The Role of Immunonutrition in Infant Health & Development

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Disclosure Information

Camilia R. Martin, MD

I have the following financial relationships to disclose:

- Consultant for: Mead Johnson, Abbott, Nestle, Fresenius-Kabi
- Grant/Research Support from: Abbott Nutritionals, Alcresta, Gilead, Sancilio
- Scientific Advisory Board: Alcresta, Sancilio

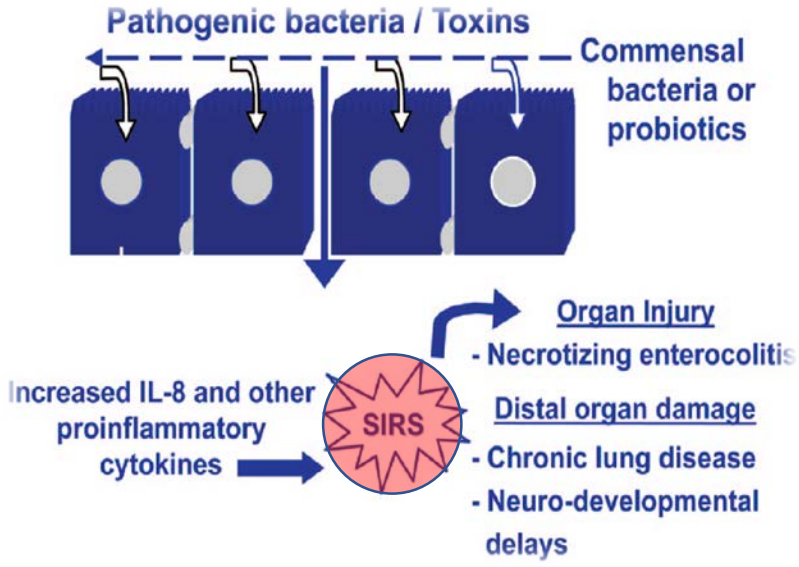
Definition of Immunonutrition

The potential to modulate the activity of the immune system by interventions with specific individual nutrients is termed *immunonutrition*. (P.Calder, 2003)

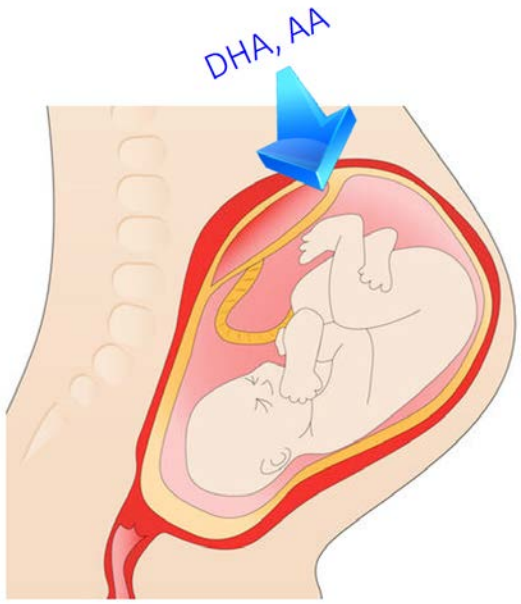
In the developing neonate, complex diets, medical practices, and individual nutrients have the potential to modulate the activity of the immune system, inflammation, and organogenesis -- *nutritional programming*.

