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Regulatory implications of nutritional influences on outcomes of preterm birth

Mark Turner, Mary Hise Co-chairs

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Regulatory implications of nutritional influences on outcomes of preterm birth

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Who Receives Parenteral Nutrition In the NICU? (United States)

- Very Low Birth Weight Infants (<1500g) totaling about 55,000 babies per year
- Infants with congenital bowel abnormalities or intestinal perforations
- Infants with infections/sepsis or necrotizing enterocolitis (NEC)
- Infants with major health issues, most notably congenital heart disease

Proceedings From FDA/A.S.P.E.N. Public Workshop: Clinical Trial Design for Intravenous Fat Emulsion Products, October 29, 2013. JPEN J Parenter Enteral Nutr. 2014 Dec 4. DOI: 10.1177/0148607114560825

Goal of Parenteral Nutrition in Preterm Infants

Parenteral Nutrition (PN) may be indicated when oral or enteral nutrition is not possible, insufficient, or contraindicated

The goal of PN in the preterm infant is to provide appropriate nutrient supply to prevent nutrient deficits, growth faltering and to impact other clinical outcomes

Almost all Very Low Birth Weight Infants should receive parenteral nutrition on the first day of life

PN Background

- Parenteral Nutrition (PN) includes the delivery of nutrients that may include up to 40 active pharmaceutical ingredients (APIs)

- These PN APIs are obligate precursors for metabolism in the body which include energy substrates, minerals and other essential nutrients necessary for critical functions that sustain life

- APIs that may be found in Parenteral Nutrition:

Dextrose, Lipids and Essential fatty acids, Amino Acids (Essential and Conditionally Essential), Vitamins A, K, E, D, Vitamin C, Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Biotin, Potassium, Sodium, Chloride, Sulfate, Calcium, Phosphorus, Magnesium, Iron, Copper, Chromium, Manganese, Zinc, etc …

Parenteral Nutrition

- Standardization of PN has demonstrated better provision of nutrition, decreased risk of microbial contamination and improved weight gain versus an individualized approach
- Standardization of nutrition therapy may decrease the incidence of NEC
- Early amino acid delivery is a significant factor in growth and development and therefore may impact long term outcomes (i.e. neurodevelopment)
- Fatty acids impact signal transduction pathways, production of mediator molecules, gene expression regulation and may influence retinopathy of prematurity (ROP)

Parenteral Nutrition Impact

Because these nutrients are essential for metabolic functions, their ability to influence results as a potential confounder in clinical trials should merit further consideration

Lack of standardized nutrition approaches may impact clinical trial design for all neonatology drug development plans

References

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Parenteral Amino Acid Solution in the NICU Opportunities for Growth

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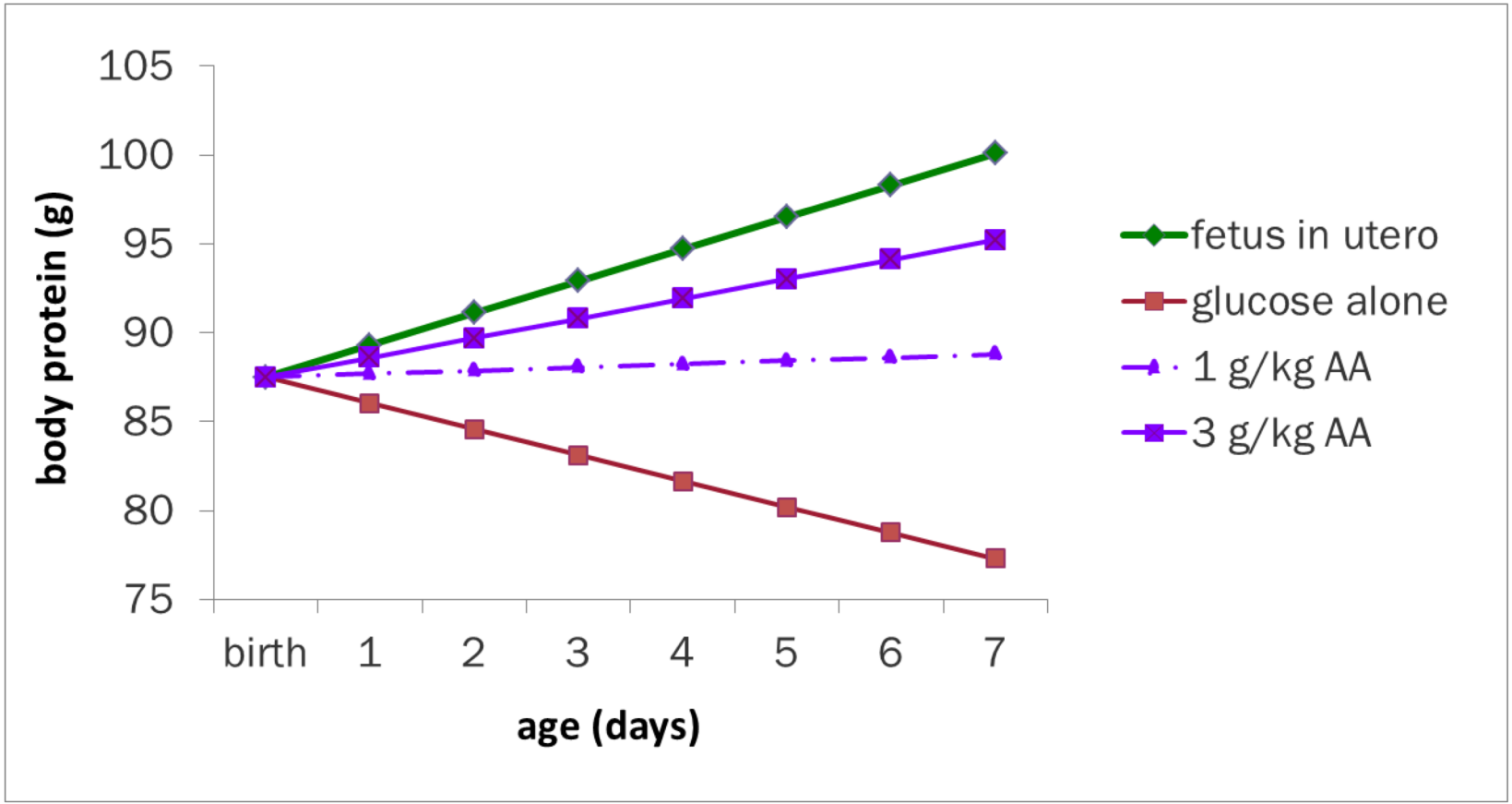
Evidence Supporting Early Parenteral Amino Acids

- Several randomized clinical trials of amino acid dose and advancement strategy to evaluate short-term tolerance, protein balance, and safety
- Good evidence that early deficiencies in protein contribute to poor growth outcomes
- Observational studies have found improved growth outcomes in response to early, more aggressive approach
- Positive correlation between protein intake in the first week of life and Bayley MDI at 18 months

Parenteral AAs Minimize Protein Losses in ELBW Infants



3 Generations of AA Solutions

- 3 “generations” of development
  - Casein hydrolysates
  - Crystalline AA mixtures
    (Aminosyn, FreAmine III, Travasol)
  - Special pediatric preparations
    (Aminosyn PF, TrophAmine, Premasol, Primene)
    **none specifically designed for the ELBW infant

Composition of Parenteral AA Solutions

	Aminosyn-PF	TrophAmine Premasol	Primene
Histidine	312	480	380
Isoleucine	760	820	670
Leucine	1200	1400	1000
Lysine	677	820	1100
Methionine	180	340	240
Phenylalanine	427	480	420
Threonine	512	420	370
Tryptophan	180	200	200
Valine	673	780	760
Alanine	698	540	800
Arginine	1227	1200	840
Proline	812	680	300
Serine	495	380	400
Taurine	70	25	60
Tyrosine	44	240†	45
Glycine	385	360	400
Cysteine	—	<16	189
Glutamic Acid	820	500	1000
Aspartic Acid	527	320	600

- TrophAmine/Premasol – developed to match plasma AA of term, breastfed infants
- Primene – developed to match fetal and neonatal cord blood levels; available outside U.S.

