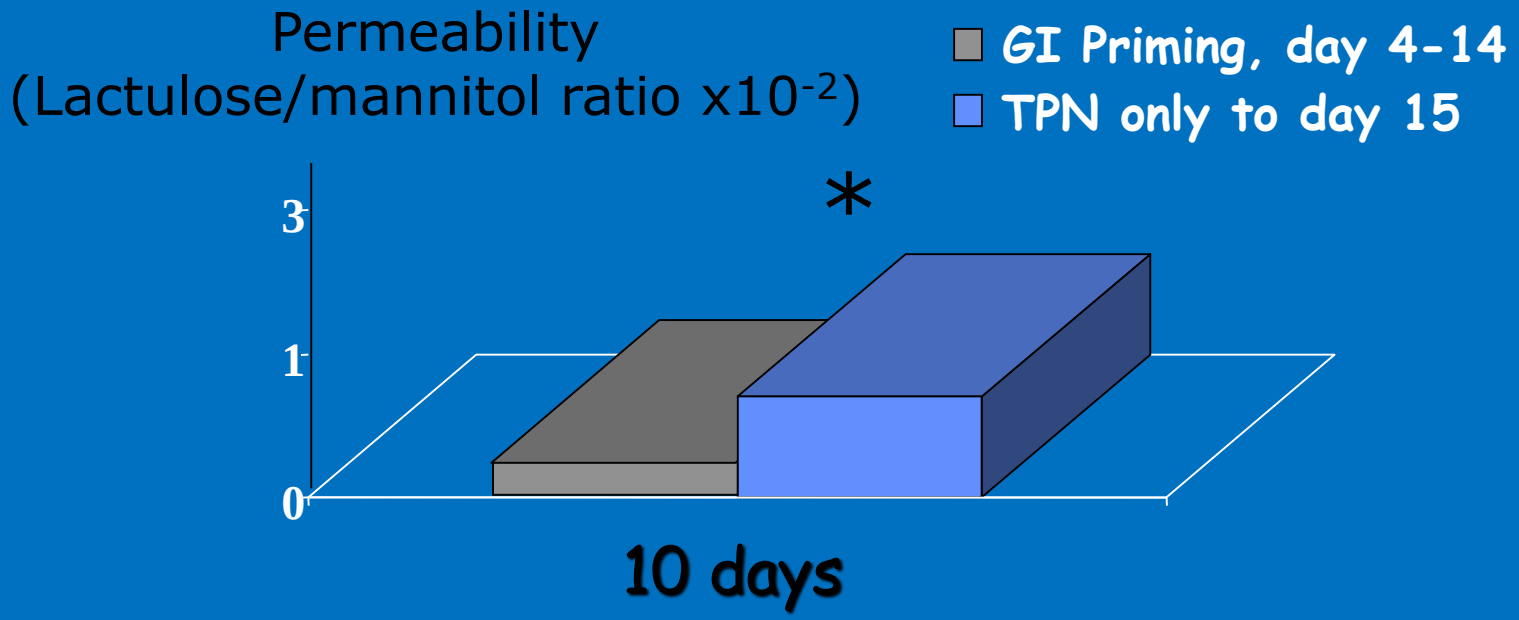
Plasma [GI Hormone] in Premature Infants



Lucas, Acta Paediatr Scand 1986; 75:719

Effect of GI Priming on Intestinal Permeability

Birth weight 1 kg
Gestational age 28 wk



Shulman et al, Pediatr Res 1998;44:519

PLOS ONE

RESEARCH ARTICLE

Late Enteral Feedings Are Associated with Intestinal Inflammation and Adverse Neonatal Outcomes

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July, 2015

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?

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

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.