The Effects of Nutritional Programming in the NICU

Medical Practices & Enteral Diets on Gut Health, to Systemic Health



Inadequate Replacement of Critical Nutrients in the Early Postnatal Period

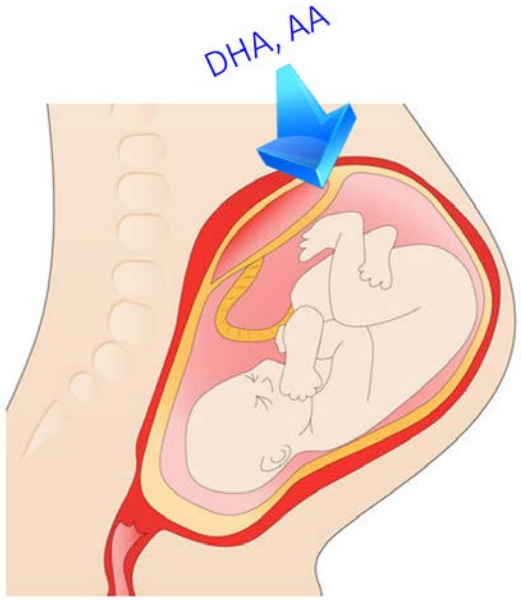


The Effects of Nutritional Programming in the NICU
Objectives

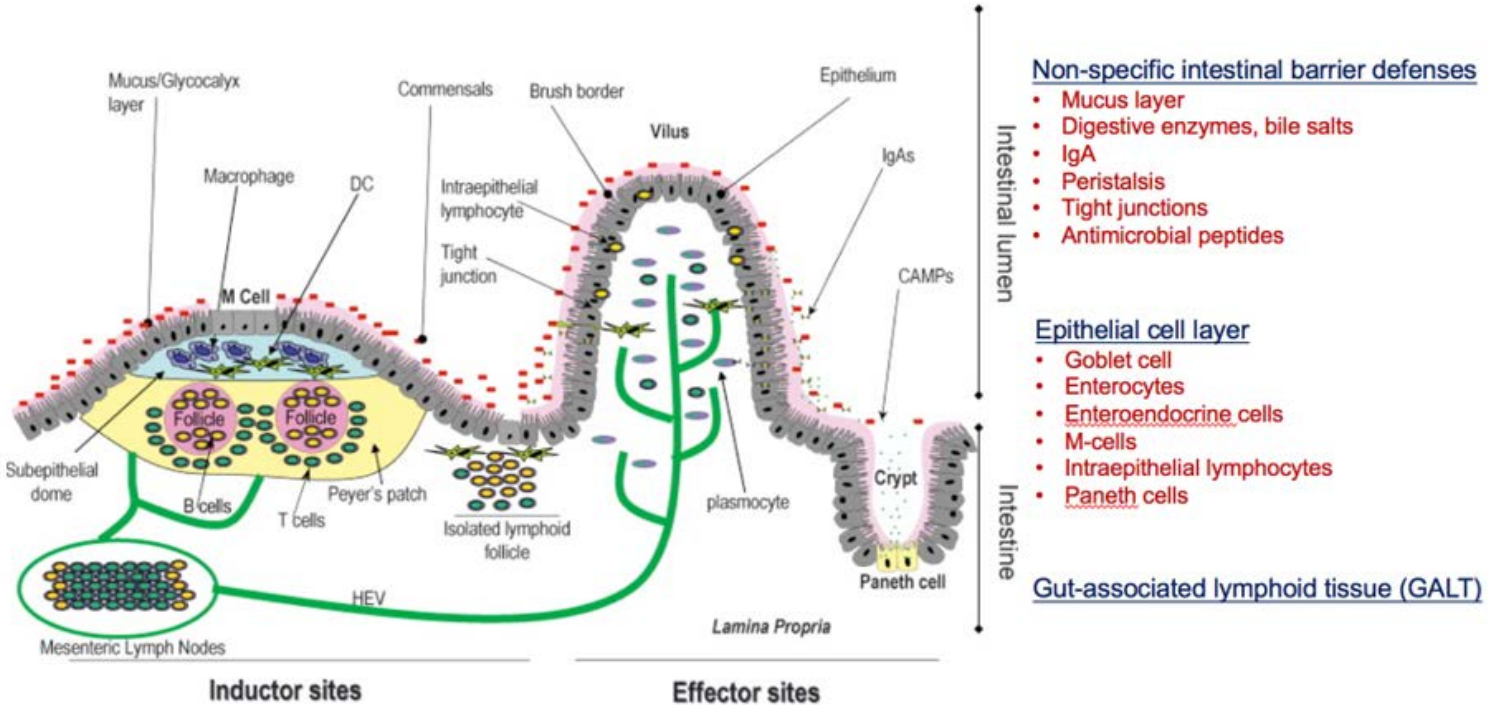
Medical Practices & Enteral Diets on Gut Health, to Systemic Health

- Describe the processes involved in postnatal intestinal adaptation
- Postulate a link b/w local, intestinal health and systemic disease risk
- Propose strategies to optimize gut health within the sphere of nutritional delivery

Inadequate Replacement of Critical Nutrients in the Early Postnatal Period



Immune Function of the Intestinal Tract



From Magalhaes JG, Tattoli I, Girardin SE. The intestinal epithelial barrier: how to distinguish between the microbial flora and pathogens. *Semin Immunol.* Apr 2007;19(2):106-115.