Quality of AA Solutions

- Protein accretion depends on providing the “perfect balance” of amino acids – deficiency of one essential AA could limit overall protein synthesis
- “Conditionally essential” amino acids in premature infants include cysteine, tyrosine, arginine, glycine, histidine, and possibly glutamine

Plasma Amino Acid Concentrations – Reference Studies

Setting	Population	*n*	Ref
Standard AA vs early/high AA	≤ 1000 g	62	Blanco 2011
RCT of parenteral glutamine (TrophAmine)	≤ 1000 g	141	Poindexter 2003
1 vs 3 g AAs	≤ 1300 g	28	Thureen 2003
Human milk (± HMF)	preterm	14	Kashyap 1990
Cord blood	29 wks GA	8	Pittard 1988
Receiving TrophAmine	LBW	28	Heird 1988
Human milk fed	term	16	Wu 1986

Approaches to Determine AA Requirements

- Intake of fetus at similar gestational age
- Cord blood measurements of amino acids (term infants at time of elective cesarean section)
- Factorial approach
- Human milk approach
- Clinical studies with growth, anthropometrics, nitrogen balance, whole body nitrogen kinetics, specific amino acid kinetics

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Regulatory implications of nutritional influences on outcomes of preterm birth

PN in premature infants – Recent issues

Thibault Senterre (Liege University Hospital)

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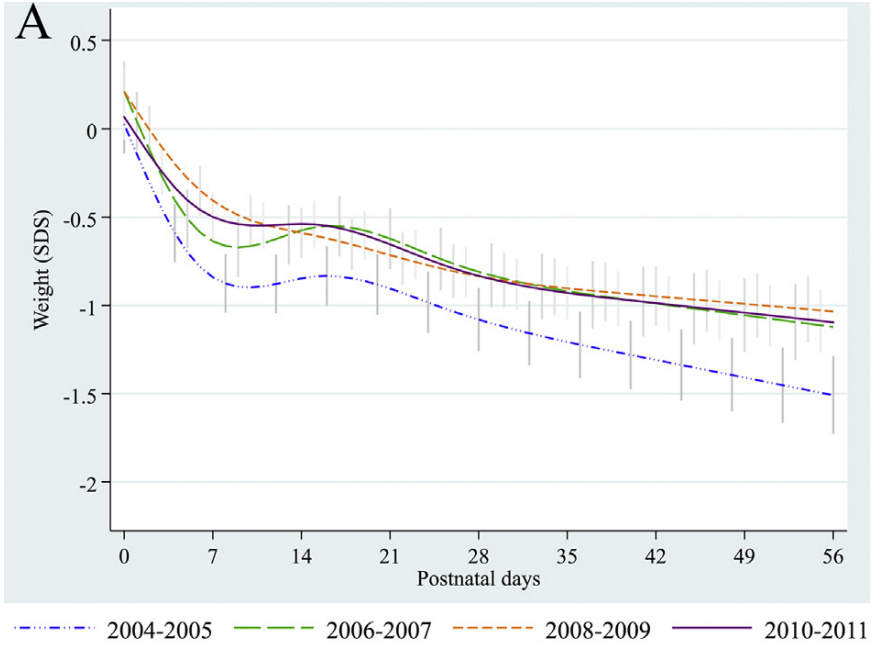
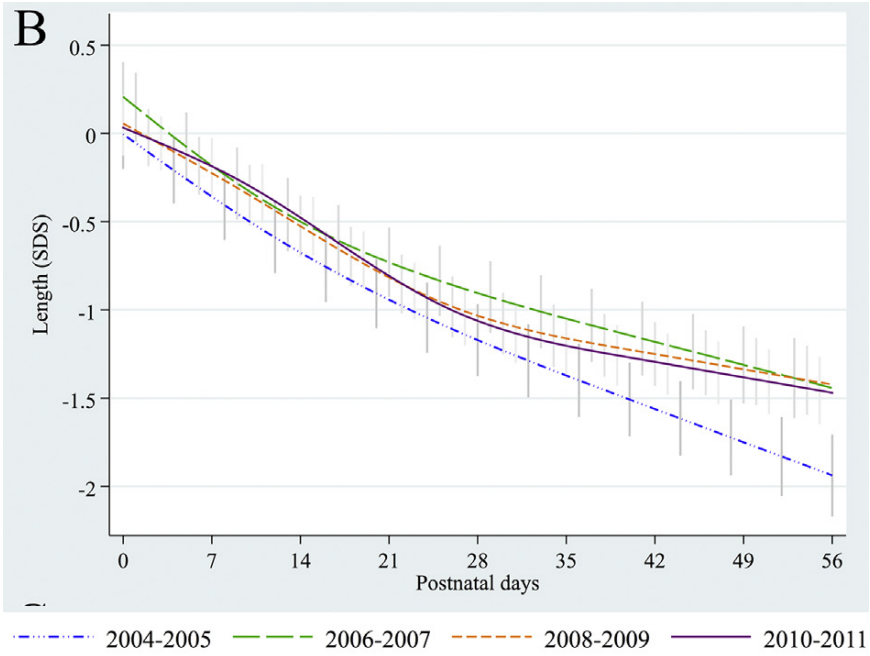
Westin et al. Clin Nutr ESPEN 2018

- A population based observational study in extremely premature infants (<27 weeks)

- Enhanced focus, education of personnel, and facilitating software had a combined impact leading to
  - increased nutritional intake from 2004 to 2011
  - improved growth
- However,
  - Most infants born during the later years still did not reach the recommended macronutrient intake levels
  - Significant PNGR remains an important issue during NICU stay

Westin et al. Clin Nutr ESPEN 2018





Iacobelli et al. BMC Pediatr 2015

- An assessment of compliance to nutrition guidelines in moderately premature infants (30-33 weeks)

➢ Nutritional practice intentions and actual intake were not in compliance with recommendations

=> Undernutrition during the first weeks of life

➢ Poor growth remains an important issue

- ➢ **36.7%** of moderately premature were SGA at 36 weeks PMA
- ➢ In former AGA infants at birth, **24.2%** were SGA at 36 weeks PMA

Fenton et al. Pediatrics 2017

- A systematic review on studies that measured growth as a main outcome in preterm neonates

- ➢ A variety of methods (units, calculation, references, period) were used
- ➢ Variable definitions were used for growth restriction
- ➢ The lack of standardization makes comparisons between studies difficult and presents an obstacle to using research results to guide clinical practice

Beauport et al. J Pediatr 2017

- Retrospective study to investigate the association between early nutritional intake and brain development assessed by magnetic resonance imaging (MRI) in very preterm infants

➢ Energy intakes were lower than recommended, especially lipid intakes

➢ Undernutrition (low energy and low lipid intakes) during the first 2 weeks after birth was associated with a higher incidence of brain lesions and dysmaturation at term equivalent age in preterm neonates

Intravenous lipid emulsion - LCPUFAs

- ω-6 linoleic acid (LA) and ω-3 α-linolenic acid (ALA) are the two EFAs for human
  - High ω-6 LC-PUFA in IV LE have proinflammatory and prooxidative effects and include high phytosterol content

- ω-6 arachidonic acid (AA) and ω-3 docosahexaenoic acid (DHA) are now recognized as conditionally EFAs in premature infants
  - They are essential for normal structural and functional development of the fetus
  - They influence immune responses and inflammation processes
  - They are selectively transferred from the mother to the fetus during gestation
  - AA and DHA are lacking in commonly used IV LE use for PN in premature infants
  - The resultant deficiency is thought to contribute to prematurity related morbidities

Biagetti et al. Clin Nutr 2016

- RCT to assess the effect of 10% FO LE on lipogenesis in VLBW infants
  - 50% MCT, 40% SO, and 10% FO (Lipidem®; B. Braun, Milan, Italy)
  - 50% MCT, 50% SO (Lipofundin MCT®; B. Braun)

➢ Cholesterol biosynthesis was not affected

➢ 10% FO caused a statistically significant reduction in the lipogenesis of selected fatty acids and an overall tendency towards a reduced lipogenesis.

