How Can Nutrition Support Neonatal Neuro Development & Protection?

The Gut-Brain Axis

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1

Disclosure Statement

- **Disclosure Statement**
  - I am an employee of Prolacta Bioscience
  - I currently present and receive financial reimbursement
    - Prolacta Bioscience
    - Abbott Nutrition Health Institute (ANHI)
- **I personally developed this slide deck for strictly educational purposes and audiences**
  - Images & photographs used in the presentation are from publicly accessed sources
  - It without bias, branding or commercial influence; it is evidenced-based
  - I will make no recommendation for any off-label use of any drug, nutritional, or medical device

2

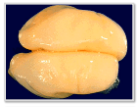
Nutrition: The Gut-Brain Axis

- **Behavioral Objectives**
  - Review the nutritional needs of the fetal/neonatal brain and the growth needs of emerging neurodevelopment.
  - Describe the reduction of two comorbidities of prematurity reduced with early aggressive nutrition.
  - Discuss the benefits of early enteral nutrition and growth and development of the infant's immune system.
  - Identify factors associated with the development of "dysbiosis" in the premature infant gut.
  - Describe the "Gut-Brain Axis" (GBA) and its potential vulnerability in the preterm infant.
  - Identify two benefits of human milk human feeding on modulating intestinal dysbiosis.

3

The Significance of Growth

- **Why *"Significant"* and Not Just *"Important"* ?**
  - Significance implies
    - ***The extent to which something matters"***
    - ***"Unlikely to have occurred by chance"***
    - ***"Implies relative or quantifiable importance"***



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The Significance of Growth

- **The Neonatal Brain**
  - Human infant brain is comparatively underdeveloped

"A human fetus would have to undergo a gestational period of 18 to 21 months to be born at a neurological and cognitive development stage comparable to that of a chimpanzee newborn".

Wong K 2012 Why humans give birth to helpless babies; Observation: Scientific America; August 28, 2012 https://blogs.scientificamerican.com/observations/why-humans-give-birth-to-helpless-babies/

5

The Significance of Growth

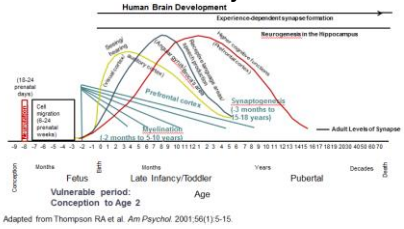
- **Five Basic Processes I Brain Development**
  - **Neurogenesis** – formation of neurons
  - **Neural migration** - process of organizing the brain by moving neurons to specific areas based on the functions these cells will perform
  - **Myelination** - process of coating the with a lipoprotein that protects the neuron and helps it conduct signals more efficiently
  - **Synaptogenesis** - process of forming networks of connections/synapses in both CNS/periphery
  - **Pruning** - process of eliminating unnecessary/obsolete connections and strengthening the important ones

Ramel DE & Georgieff MK (2014). Preterm nutrition and the brain. World Rec Nutr Diet. World Rev Nutr Diet. 2014;110:190-200. doi: 10.1159/000358467. Epub 2014 Apr 11.

6

The Significance of Growth

The First 1000 Days of Life



Adapted from Thompson RA et al. *Am Psychol.* 2001;56(1):5-15.

7

The Significance of Growth

"The brain is the most highly metabolic organ in the preterm neonate and consumes the greatest amount of nutrient resources for its function and growth."

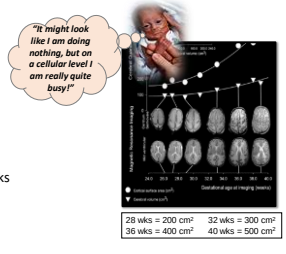
Ramel DE & Georgieff MK (2014). Preterm nutrition and the brain. World Rec Nutr Diet. World Rev Nutr Diet. 2014;110:190-200. doi: 10.1159/000358467. Epub 2014 Apr 11.