The intestinal tract is 70% of the immune system

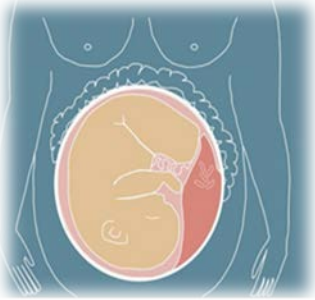
Fetal Development of the Gastrointestinal Tract

Developmental Feature	Gestational Age, weeks
Specialized cells	
Intraepithelial lymphocytes	8
Intestinal absorptive epithelium	9
Goblet cells	8-10
Enteroendocrine cells	9-11
Paneth cells	11-12
Microfold cells (M-cells)	17
Dendritic cells	19
Advanced structural components	
Tight junctions	10
Crypt-villus architecture	12
Peyer's patches	19
Elements of innate mucosal immunity	
Mucin	8-10
Defensins	13
Lysozyme	20
Toll-like receptors: TLR2, TLR4	20

Amniotic Fluid

Hormones	growth hormone, gastrin-releasing peptide, prolactin
Trophic or growth factors	epidermal growth factor, transforming growth factor-alpha, transforming growth factor beta-1; insulin-like growth factor I; erythropoietin, granulocyte colony-stimulating factor; hepatocyte growth factor, vasoactive endothelial growth factor
Nutrients and other proteins	water, electrolytes, carbohydrates, amino acids, lipids, albumin, serotransferrin, ceruloplasmin, alpha-fetoprotein, vitamin d-binding protein; apolipoprotein a1
Modulators of coagulation	antithrombin III, plasminogen
Modulators of immunity and inflammation	immunoglobulins, interleukins, complement, a-defensins, lactoferrin, lysozyme, calprotectin, cathelicidin, alpha1-antitrypsin, alpha1-microglobulin
Cell growth and differentiation	fibronectin; periostin; TGF-beta induced protein ig-h3 precursor; polyamines
Microbes	*?*

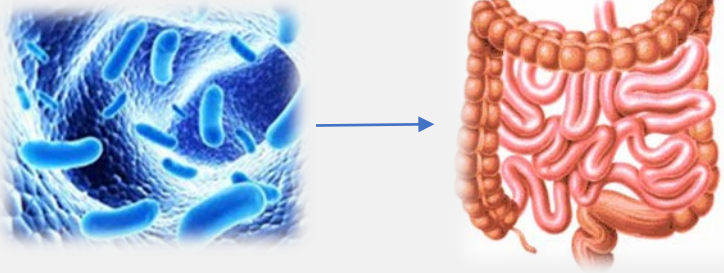
Influences on Postnatal Gut Development



Maternal/Fetal Microbiome & Vaginal Delivery

Cesarean section

Skin-to-Skin



Hospitalization

Medications

Breastfeeding

Delayed feedings/Formula
Limited MM/DM

Cesarean section

Hospitalization

Medications

Delayed feedings/Formula
Limited MM/DM

Cesarean section

Hospitalization

Medications

Delayed feedings/Formula
Limited MM/DM

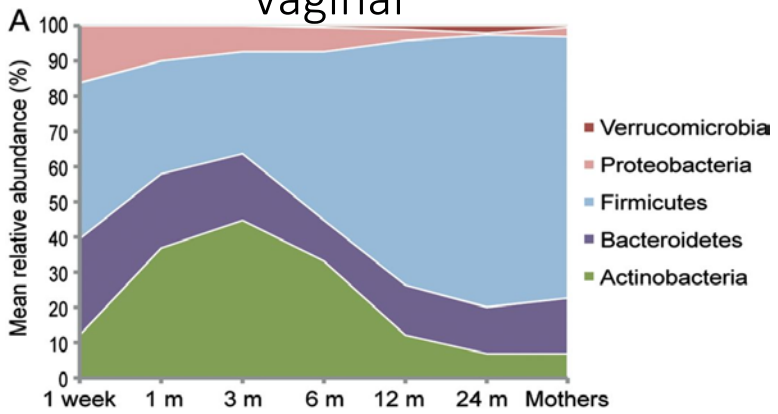
ORIGINAL ARTICLE

Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by Caesarean section

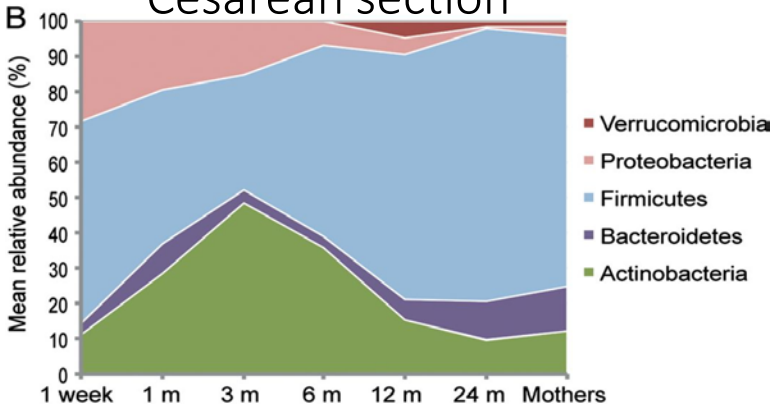
Hedvig E Jakobsson,[1,2] Thomas R Abrahamsson,[3] Maria C Jenmalm,[3,4] Keith Harris,[5] Christopher Quince,[5] Cecilia Jernberg,[1] Bengt Björkstén,[6,7] Lars Engstrand,[2] Anders F Andersson[8]

Gut 2014;**63**:559–566.