➢ The magnitude seems to be limited and the biological significance is unknown

Najm et al. Clin Nutr ESPEN 2017

- RCT to assess the effect of 15% FO LE on PUFA profiles, growth and morbidities in EPT infants
  - 30% SO, 30% MCT, 25% OO, and 15% FO (SMOFlipid®)
  - 80% OO, 20% SO (Clinoleic®)

➢ Treatment groups did not differ in ROP, othermorbidities or growth

➢ SMOFlipid® induced
  - ➢ Higher fractions of ω-3 LCPUFAs eicosapentaenoic acid (EPA)
  - ➢ Slightly higher DHA fraction
  - ➢ Lower ARA with lower ARA:DHA ratio

Senterre et al. J Pediatr Gastroenterol Nutr 2011 and 2015

- The benefits of standardized PN solution in VLBW infants

- ➢ Improved protein and energy intakes meeting guidelines from day 4-5
- ➢ Low PNGR rate (**6%** of AGA became SGA)
- ➢ Optimizing nutritional intakes with a balanced standardized PN solution may improve electrolyte and mineral homeostasis in VLBW infants
- ➢ These data, in addition with some other recent publications, suggest that PN guidelines for VLBW infants need to be revised, especially during the first week of life
  - ➢ Higher P with Ca:P ratio ~1 (mmol/mmol) - higher K - higher Na
  - ➢ It will be included in future EU PN guidelines (Clinical Nutrition 2018)

Potential question

- Do you think including standardized nutritional data (i.e. parenteral and enteral intakes, blood homeostasis, growth) in premature infant studies in addition of other morbidities might be necessary and/or beneficial to interpret relevant clinical outcomes?

  A. I agree, it should be a #1 priority for an INC workshop

  B. I agree, it should be a #2 priority for an INC workshop

  C. I do not agree

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Thank you for your attention

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Impact of nutrition on long term outcomes in very-low-birth-weight infants: Japanese experience

Satoshi Kusuda (Kyorin University, Japan)

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Background and Aim

- It is frequently difficult to give nutrition enterally in very-low-birth-weight (VLBW) infants. Thus, parenteral nutrition may have potential benefits on short and long term outcomes. However, there is very little scientific evidence that the infants received parenteral nutrition show better outcomes.

- The objective of this study is to determine whether parenteral nutrition is associated with improved outcomes in VLBW infants using a neonatal database in Japan.

Methods

- Subjects: VLBW infants registered on the network database in Neonatal Research Network of Japan
- Inclusion criteria: Born between 2003 and 2012, and at less than 32 GW
- Study method: Retrospective case-control study
- Definition:

Parenteral nutrition: intravenous fluid containing glucose and amino acids together with lipid infusion

NDI (neurodevelopmental impairment):

