NEW INSIGHTS IN HUMAN MILK COMPOSITION AND BENEFITS FOR PRETERM INFANTS

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4TH SIGNEC LONDON UK 27 SEPT 2016

DISCLOSURE

Employee of Nutricia Research Utrecht, The Netherlands

NEW INSIGHTS IN HUMAN MILK COMPOSITION AND BENEFITS FOR PRETERM INFANTS

- Preterm infants and NEC
- Risk factors for NEC
- Human milk composition

  (quantity & quality)
- Role of storage and pasteurisation
- Conclusions

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1. Trends and Outcomes of Patent Ductus Arteriosus Treatment in Very Preterm Infants in Canada.
Lokku A, Mirea L, Lee SK, Shah PS; Canadian Neonatal Network.
Am J Perinatol. 2016 Sep 20. [Epub ahead of print]
PMID: 27649293
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PATHOPHYSIOLOGY NEC

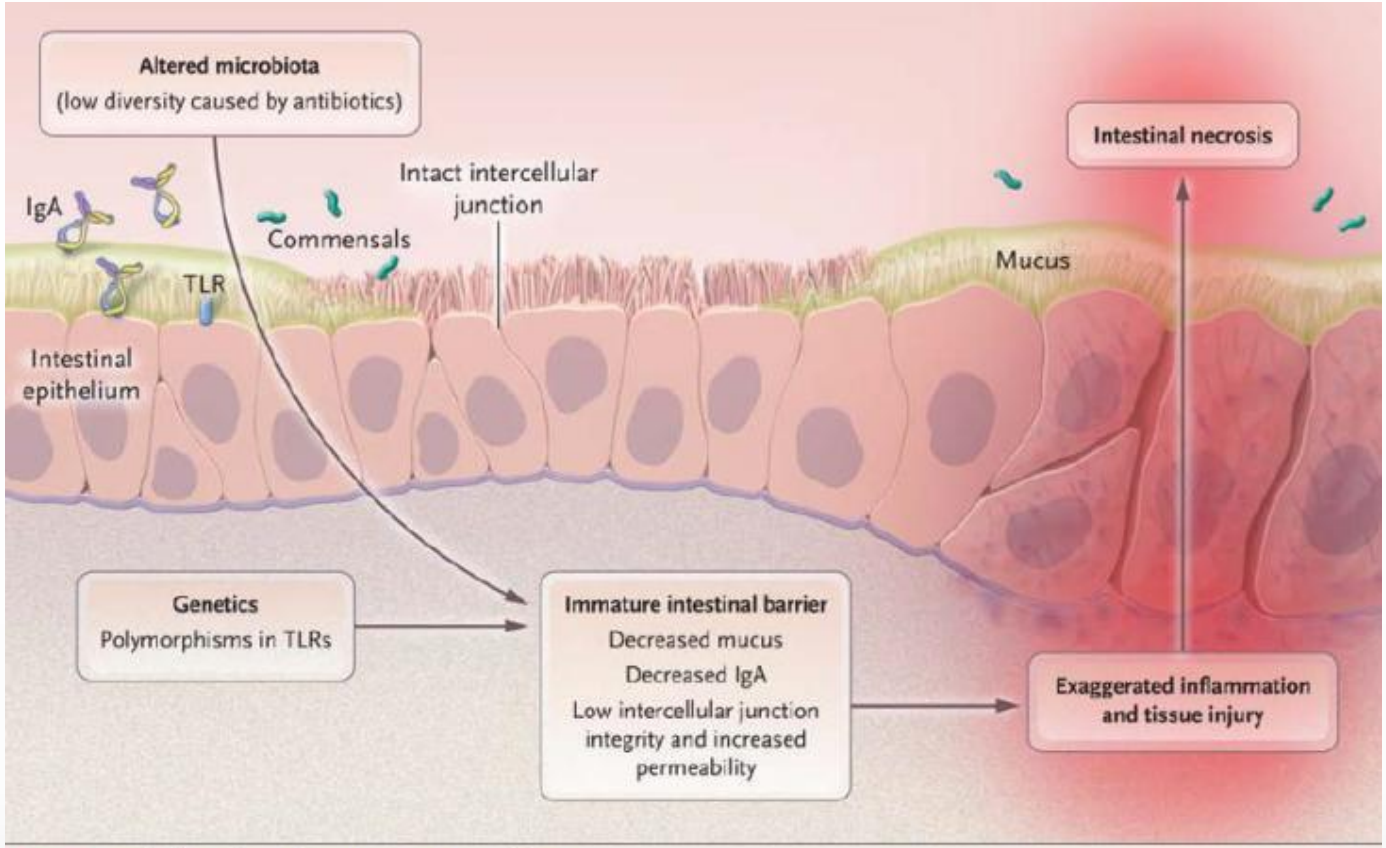

Figure 2. Pathophysiology of Necrotizing Enterocolitis.
Factors conferring a predisposition to necrotizing enterocolitis include genetic factors and several immature characteristics of the fetal intestine, including altered microbiota, inadequate intestinal barrier function, and an excessive inflammatory response. These factors contribute to the severe necrosis of the small intestine that is characteristic of this disease. TLR denotes toll-like receptor.