Vaginal



Cesarean section



Cesarean section

Hospitalization

Medications

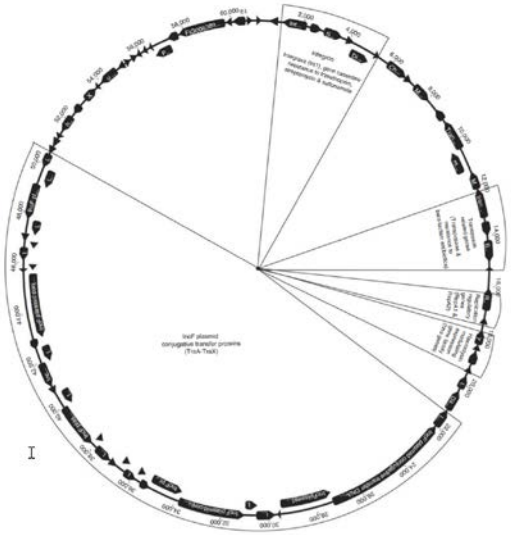
Delayed feedings/Formula
Limited MM/DM

✓Indwelling devices – NG tube, endotracheal tube, central lines

Association of the gut microbiota mobilome with hospital location and birth weight in preterm infants

Anuradha Ravi[1], Eva Lena F. Estensmo[1], Trine M. L'Abée-Lund[2], Steven L. Foley[3], Bernhard Allgaier[4], Camilia R. Martin[5], Erika C. Claud[6] and Knut Rudi[1]

Pediatr Res. 2017 Nov;82(5):829-838.



- Mobilome = **mobile, transposable elements** found in transposons, plasmids, bacteriophages
- Major constituents of the gut mobilome are **conjugative plasmids**
- These functional elements **help maintain long-term stability in a microbial population** (antibiotic resistance)

Cesarean section

Hospitalization

Medications

Delayed feedings/Formula
Limited MM/DM

Pediatrics
January 2009, VOLUME 123 / ISSUE 1

Prolonged Duration of Initial Empirical Antibiotic Treatment Is Associated With Increased Rates of Necrotizing Enterocolitis and Death for Extremely Low Birth Weight Infants

C. Michael Cotten, Sarah Taylor, Barbara Stoll, Ronald N. Goldberg, Nellie I. Hansen, Pablo J. Sánchez, Namasivayam Ambalavanan, Daniel K. Benjamin, Jr for the NICHD Neonatal Research Network

Outcome	Duration of Initial Empirical Antibiotic Treatment (Odds per Day)		Prolonged Initial Empirical Antibiotic Treatment	
	OR (95% CI)	*P*	OR (95% CI)	*P*
NEC or death (total, $N = 3883$; with outcome, $n = 884$)	1.04 (1.02–1.06)	<.01	1.30 (1.10–1.54)	<.01
NEC (total, $N = 3899$; with outcome, $n = 427$)	1.07 (1.04–1.10)	<.001	1.21 (0.98–1.51)	.08
Death (total, $N = 3882$; with outcome, $n = 631$)	1.16 (1.08–1.24)	<.001	1.46 (1.19–1.78)	<.001

Cesarean section

Hospitalization

Medications

Delayed feedings/Formula
Limited MM/DM

SCIENTIFIC REPORTS

OPEN

Effects of One-Week Empirical Antibiotic Therapy on the Early Development of Gut Microbiota and Metabolites in Preterm Infants

Received: 18 July 2016
Accepted: 13 July 2017
Published online: 14 August 2017

Danping Zhu[1,2,3,4], Sa Xiao[1,2,3,4], Jialin Yu[1,2,3,4,5], Qing Ai[1,2,3,4], Yu He[1,2,3,4], Chen Cheng[1,2,3,4], Yunhui Zhang[1,2,3,4] & Yun Pan[1,2,3,4]

- reduction of bacterial diversity
- enrichment of harmful bacteria such as Streptococcus and Pseudomonas