8

The Significance of Growth

Brain Development

- Neurons generated at a rate of 250,000 per minute
- 1.8 million new synapses form every second
- Fetal brain increases in size/mass by 5% every 48 hours
- Cerebral cortex is last to develop increasing 5-fold from 35-41 weeks
- ***70% of every calorie is used for brain growth***



28 wks = 200 cm² 32 wks = 300 cm²
36 wks = 400 cm² 40 wks = 500 cm²

9

The Significance of Growth

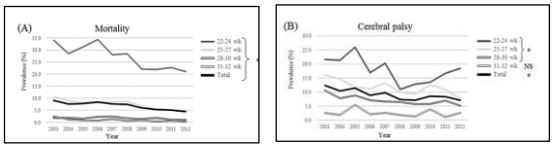
- **Trends in Neurodevelopmental Outcomes - Study Design**
  - A retrospective multicenter cohort of 30,793 preterm infants
  - Born at a gestational age ≤32 weeks, between 2003 and 2012
  - Part of the Neonatal Research Network, Japan
  - N=13,661 infants were followed-up until 3 years of age
  - Evaluated for neurodevelopmental outcomes, including:
    - Cerebral palsy (CP)
    - Home oxygen therapy
    - Visual, hearing, and cognitive impairments
  - Multivariable logistic regression analysis was performed

Nakanishi H et al **Trends in the neurodevelopmental outcomes among preterm infants from 2003–2012: a retrospective cohort study in Japan.** ***J Perinatol*** **38; 917-928 (2018) https://doi.org/10.1038/s41372-018-0061-7**

10

The Significance of Growth

- **Trends in Neurodevelopmental Outcome**



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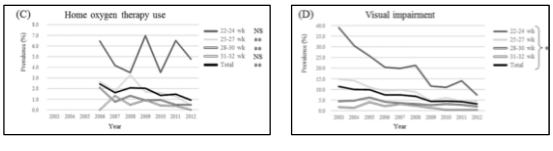
The Significance of Growth

- **Trends in Neurodevelopmental Outcome**

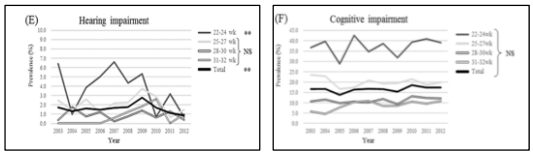


Nakanishi H et al **Trends in the neurodevelopmental outcomes among preterm infants from 2003–2012: a retrospective cohort study in Japan.** ***J Perinatol*** **38; 917-928 (2018) https://doi.org/10.1038/s41372-018-0061-7**

12

The Significance of Growth

- **Trends in Neurodevelopmental Outcome**



Nakanishi H et al **Trends in the neurodevelopmental outcomes among preterm infants from 2003–2012: a retrospective cohort study in Japan.** ***J Perinatol*** **38; 917-928 (2018) https://doi.org/10.1038/s41372-018-0061-7**

13

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- **Outcome Discussion**
  - ***Nutritional support remained correlated with long-term neurodevelopmental outcomes***
  - The AOR of time to establishment of enteral feeding (with 5-day increments) for all disabilities suggested that the ***shorter the time to the establishment of full enteral feeding, the lower the prevalence of abnormal long-term neurodevelopmental outcomes***

Nakanishi H et al **Trends in the neurodevelopmental outcomes among preterm infants from 2003–2012: a retrospective cohort study in Japan.** ***J Perinatol*** **38; 917-928 (2018) https://doi.org/10.1038/s41372-018-0061-7**

14

The Significance of Growth

- **Adverse Outcomes to Adults Born Premature/LBW**

PARAMETER	ADVERSE SEQUELAE IN ADULTS BORN PRETERM/LBW
Neurological	Significant decrease in brain volume
	Increased risk of neurological disabilities
Cardiovascular/Metabolic	↓ Insulin sensitivity, hypertension
	↑ Intrabdominal fat; ↑ Risk metabolic complications
	↑ Arterial stiffness
	↑Risk of metabolic syndrome
	↓ Ventricular size and volume
	Impaired systolic function
Bone Health	Significantly lower bone/mineral density
	Short stature

15

The Significance of Growth

16

The Significance of Growth

- **Early Aggressive Nutrition**

"Nutritional requirements do not stop at birth."