Any of following disabilities assessed between 1 and 3 years old

visual impairment more than amblyopia

hearing loss needs hearing aid

cognitive impairment DQ less than 70

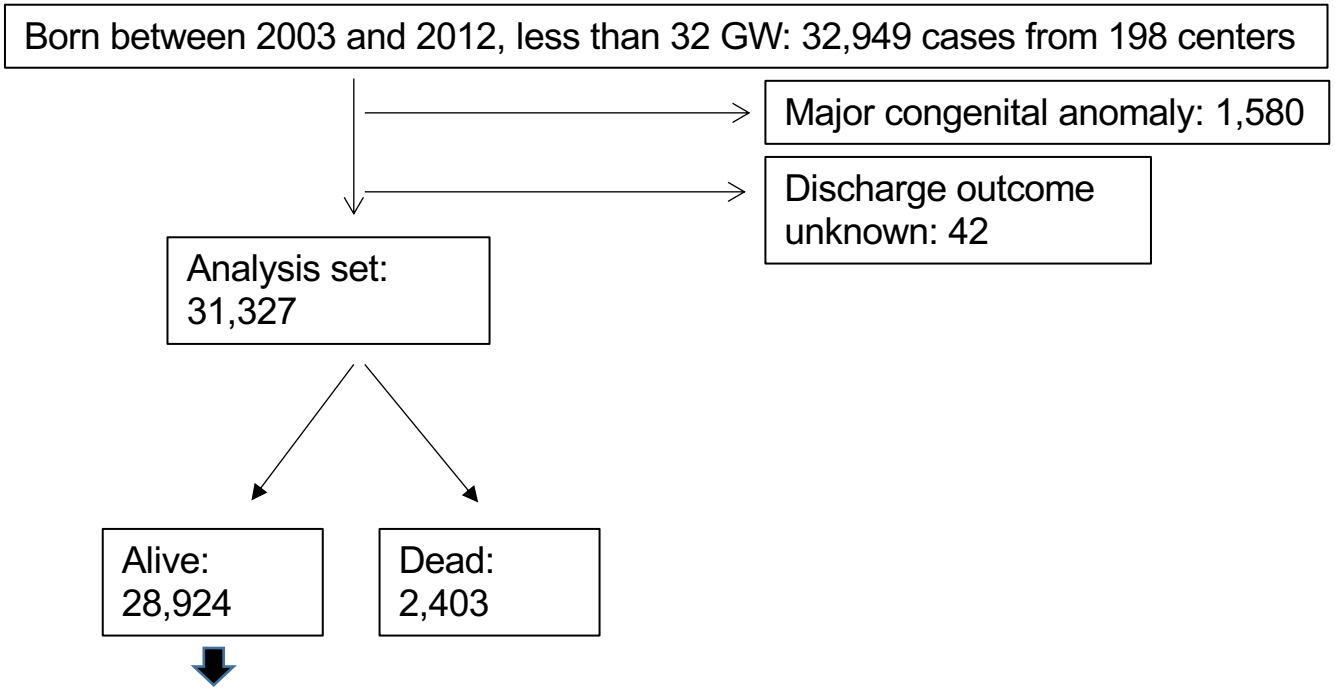
cerebral palsy

Statistical analyses

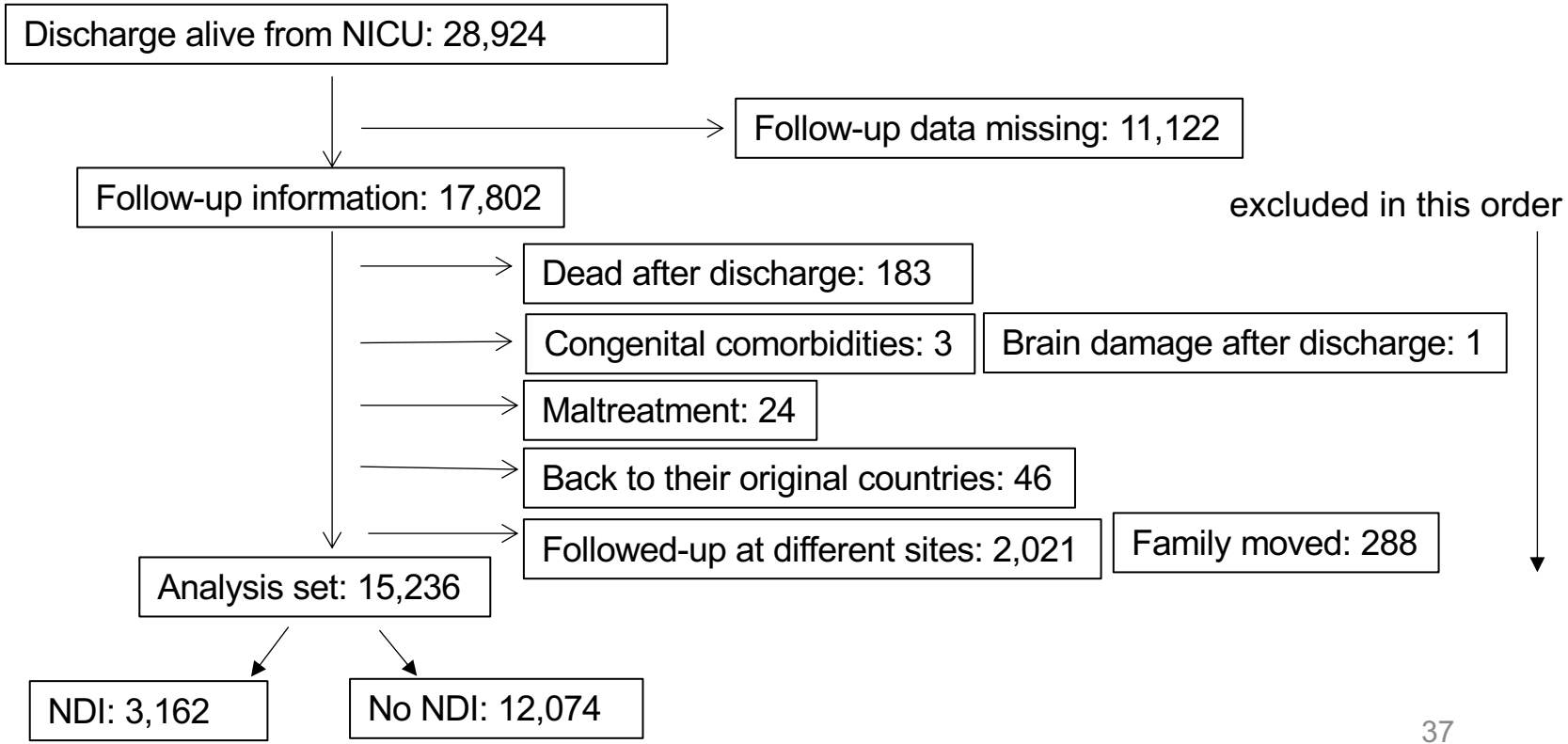
- Statistical methods
  - Chi-square test
  - Multivariable logistic analysis
  - Mantel-Haenszel test for trend
  - Mantel-Haenszel estimate for a odds ratio

- Risk adjustment
  - year, site, antenatal steroid, gender, GW, LFD, Apgar, RDS, CLD, PDA, IVH, PVL, Sepsis, NEC
  - propensity score for NDI