Cesarean section

Hospitalization

Medications

Delayed feedings/Formula
Limited MM/DM

Pediatrics
January 2009, VOLUME 123 / ISSUE 1

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Pediatrics
February 2006, VOLUME 117 / ISSUE 2

Association of H2-Blocker Therapy and Higher Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants

Ronnie Guillet, Barbara J. Stoll, C. Michael Cotten, Marie Gantz, Scott McDonald, W. Kenneth Poole, Dale L. Phelps for members of the National Institute of Child Health and Human Development Neonatal Research Network

Late Enteral Feedings Are Associated w/ Intestinal Inflammation & Adverse Neonatal Outcomes

Cesarean section

Hospitalization

Medications

Delayed feedings/Formula
Limited MM/DM

Konnikova Y, et al. Plos one, 2015
< 33 wks; n=130

Table 8. Adjusted Linear and Logistic Regression for Main Outcome Effects by Late Initial Feedings in a Restricted Cohort of Non-Growth Restricted, Extremely Low Birth Weight (n = 45).

Intestinal Inflammation	B-Coefficient (95%CI)	p-Value
Fecal IL-8 Level	1.62 (0.47–2.77)	0.007
Fecal IL-10:IL-8 Ratio	-1.56 (-2.83–0.29)	0.02
Neonatal Morbidities	**OR (95% CI)**	**p-Value**
CLD	5.97 (1.30–27.4)	0.02
ROP	1.97 (0.31–12.69)	0.48

Cesarean section

Hospitalization

Medications

Delayed feedings/Formula
Limited MM/DM

Influence of Diet on Intestinal Gene Expression

Table 2 Relative gene expression levels in breast-fed (BF) versus formula-fed (FF) infants following a 3-month feeding period

Gene	BF/FF	*P*-value	q-value
TACR1	1.80	0.0189	0.1670
REL	1.62	0.0047	0.1026
DUOX2	1.45	0.0215	0.1670
VAV2	1.36	0.0088	0.1404
NDST1	0.79	0.0103	0.1477
AOC3	0.78	0.0202	0.1670
SP2	0.76	0.0030	0.0860
IL1A	0.71	0.0089	0.1389
ALOX5	0.69	1.40E-05	0.0008
BPIL1	0.37	1.43E-05	0.0008
KLRF1	0.35	3.16E-05	0.0015

Fold change represents relative expression level in BF divided by FF infants for the 11 genes exhibiting the strongest multivariate relationships to microbiota virulence characteristics.

Formula v BM:

- lower phylogenetic heterogeneity (and decreased diversity) of the microbiome
- lower overall gene expression by the intestinal epithelium

gut motility, bacterial-mediated reactive oxygen species signaling, epithelial homeostasis

mucosal inflammatory responses, permeability-increasing, vascular adhesion

Schwartz et al, Genome Biology 2012

Cesarean section

Hospitalization

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Human Milk Highlight the Importance of Specific Nutrients in Infant Development

- Lactoferrin
- Oligosaccharides
- LCPUFAs
- Gut hormones
- Growth factors
- Live cells, stem cells
- Microbiota

Human Milk Highlight the Importance of Specific Nutrients in Infant Development

Cesarean section

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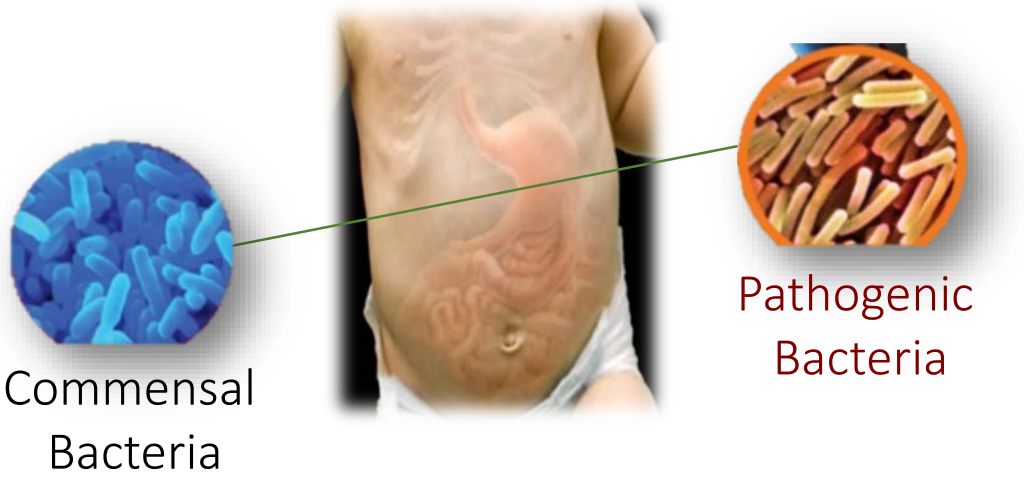
- Lactoferrin
- Oligosaccharides
- LCPUFAs
- Gut hormones
- Growth factors
- Live cells, stem cells
- Microbiota

Challenges:

- When to give?
- How to deliver?
- How much to give?
- Markers of success?