Thus, delaying nutrition after birth 'until the infant is stable' ignores the fundamental point that ***without nutrition starting immediately after birth, the infant enters a catabolic condition, and catabolism does not contribute to normal development and growth."***

"NUTRITIONAL RESUSCITATION"

17

The Significance of Growth

- **Benefits of Early Aggressive Nutrition**
  - Higher verbal intelligence quotient (IQ) scores and improved cognitive function long term
  - Better nutrition in the early postnatal period in preterm infants results in ↑protein and energy intake during the first week of life in extremely LBW infants
  - ***This is associated with higher mental development index scores and lower risk of growth retardation at 18 months***

Isaacs EB, Gadian DG, Sabatini S, Chong WK, Quinn BT, Fischl BR, et al. The effect of early human diet on caudate volumes and IQ. *Pediatr Res* (2008) 63:308–14. doi:10.1203/PDR.0b013e318163a271
Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron M, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. *Pediatrics* (2009) 123:e101–9. doi:10.1542/peds.2008-1352

18

The Significance of Growth

- **Benefits of Early Aggressive Nutrition**
  - Early/higher protein + energy intake correlated with faster ↑ head growth and head circumference in preterm infants
  - ↑ in head circumference has been positively correlated with improved cognitive outcomes
  - ***Administration of early aggressive nutritional enteral and parenteral support may help improve growth and developmental outcomes in preterm LBW infants***

Brandt I, Sticker EJ, Lentze MJ. Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. *J Pediatr* (2003) 142:463–8. doi:10.1067/mpd.2003.149
Morgan C, McGowan P, Herwitker S, Hart AE, Turner MA. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. *Pediatrics* (2014) 133:e120–8. doi:10.1542/peds.2013-2207
Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? *Semin Perinatol* (2007) 31:48–55. doi:10.1053/j.semperi.2007.02.001

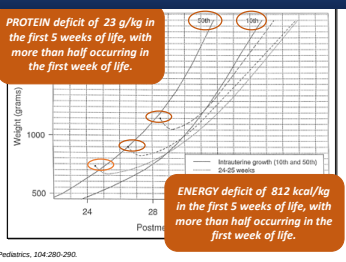
19

The Significance of Growth

Preterm infants less than 30 weeks gestation develop a…

THIS IS SO 1999!

PROTEIN deficit of 23 g/kg in the first 5 weeks of life, with more than half occurring in the first week of life.

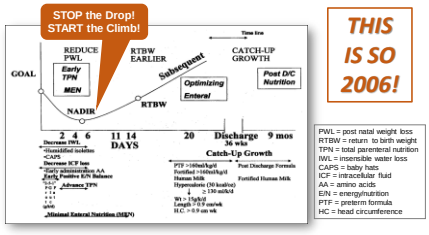


ENERGY deficit of 812 kcal/kg in the first 5 weeks of life, with more than half occurring in the first week of life.

Ehrenkrantz, R.A. (1999). *Pediatrics, 104:280-290.*

20

The Significance of Growth



THIS IS SO 2006!

PWL = post natal weight loss
RTBW = return to birth weight
TPN = total parenteral nutrition
IWL = insensible water loss
CAPS = baby hats
ICF = intracellular fluid
AA = amino acids
EIN = energy/nutrition
PTF = preterm formula
HC = head circumference

Adamkin, D. H. (2006). Nutrition management of the very low birthweight infant. *NeoReviews, 7(12)*; e602.