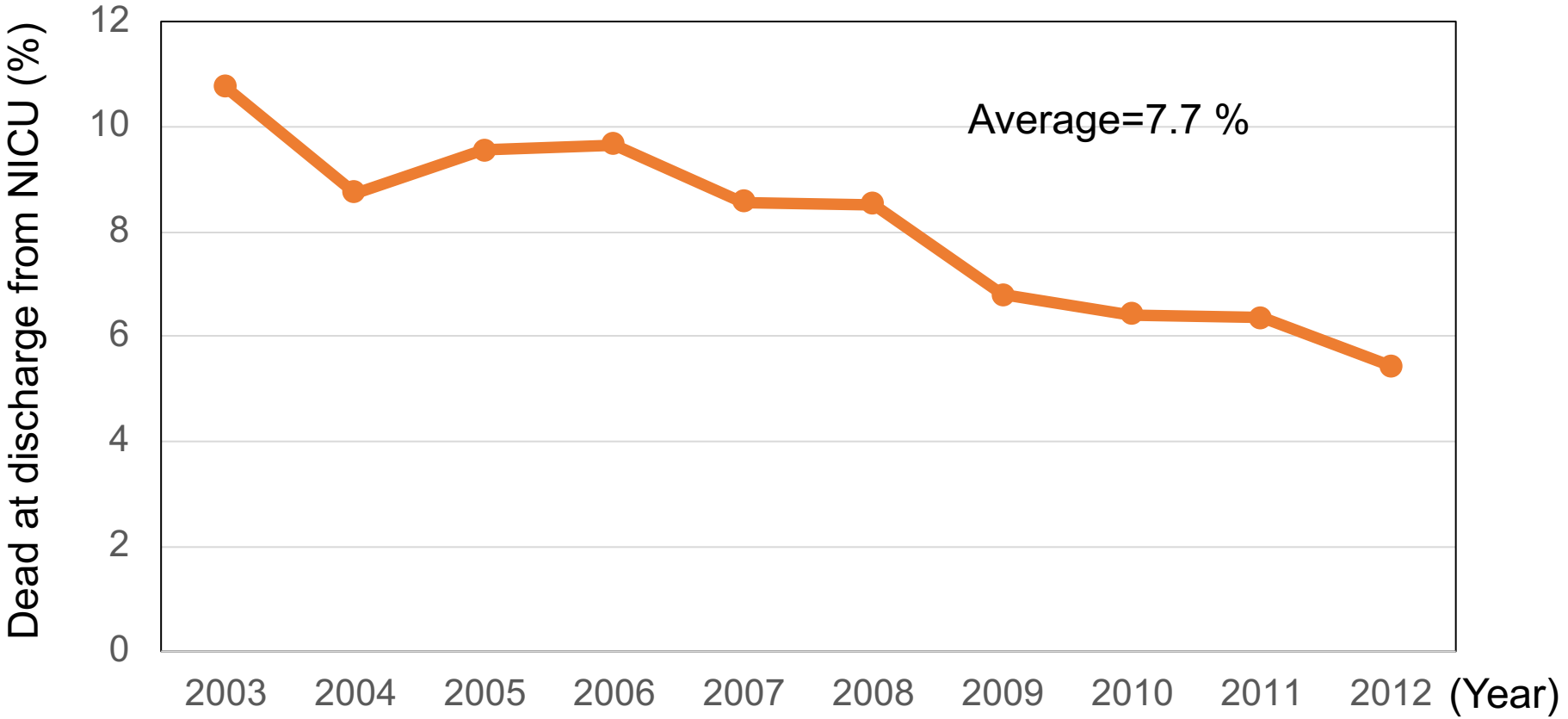
Short term outcome



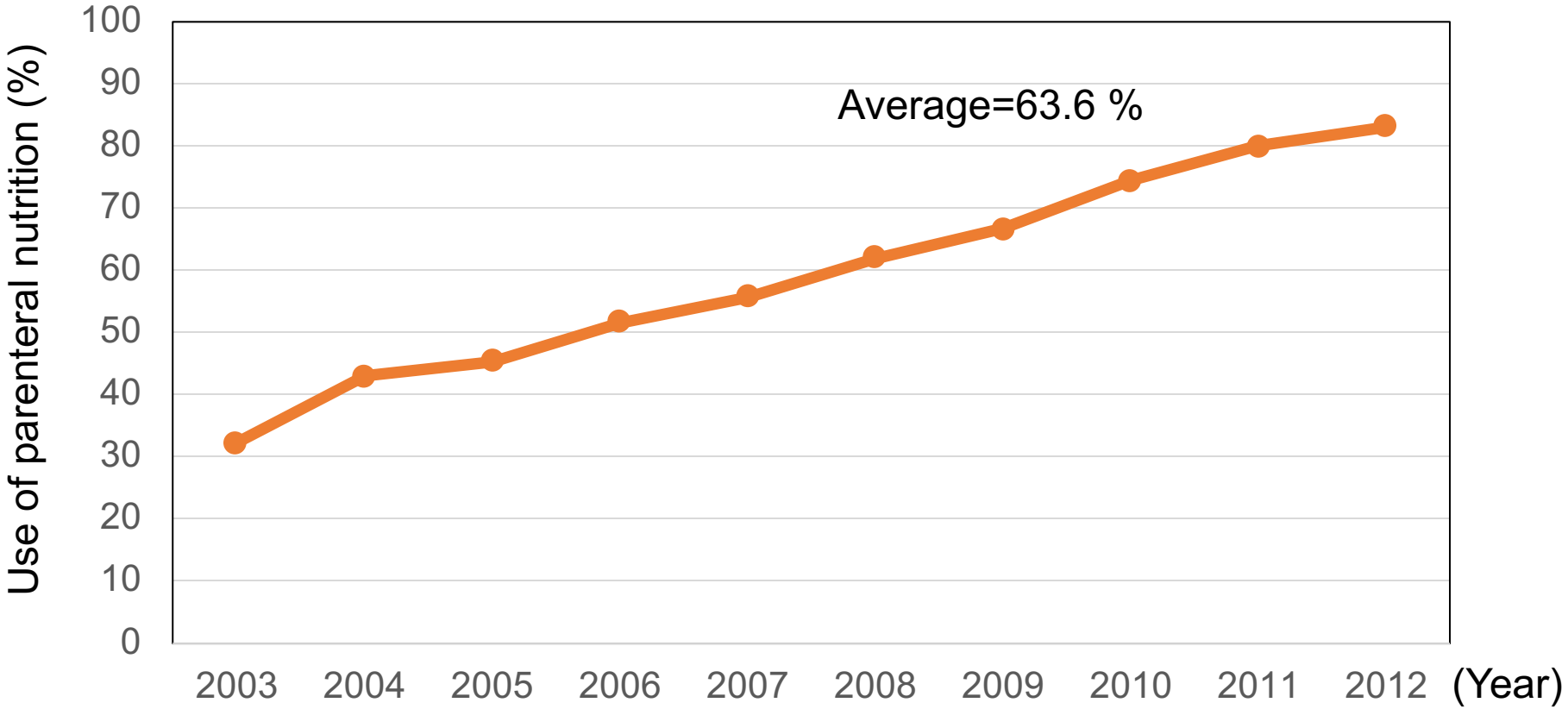
Long term outcome



Trends in survival rate



ResultsTrends in usage of parenteral nutrition



Short term outcome

	Dead at discharge		Mortality (%)
Parenteral nutrition	-	+	
+	18735	1205	6.0
-	10189	1198	10.5

Dead at discharge						
	Crude			Adjusted		
Parenteral nutrition	0.55	(0.504	0.595)	0.276	(0.245	0.311)

Long term outcome

	NDI		NDI(%)
Parenteral nutrition	-	+	
+	8108	2309	22.2
-	3966	853	17.7

NDI									
	Crude			Risk adjusted			Propensity score adjusted		
Parenteral nutrition	1.324	(1.213	1.445)	0.89	(0.802	0.988)	0.905	(0.822	0.997)

Conclusions

- Impact of parenteral nutrition on short and long term outcomes evaluated using Japanese network database.
- Difficult to show short term benefits.
- Some significant benefit on neurodevelopmental outcomes.
- Many cofounders on outcomes

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Infant Formula Regulation

Andrea Lotze (FDA)

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Infant Formula Regulation

- Federal Food, Drug, and Cosmetic Act established a new section 412 (21 U.S.C. 350a) and created a separate category of food designated as infant formula in 1980 and amended in 1986

- June 10, 2014 Publication of the Infant Formula Final Rule Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula final rule was published
  - https://www.federalregister.gov/articles/2014/06/10/2014-13384/current-good-manufacturing-practices-quality-control-procedures-quality-factors-notification

Infant Formula Act Regulatory Categories

- **Non-exempt**
  - Term infants
- **Exempt**
  - Low birth weight (preterm)
  - Inborn errors of metabolism
  - Unusual medical or dietary problem

Exempt Infant Formulas

- Exempt infant formulas (21 CFR 107.50)
- Exempt from specific nutrient requirements due to specific disease states
- Age of use less than 12 months
- Regulated as an exempt infant formula

Typical Products Available in the NICUs

- Products designed to meet the nutritional needs of “low birth weight” infants who are often preterm infants
- Products have a higher levels of specific nutrients
- Some of these nutrients exceed the regulatory maximum levels and an exemption must be requested
- If an exemption is requested, the manufacturer must provide the medical, nutritional, scientific or technological rationale for the difference from the nutrient requirements

Exempt Infant Formulas

- NICU products for preterm infants are manufactured by
  - Abbott, Mead Johnson, Nestle
- Caloric range from 20 kcal/oz to 30 kcal/oz
- Higher levels of protein per 100 kcal
- Higher levels of specific nutrients per 100 kcal

Maximum level per 100 kcal

- Maximum levels for protein, fat, vitamins A, vitamin D, iodine, iron, sodium, potassium, chloride and selenium
- Protein 4.5g
- Vitamin A 750 IU
- Vitamin D 100 IU
- Iron 3 mg
- Calcium and Phosphorus: No maximum
    - ratio must be no less than 1:1 and no greater than 2

Fortifiers:

- Liquid fortifiers: sterile, for human milk
  - Extensively hydrolyzed protein (Abbott)
  - Acidified (Mead Johnson)
  - Human Milk (Prolacta)

Summary

- Infant formula is the most regulated of all foods
  - 90-day pre-market notification **not** pre-market approval
  - Review of product and its label/labeling
  - Meets the requirements for an exempt infant formula under 21 CFR 107.50
  - FDA has recall authority
  - Annual inspection of all infant formula plants

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Regulatory Considerations for Neonatal Parenteral Nutrition Products

Suna Seo MD MSc
Division of Gastroenterology and Inborn Errors Products
Center for Drug Evaluation and Research
Food and Drug Administration

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Disclaimer

- The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA
- I have no financial relationships to disclose related to this presentation

Evidentiary Standard for Effectiveness

- Substantial evidence of benefit requires adequate and well-controlled clinical studies (§314.126)
- Study is designed well enough "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation" (§314.126)

Adequate and Well-Controlled Studies

- Studies that have been designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation" (21 CFR 314.126)

- Adequate and well-controlled trials have:
  - Clear statement of purpose
  - Appropriate control for valid comparison
  - Appropriate selection of subjects
  - Appropriate assignment of subjects to treatment and control
  - Adequate measures to minimize bias
  - Well-defined and reliable methods of assessing response
  - Prospectively planned analyses

Defining Clinical Benefit

- Clinical benefit is a favorable effect on a meaningful aspect of how a patient ***feels***, ***functions,*** or ***survives*** as a result of treatment.

Nutritional Indications Regulatory Paradigms

Treatment	Prevention	Source of Nutrition

Benefit – Risk Assessment

- Clinical reviews of products at FDA are centered on the **balance** between **potential benefit** for a specific indication and **potential risk** of using the product

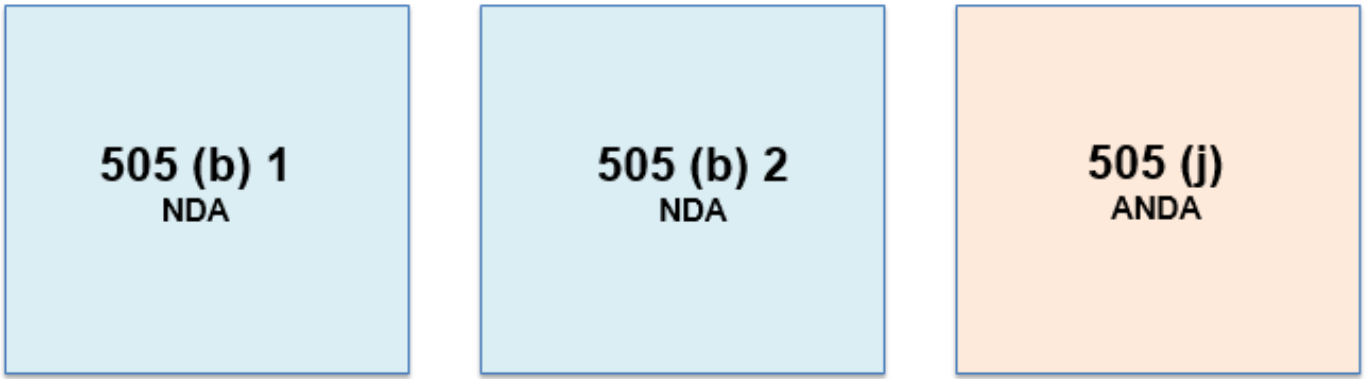
Regulation on Parenteral Products

- CFR 21 Section 310.509(a)
  - Any parenteral drug product packaged in a plastic immediate container is a “new drug”