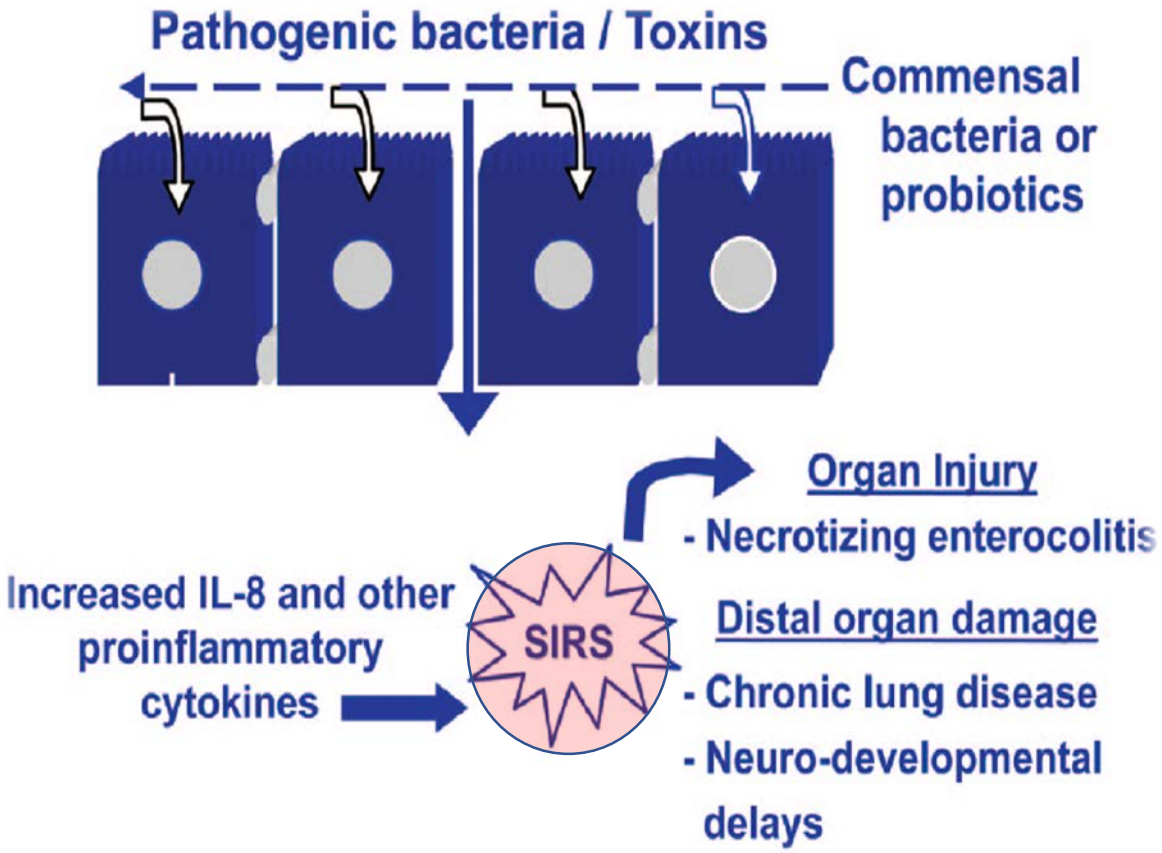
Microbiome & Gut Development Influence Local & Systemic Health



- Maintain integrity of mucosal barrier
- Regulate appropriate bacterial colonization
- Activate intestinal immune defenses
- Modulate intestinal inflammation