21

The Significance of Growth

- **Nutritional Goals for Preterm Infants**
  - For infants weighing 501 to 1500 g at birth, average growth velocity (GV) increased and the percentage with postnatal growth failure decreased from 2000 to 2013.
  - ***However, in 2013, half of these infants still demonstrated postnatal growth failure and one-quarter demonstrated severe postnatal growth failure.***

Horbar JD, Ehrenkranz JA, et. al.,Weight Growth Velocity and Postnatal Growth Failure in Infants 501 to 1500 Grams: 2000–2013
Pediatrics Jul 2015, 136 (1) e84-e92; DOI: 10.1542/peds.2015-0129

22

The Significance of Growth

- **A New Diet in the NICU**
  - Sustainable

ALL HUMAN SOURCED NUTRITION

23

The Significance of Growth

- **Exclusive Human Milk Diet (EHMD)**
- **Ex-clu-sive** [ik-SKLOO-siv, -ziv]
  - Not admitting of something else or other things
  - Limited to the object or objects designated
  - Shutting all others from a part or share

"Exclusive"
The state of being in a relationship with someone where you are officially boyfriend and girlfriend, ***and there is no one else involved***. It's usually attained after going on a couple of good dates.

Dictionary.com, meanings and definitions of words
http://www.dictionary.com/browse/exclusive

The Urban Dictionary, compiled by Aaron Peckham
http://www.urbandictionary.com/define.php?term=exclusive

24

The Significance of Growth

- **EHMD Feeding Protocol**

THIS IS SO 2020!

Birthweight 751-1250g Feeding Guidelines					
DOL	**Kcal/oz EBM or DM**	**Feeding Volume (mL/kg/day)**	**TPN (mL/kg/day)**	**Lipids (mL/kg/day)**	**Total Fluids[2]= Enteral + TPN + IL (ml/kg/day)**
1	20	15-20	90-100	5-10	120
2	20	15-20	95-105	10-15	130
3	20	15-20	115-120	15	150
4	20	40	95	15	150
5	26 (Prolact+6)	60	75	15	150
6	26 (Prolact+6)	80	55-70	15 or Off Lipids	150

Guidelines for Acute Care of the Neonate, 23rd Edition, 2016-2017.
Section of Neonatology, Department of Pediatrics, Baylor College of Medicine, Texas Children's.

25

The Significance of Growth

- **EHMD Feeding Protocol**

THIS IS SO 2020!

Birthweight 751-1250g Feeding Guidelines					
DOL	**Kcal/oz EBM or DM**	**Feeding Volume (mL/kg/day)**	**TPN (mL/kg/day)**	**Lipids (mL/kg/day)**	**Total Fluids[2]= Enteral + TPN + IL (ml/kg/day)**
6	26 (Prolact+6)	80	55-70	15 or Off	150
7	26 (Prolact+6)	100	50	0	150
8	26 (Prolact+6)	120	Off TPN	0	120 Off TPN or IV Fluids
9	26 (Prolact+6)	140	0	0	140
10	26 (Prolact+6)	160	0	0	160 Full Enteral Feeds
10-14	26 (Prolact+6) +Cream	160	0	0	160

26

26

The Significance of Growth

- **Immunity and Nutrition**

"Nutrition is a critical determinant of immune responses and malnutrition is the most common cause of immunodeficiency."

27

The Gut-Brain Axis

- **Immunity and Nutrition**
  - **Protein-energy malnutrition associated with**
    - Significant impairment of cell-mediated immunity
    - Impaired phagocyte function
    - Deficiencies in the complement system
    - Decreased secretory immunoglobulin antibody concentrations
    - Lowered cytokine production
  - **Deficiency of single nutrients alters immune responses**
    - Selenium, copper, folic acid, zinc
    - Vitamins A, C, E, and B-6

Chandra, RK Nutrition and the immune system: an introduction. *Am J Clin Nutr*, 1997 Aug;66(2):460S-463S.

28

The Significance of Growth

- **Immunity and Nutrition**
  - **Neonatal Innate Immunity**
    - First line of defense at birth
    - Provides immediate protection at a local/cellular level
    - Acts with non-specific responses
    - Uses ***"pro-inflammatory"*** mechanisms
    - Vasodilatation, cellular activation, microvascular permeability, coagulation
    - Secondary collateral damage

Cacho NT & Lawrence RM (2017), *Front. Immunol.*, 29 May 2017 https://doi.org/10.3389/fimmu.2017.00584
Jakaitis BM & Denning PW (2014) *Clinics in Perinatology*; 41423-435 http//dx.doi.org/10.1016/j.clp.2014.02.011