New Drug Applications - Regulatory Pathways

Food, Drug & Cosmetic Act

Chapter V (Drugs and Devices), Part A (Drugs and Devices)



505(b)2 Applications

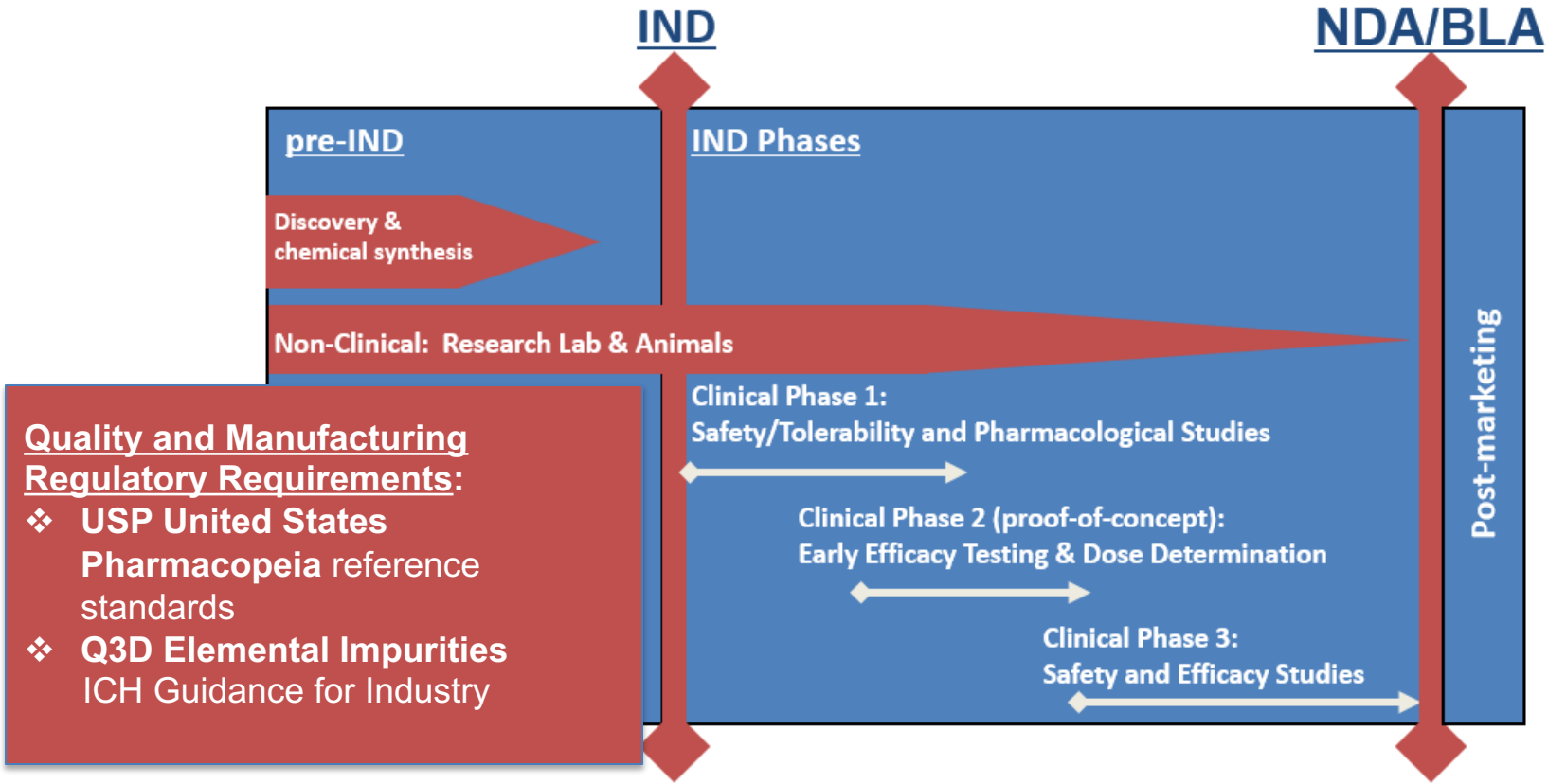
- Approval standards are the same
- Reliance on:
  - Finding of safety and effectiveness for a listed drug(s)
    - Cannot rely on drugs approved outside the US
  - Published literature
    - General recognition of safety and effectiveness is inadequate

(21 U.S.C. 355(b)(2))

Challenges with Parenteral Products

- Marketed unapproved products with no approved formulations
- Long history of use in clinical practice
- Literature based evidence of efficacy and safety

New Drug Development Process



https://www.fda.gov/downloads/drugs/guidances/ucm371025.pdf

Clinical Trial Considerations for Nutritional Products

Efficacy

- Source of calories
- Source of nutritional support
- Growth
- Treatment of deficiency
- Prevention of deficiency

Safety

- Specific disease population
- Short term adverse events
- Long term adverse events


FDA
U.S. FOOD & DRUG
ADMINISTRATION

21 CFR 300.50

Fixed Combination Prescription Drugs for Humans

- Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects
- The dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy
- Often factorial studies are needed to show the contribution of each component of a fixed-combination drug
- The current rule is being proposed for revision. Although not yet finalized, the preamble to the proposed rule in the Federal Register notice describes FDA's longstanding policy on how applicants can demonstrate the contribution of each component

https://www.federalregister.gov/articles/2015/12/23/2015-32246/fixed-combination-andco-packaged-drugs-applications-for-approval-and-combinations-of-active

Statutory Background: PREA

- PREA applies for submissions involving a
  - new active ingredient,
  - new indication,
  - new dosage form,
  - new dosing regimen, or
  - new route of administration
- Sponsors are required to provide a pediatric assessment (using an age-appropriate formulation) to support dosing, safety, and effectiveness for the claimed indication for all pediatric ages, unless this requirement is waived or deferred.

Goals from Scientific and Policy Perspective

- Preserve the intent and availability of an abbreviated licensure pathway for biological products
- Preserve the intent of PREA
- Ensure that a proposed biosimilar and the reference product:
  - Is fully labeled for all relevant pediatric populations
  - Is available in age appropriate formulations for relevant pediatric subpopulations where appropriate
- Consistent approach to pediatric labeling across review divisions

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Johannes Taminiau
PDCO-EMA
Pediatric gastroenterologist

Bethesda 12 April 2018

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Questions in premature babies

- ***Question 1:***
- Does knowledge of body composition make a difference in nutrition guidance.
- Does knowledge of body composition make a difference in drug prescription.
- ***Question 2:***
- Does the use of GI function tests improve nutrition
- Does the use of GI function tests improve drug prescription

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Premature babies drug studies
BW as co-variate
Body weight and body composition

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EMA Body weight < 1500 gr influence on drug studies

- BW as co-variate
- Drug studies show discrepancy between BW and age (PCA-PNA) in PK/PD data

- How to study:
  - Age range from 500 grams upwards (low end of large cohort)
  - Pop-PK
  - Assessment of inflammatory status (CRP)
    - Assessment of metabolism (CYP)
  - Genetic variation (Morphine metabolism)
  - ARC

Body weight in less than 1500 gram premature baby

Body weight highly variable in composition in premature babies

Body composition measurement:

Impedance Plethysmography from 1000-1500 gr if three minutes without oxygen

BIA too much fluctuation of extracellular water

DEXA from term

MRI neonatal incubators mainly for abdominal fat, Incr-AA vs Imm-RDA no difference

Indirect methods:

Indirect calorimetry with stable isotope protein synthesis

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Assessment of gastro intestinal function

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PN Fasting: Observations in premature babies

Fasting versus early enteral feeding:

No difference with early and late introduction of tube feeding on NEC

Low arginine and citrulline (measure of small bowel functional area) in premature babies with NEC

PN and microbiome: Staphylococci presence, risks?