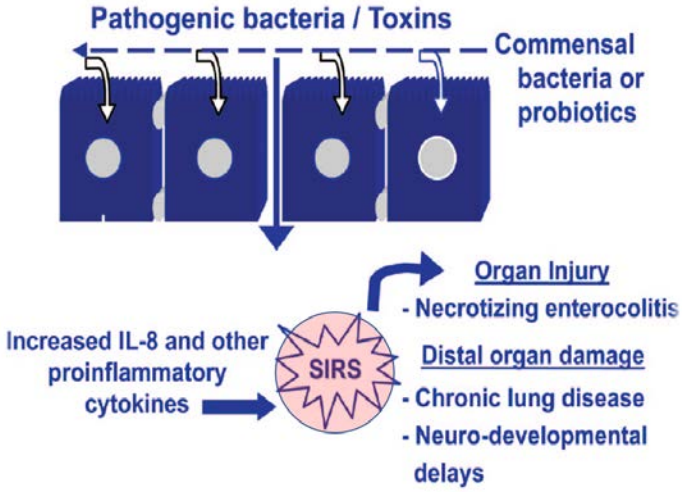
Balance between appropriate tolerance & inflammatory attack

Impaired Host Immunity/Microbiome Leads to Local and Systemic Morbidity



Caicedo et al, Pediatr Res, 2005

Evidence for: Gut to Systemic Health Link



- Delayed feedings after 3 days leads to detectable inflammation at 2 weeks postnatal age & increased risk of CLD at 36 weeks PMA

Konnikova et al, Plos one 2015

- Intestinal injury leads to sustained *systemic* inflammatory response; sustained systemic inflammatory response leads to poor neurocognitive outcomes, as does NEC

O'Shea et al 2012; Carlo et al 2011

- NEC a common node in clustering of neonatal morbidities

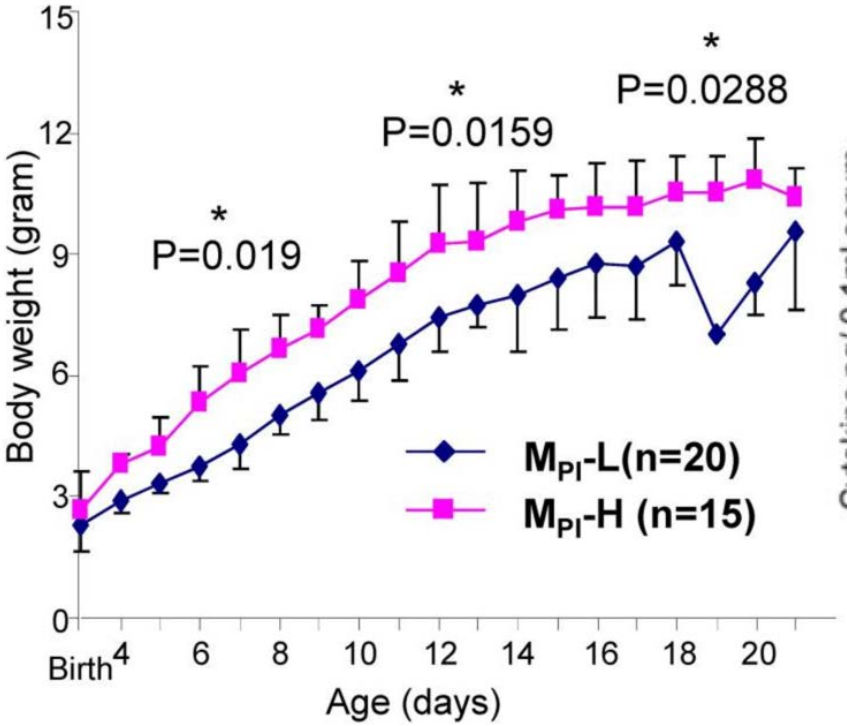
	Bowel	Brain	Retina	Lung
	NEC*	VM/EL	ROP†	BPD‡
Bowel		**2.3 (1.2, 4.3)**	**3.1 (1.7, 5.8)**	**3.7 (1.9, 7.1)**
Brain	14/6.9		1.1 (0.8, 1.6)	1.0 (0.6, 1.7)
Retina	30/14.5	61/50.8		2.6 (1.7, 3.9)
Lung	18/6	19/17	62/34	
Blood early	3/3.2	14/11.1	35/23.3	5/8.0
Blood late	17/12.6	52/44.1	118/92.6	42/31.6