29

The Significance of Growth

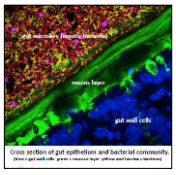
- **Immunity and Nutrition**
  - **Neonatal Adaptive Immunity**
    - Later developed immune response
    - Requires exposure to antigens
    - Amplifies with repeated exposure
    - High ***"specificity"*** of response
    - Relies on T & B cells and ***"memory"***
    - Elaborate cascade of responses
    - Balanced response

Cacho NT & Lawrence RM (2017), *Front. Immunol.*, 29 May 2017 https://doi.org/10.3389/fimmu.2017.00584
Jakaitis BM & Denning PW (2014) *Clinics in Perinatology*; 41423-435 http//dx.doi.org/10.1016/j.clp.2014.02.011

30

The Gut-Brain Axis

- **Insults Affecting the Premature Gut**
  - Immaturity of the end organ system
  - Hypoxic-ischemic reperfusion injuries
  - Infection/inflammation
  - Impaired gut lumen integrity
  - Mode of delivery
  - Antibiotic exposure
  - Luminal starvation
  - **ALTERED MICROBIAL COLONIZATION**



Cross section of gut epithelium and bacterial community

Neu J & Bernstein, H Update on host defense and immunonutrients *Clinics in Perinatology 29(1); 2002.*
Jakaitis BM & Denning PW (2014) *Clinics in Perinatology*; 414243Shttp//dx.doi.org/10.1016/j.clp.2014.02.011

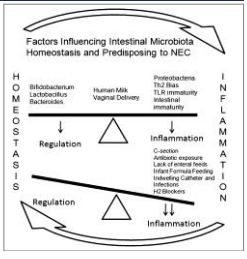
31

The Gut-Brain Axis

Factors Influencing the Intestinal Microbiome and Predisposing to Feeding Intolerance and NEC

Dysbiosis

"probably the key event associated with the pathogenesis of NEC".



Torrazza RM & Neu J *Clin Perinatol* 40 (2013) 93-108
http://dx.doi.org/10.1016/j.clp.2012.12.009
Sherman MP, Zaghouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

32

The Gut-Brain Axis

- **The Gut Brain Axis (GBA)**

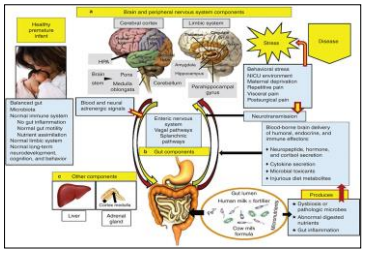
"While microbial colonization of the gut is important for immune system development, it also acts in concert with diet to promote healthy brain development."

Diaz Heijtz R, Wang S, Anuar F, et al Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci USA* 2011;108:3047-52.
Douglas-Escobar M, Elizabet Elliott E, Josef Neu Effect of intestinal microbial ecology on the developing brain. *JAMA Pediatr Clin North AM* 2013;60:189-207.

33

The Gut-Brain Axis

Neonatal GBA
"Gut-Brain Axis"



Sherman MP, Zaghouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

34

The Gut-Brain Axis

- **"GBA: Gut-Brain Axis" in Preterm/Sick Newborns**
  - ↓ Gut barrier function
  - ↑ Bacterial translocation
  - ↑Activation of immune cells/inflammation
  - ↑ Activation of HPA (Hypothalamic Pituitary Axis)
  - ↑ Physiologic stress → ↑ cortisol release
  - Triggering further pro/anti-inflammatory downstream activity

Inflammation and Hypermetabolic State

Sherman MP, Zaghouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

35

The Gut-Brain Axis

- **GBA: Gut-Brain Axis in Preterm and Sick Newborns**
  - Activation of peripheral components GBA
  - Including activation of the CNS, ANS and SNS
  - Transmitted via the Enteric Nervous System
  - Gut microbes modulate neural signaling
  - ↓ Barrier function; ↑ bacterial translocation
  - ↑ Activation of immune cells/inflammation