Lipid emulsion <72 hours 95% fat absorption (fat intake/fecal fat)

URSO and prevention of PN cholestasis: Early fat feeding induces bile flow, hormonal stimulation of bile flow

Nutrition intervention might be disease modifying

Limitations PN transition to EN

- Nutritional tolerance
  - Clinical symptoms and signs, food residuals
- Nutritional function
  - Food quantity tolerated, no digestive symptoms, weight gain
- GI maturation
  - Delay of normal functions assumed
- Motility
  - Immaturity assumed

Drugs and the gut function in premature babies

GI Maturation knowledge challenged by drug study data

PPI studies normal acid secretion in neonates

GERD studies showed normal gastric emptying

So far drugs targeting GI Maturation or GI function like digestion, absorption, secretion, are limitedly investigated, like BW, reduction PN, fecal fat

Strength of primary endpoint, failed studies?

Drug transporters in the gut are equal, less or more active in neonates, although in premature babies no data

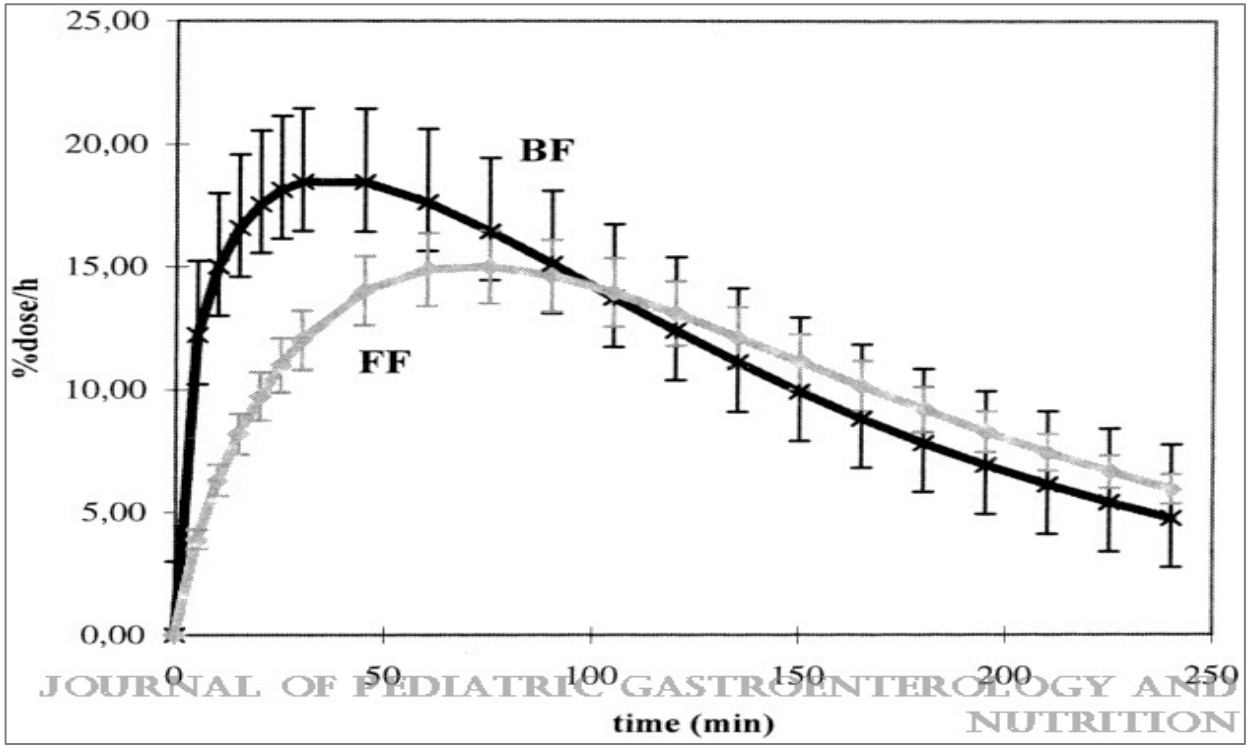
No CYP3A4 activity in the gut, low in the liver leading to higher systemic drug exposure

High variability due to gut length data, not measured related to surface area

Gastro-intestinal function in premature

- Gastric emptying can be studied with C8 stable isotopes
  - 13C Na-octanoate breath test
  - Residuals do not match gastric emptying
- Stable isotopes are another possibility for lactose, sucrose and malto-dextrin with expired air collected by tube in pharyngeal air, is less well developed, but in principle a mode to test total absorptive small bowel surface area
  - Fasting plasma citrulline, whole gut surface
- Long chain fatty acids mucosal absorption at 32 weeks PCA is decreased compared to a gradual increased level, reaching normal values at 54 weeks PCA. Has to be measured with stable isotope fatty acids in plasma after duodenal absorption in premature neonates
- Fat digestion tested by fecal fat related total intake
  - Stable isotope triglyceride digestion test
  - Stable isotope fatty acid absorption test

Comparative nutritional studies in neonates among infant formulas



[Gastric Emptying in Formula-Fed and Breast-Fed Infants Measured with the 13C-Octanoic Acid Breath Test]

Van Den Driessche, Mieke; Peeters, Kristel; Marien, Paul; Ghoos, Yvo; Devlieger, Hugo; Veereman-Wauters, Gigi
Journal of Pediatric Gastroenterology and Nutrition29(1):46-51, July 1999.
doi:

Mean (SEM) gastric-emptying curves of breast-fed (BF) infants and formula-fed (FF) infants.

Premature babies: 33 weeks GA 17 days PNA

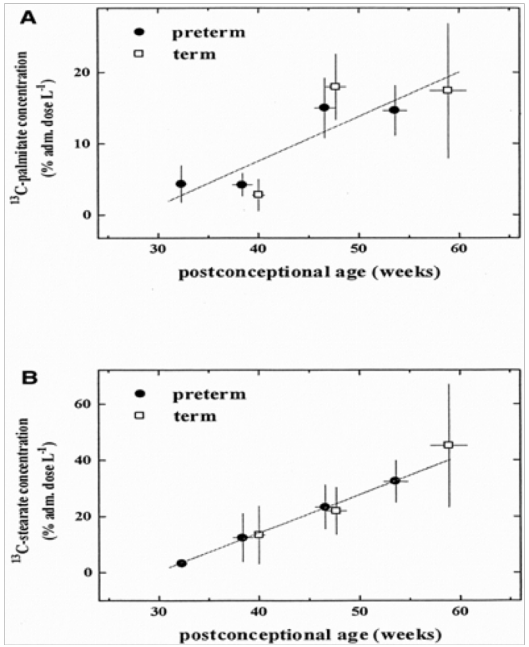
Gastric emptying in GERD

Gastric emptying	Right side	Left Side
Mean T1/2 (min)	34.9 ± 6.9	75.3 ± 5.3
Mean Tmax (min)	22.5 ± 1.6	34.9 ± 2.1
Mean Tlag (min)	60.9 ± 4.3	91.7 ± 4.6
Mean gastric emptying coefficient	3.99 ± 0.22	3.40 ± 0.14

Fat absorption after oral load C13-Palmitic acid as Triacylglycerol and C13-Stearic acid as long chain fatty acids in serum and stools premature and term infants at 40 weeks PCA and 46 weeks PCA to 56 weeks