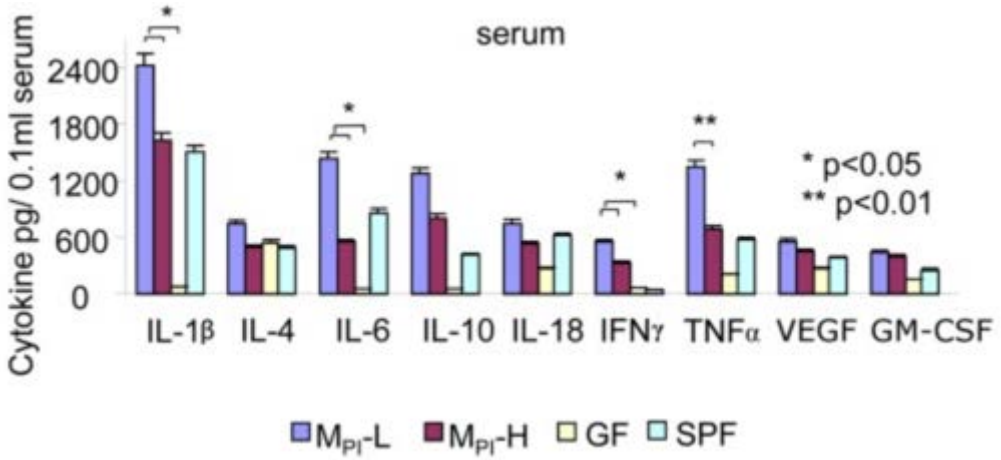
Leviton et al, ActaPaediatrica, 2010

- Humanized gnotobiotic mice with preterm microbiota results in dysregulated systemic inflammation & altered growth

Lu L, Yu Y, Guo Y, Wang Y, Chang EB, Claud EC. PLoS One. 2015

Modulation of Intestinal Innate Defense/ Inflammation Genes by Preterm Infant Microbiota





Lu L, Yu Y, Guo Y, Wang Y, Chang EB, Claud EC. Transcriptional modulation of intestinal innate defense/inflammation genes by preterm infant microbiota in a humanized gnotobiotic mouse model.
PLoS One. 2015 Apr 30;10(4):e0124504.

Maximal Opportunity to Nutritionally Influence Health Outcomes is *Early* (Hours to Days) After Delivery

PARENTERAL NUTRITION

The effect of critical illness on the risk of adverse outcomes is modulated by early total energy intake during the first week of life.[1]

For every 1 kcal/kg/day of total energy intake, the OR of adverse short and long-term outcomes was decreased by 2%.[1]

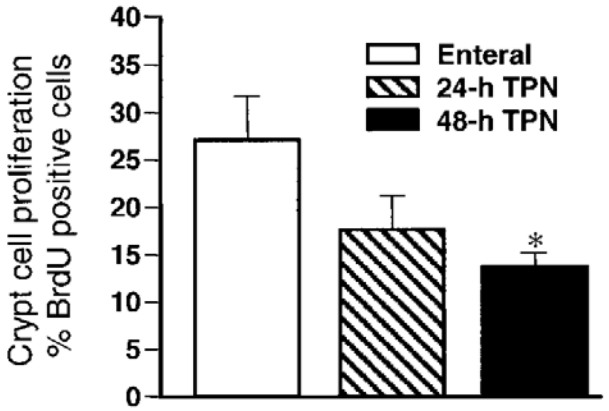
Receipt of total energy and lipids in the lowest quartile in the first week of life are associated with an increased risk of ROP. [2]

Early nutrition related to risk of ROP, Increased energy intake of 10 kcal/kg/day was associated with a 24% decrease in severe ROP.[3]

1 Ehrenkranz et al. JPeds 2011
2 VanderVeen DK et al. PLoS One 2013
3 Sjöström S et al. Arch Dis Child Fetal Neonatal Ed 2015

ENTERAL NUTRITION

Decreased cell proliferation/increased apoptosis with delayed enteral feedings.[1]



Delayed feedings after 3 days leads to detectable inflammation at 2 weeks postnatal age & increased risk of CLD at 36 wks PMA.[2]

1 Niinikoski et al, JNutr, 2004
2 Konnikova et al, Plos one 2015

Practices to Optimize Gut/Microbiome Development

Maternal Health/ Cesarean section

- Active research on maternal microbiome
- Reduce Cesarean section rates
- Early Skin-to-Skin
- Education re: HM (Prenatal)
- Early lactation support

Hospitalization

- Remove lines & tubes

Medications

- Medication stewardship

Delayed feedings/Formula Limited MM/DM

- Early nutritional support (PN & EN)
- Limit days NPO
- Colostrum care
- Human milk base diet (fortification not well studied)
- Feeding protocols (early, progressive) w/ specific stop/starts; champion; & auditing
- Targeted nutrient delivery remains investigational

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Summary

- Nutrition is not only important for somatic growth; but, is also critical in the transition from in utero to ex utero in the ongoing development of organs and their functional capabilities
- This transition must be addressed early in the postnatal course
- Gut health plays a role in systemic health
- A number of medical and nutritional practices can be implemented now to optimize microbiome, gut development, and infant health
- Targeted nutrient delivery, although promising, remains investigational

Thank You!