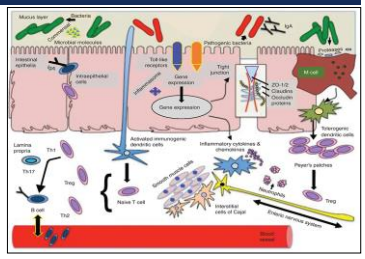
Inflammation and Hypermetabolic State

Sherman MP, Zaghouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

36

The Gut-Brain Axis

Neonatal GBA
"Gut-Brain Axis"



Sherman MP, Zaghouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

37

The Gut-Brain Axis

- **GBA: Gut-Brain Axis**
  - ↑ Activation of HPA (Hypothalamic Pituitary Axis)
  - ↑ Stress → ↑ cortisol release
  - Further activation of intestinal immune cells
  - Triggering further pro/anti-inflammatory activity
  - **Inflammasones** – multiprotein complexes
    - ↑ Pro-inflammatory cytokines (IL-1,18,33)
  - Altered brain development and function
  - Role in NEC → and ***long term ND abnormalities***

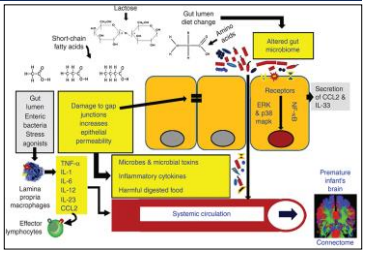
Inflammation is a Hypermetabolic State

Sherman MP, Zaghouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

38

The Gut-Brain Axis

Neonatal GBA
"Gut-Brain Axis"



Sherman MP, Zaghouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

39

The Gut-Brain Axis

- **"Gut-Brain Axis" in Preterm and Sick Newborns**
  - **Functional communication**
    - Operates in a bidirectional signaling system
      - ***"Top-down and bottom-up" effects***
    - Emerging evidence linking intestinal ***"dysbiosis"*** of the microbiome in preterm infants to:
      - Preceding late-onset neonatal sepsis and NEC
      - Neurodevelopmental disease outcomes
      - Key role in early programming of health outcomes

Inflammation and Hypermetabolic State

Cong X, XU W, Janton S, Henderson WA, Matson A, McGrath JM, et al. (2016) PLOS ONE 11(4): e0152751. doi:10.1371/journal.pone.0152751 April 25, 2016
Sherman MP, Zaqhouani H, & Niklas V. *Pediatric Research* (2015) Volume: 77, Pages:127–135 DOI:doi:10.1038/pr.2014.161

40

The Gut-Brain Axis

"Get him/her some milk!"

41

The Gut-Brain Axis

- **Human Milk Oligosaccharides (HMOs)**

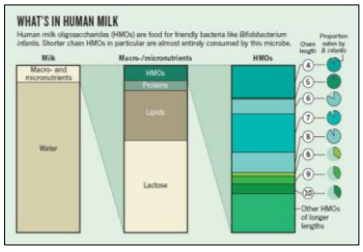
"HMO provides the newborn with a variety of bioactive factors that promote a healthy colonization of the neonatal gut and support the maturation of the neonatal immune system."

Jantscher-Krenn E & Bode L (2012). Human milk oligosaccharides and their potential benefits for the breast-fed neonate. *Minerva Pediatr*, 64(1):83-99,

42

The Gut-Brain Axis

The Benefits of a Human Milk Diet



Petherick A Development: Mother's milk a rich opportunity. *Nature* **volume 468**, pages S5–S7 (23 December 2010)

43

The Gut-Brain Axis

- **Human Milk Oligosaccharides (HMOs)**
  - Structurally complex, diverse sugars
    - Composed of 5 monosaccharide "building blocks"
    - HMOs are HMOs mount/composition varies during pregnancy
  - Wide range of interpersonal variation in HMOs
    - Not every woman synthesizes the same HMOs
    - "Partial" and/or "non-secretor" status
    - Composition influenced by maternal genetic factors and blood type

•Niklas, V & Autran C (2019) *Neonatal Intensive Care* 32(3).
•Bode L (2012). *Glycobiology* 2299); 147-162 doi:10.1093/Glycob/cws074;
•Jantscher-Renn E & Bode *L Minerva Pediatr* 2012;64:83-99