Triacylglycerol

Long Chain Fatty Acid

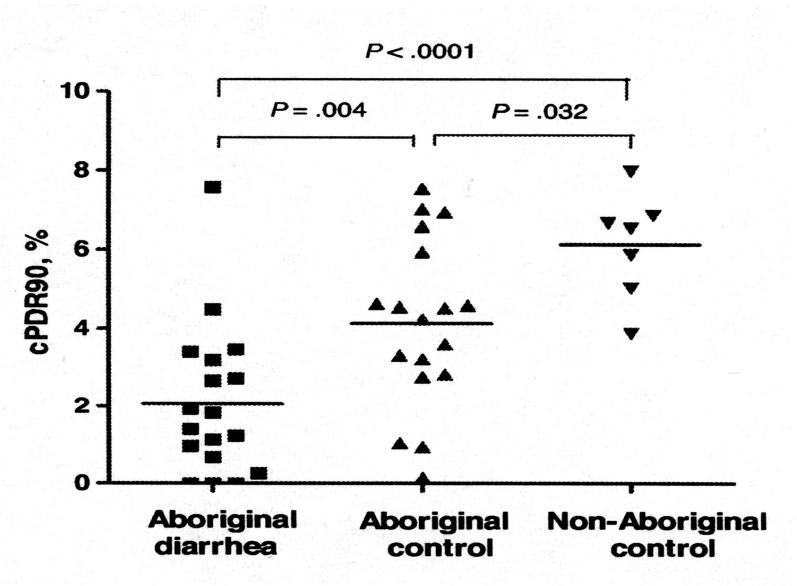


Luminal digestion not limiting factor for digestion
Fatty acid absorption from 91% in prematures to 97% in neonates

Rings E, Verkade HJ 2002

Sucrose breath test to estimate small intestinal villus integrity and functional surface area

cPDR90%= cumulative percentage dose recovery of sucrose at 90 minutes



Ritchie
Pediatrics 2009

Control children do not recover after previous gastro intestinal infections

Effect of omeprazole 0.7 mg/kg on acid GER, gastric acidity, symptom frequency, blood biochemistry and blood picture

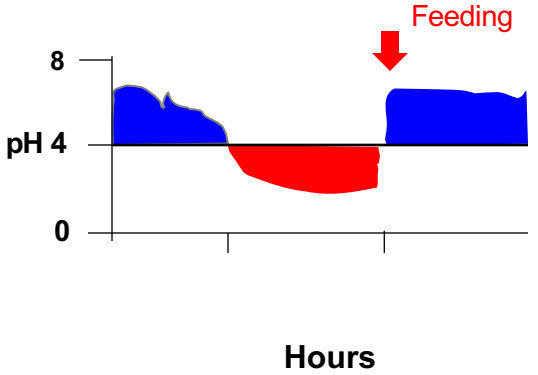
- No

	Placebo week	Omeprazole week
Esophageal pH		
No. acid GER	119.4 ± 20.9	59.6 ± 26.7*
No. acid GER >5 min	8.0 ± 2.1	3.0 ± 2.0**
Longest acid GER, min	48.6 ± 10.1	16.3 ± 8.0**
% time pH <4	19.0 ± 4.5	4.9 ± 3.4**
Gastric pH		
% time pH <4	53.8 ± 6.8	13.9 ± 5.1***
Symptom frequency (no. events)		
Vomiting	8.5 (7, 22.8)	6.5 (3, 14.3)
Apnea	0.4 (0, 1.5)	1 (0, 1.8)
Bradycardia	7.5 (1.3, 17.3)	6.5 (3, 16)
Choking	0 (0, 1)	0 (0.1.8)
Behavioral changes	17 (8.3, 27.8)	16.5 (7.3, 30.1)
Blood biochemistry		
Creatinine (mmol/L)	0.035 ± 0.003	0.037 ± 0.002
Urea (mmol/L)	2.5 ± 0.3	2.5 ± 0.3
Bilirubin total (μmol/L)	25.4 ± 7.8	27.4 ± 12.3
ALT (U/L)	15.5 ± 2.2	15.7 ± 2.5
GGT (U/L)	66.8 ± 14.0	67.4 ± 17.7
Protein totals (g/L)	48.7 ± 2.7	48.8 ± 2.3
Na (mmol/L)	139.3 ± 0.9	140.4 ± 0.9
K (mmol/L)	4.6 ± 0.1	5.1 ± 0.1
Fe (μmol/L)	16.6 ± 1.6	17.0 ± 1.8
Blood picture		
Hgb (g/L)	102.8 ± 8.5	103.9 ± 9.6
PCV	0.3 ± 0.0	0.3 ± 0.0
RBC ($\times 10^{12}$/L)	3.3 ± 0.2	3.4 ± 0.3
WBC ($\times 10^{9}$/L)	8.4 ± 0.9	9.2 ± 1.2
PLTS ($\times 10^{9}$/L)	324.3 ± 46.3	383.6 ± 30.7
Neutrophils ($\times 10^{9}$/L)	2.2 ± 0.3	2.6 ± 0.5
Lymphocytes ($\times 10^{9}$/L)	4.8 ± 0.5	5.3 ± 0.8
Monocytes ($\times 10^{9}$/L)	0.9 ±0.3	0.8 ± 0.1
Eosinophils ($\times 10^{9}$/L)	0.5 ± 0.2	0.4 ± 0.1
Basophils ($\times 10^{9}$/L)	0.0 ± 0.0	0.1 ± 0.0

Data presented as mean ± SEM or median (interquartile range). Paired *t* test: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.0005$. ALT indicates alanine transaminase; GGT, γ-glutamyl-transferase; Hgb, hemoglobin; PCV, packed cell volume; WBC, white blood cell count; PLTS, platelets.

Effect of Omeprazole on Acid Gastroesophageal Reflux and Gastric Acidity in Preterm Infants With Pathological Acid Reflux.
Omari, Taher; Davidson, Geoffrey

Journal of Pediatric Gastroenterology & Nutrition. 44(1):41-44



Message

- Gut function influences drug effects
- Drugs influence gut function

- Nutritional intervention: Measure GI function in relation to maturation
- Oral drugs: Measure maturation in fact gut function

Session Questions

- Can we isolate key questions from the complex topic of neonatal nutrition (if so, which questions)?
- What are the goals of nutritional research (short-term clinically important outcomes or long-term clinically important outcomes)?
- How can nutritional data support research about neonatal morbidities?
- What are the relationships between parenteral and enteral nutrition?
- What do families think about nutritional research?

INC Members – THANK YOU!

Gracias

Takk

Dzięki

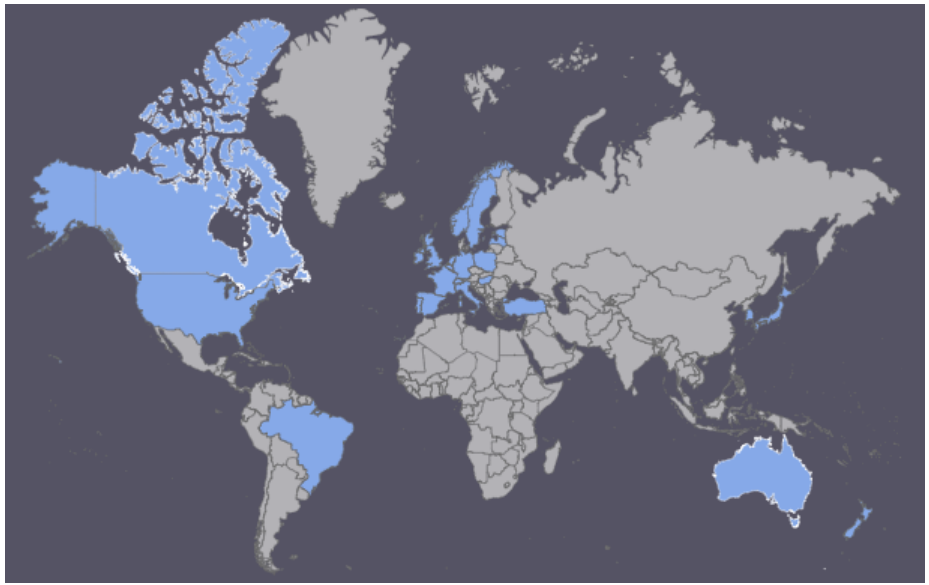
Tänan

Dank u

Paldies

감사합니다

Cheers



Merci

Kia ora

Grazie

Tack

Köszi

Danke

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Obrigado

Teşekkür ederim

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Coffee Break
30 minutes

CRITICAL PATH INSTITUTE

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Thank You

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