44

The Gut-Brain Axis

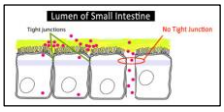
- **Human Milk Oligosaccharides (HMOs)**
  - ~150-200 HMOs present in human milk
    - Present in colostrum, early, and mature milk
    - ↑ HMO in colostrum
    - ↑ HMO in preterm infant
    - ↓HMO in mature milk
  - Diverse variety and large number in donor milk
  - ***Survive pasteurization intact***

•Niklas, V & Autran C (2019) *Neonatal Intensive Care* 32(3).
•Bode L (2012). *Glycobiology* 2299); 147-162 doi:10.1093/Glycob/cws074;
•Jantscher-Renn E & Bode *L Minerva Pediatr* 2012;64:83-99

45

The Gut-Brain Axis

- **Human Milk Oligosaccharides (HMOs)**
  - **Beneficial Role in the Neonatal Gut**
    - Function as **"PREBIOTICS"**
    - Provide food for commensal bacteria
    - Microbes then release SCFA
    - Which feed gut cells
    - Facilitate production → junction proteins
    - **↓*"translocation"* of pathogens**
    - Restricts pathogens →systemic circulation
    - Provides anti-inflammatory molecules

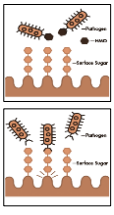


Lewis, Erin D. et al. (2016). The importance of human milk for immunity in preterm infants. *Clinics in Perinatology*, 44(1); 23-47. DOI: https://doi.org/10.1016/j.clp.2016.11.008

46

The Gut-Brain Axis

- **Human Milk Oligosaccharides (HMO)**
  - **Beneficial Roles in the Neonatal Gut**
    - Anti-adhesive antimicrobials
    - Prevent attachment of pathogens on mucosal/epithelial surfaces
    - Serve as soluble decoy receptors
    - Regulates ***immune-inflammatory processes connecting the intestine, liver, muscle, and brain (GBA)***



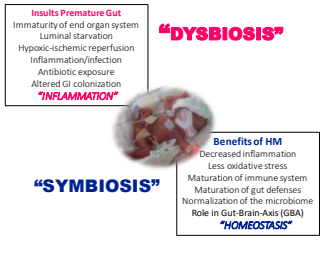
Bode L (2012). *Glycobiology* 2299); 147-162 doi:10.1093/glycob/cws074; Jantscher-Renn E & Bode L *Minerva Pediatr 2012;64:83-99*

47

The Gut-Brain Axis

- **Immunonutrition**

"The modulation of the immune and inflammatory responses in critically ill patients with the use of enteral feedings enriched with immune-enhancing ingredients".

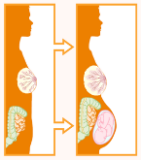


Torrazza RM & Neu J *Clin Perinatol* 40 (2013) 93-108
http://dx.doi.org/10.1016/j.clp.2012.12.0099

48

The Gut-Brain Axis

- **Human Milk Microbiome**
  - Directly shapes the infant's intestinal microbiome
  - Human milk oligosaccharide (HMO) drives the growth of these microbes within the gut



*"This unique milieu of enhanced immune protection with **diminished inflammation** results from a complex interaction of **anti-inflammatory and anti-oxidative factors provided by human milk to the intestine."***

Cacho NT & Lawrence RM (2017). Innate immunity and breast milk. *Front. Immunol.*, 29 May 2017 |https://doi.org/10.3389/fimmu.2017.00584

49

The Gut-Brain Axis

"Further improvements in growth for VLBW infants will require NICU teams to accept that postnatal growth failure is a serious morbidity amenable to prevention and to engage in quality improvement initiatives designed to implement nutritional practices supported by currently available evidence".

Horbar JD, Ehrenkranz JA, et. al.,Weight Growth Velocity and Postnatal Growth Failure in Infants 501 to 1500 Grams: 2000–2013 *Pediatrics* Jul 2015, 136 (1) e84-e92; DOI: 10.1542/peds.2015-0129

50

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51