Neu & Walker NEJM 2011;364:255-64

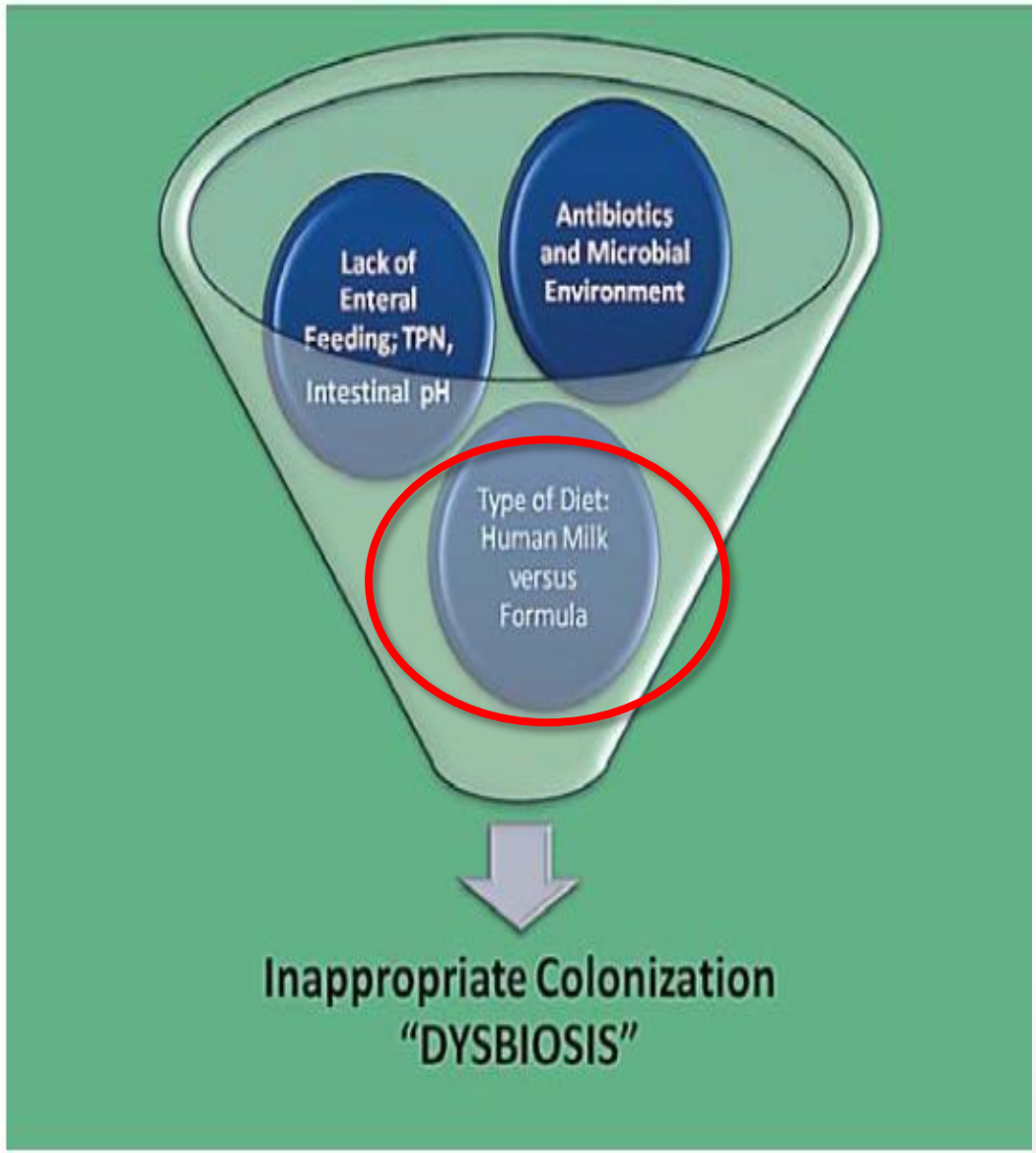

Fig. 1. Inappropriate colonization or 'dysbiosis'.

Neu Neonatology 2014;106:289-95

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RISK FACTORS FOR NEC

- Preterm birth
- Altered intestinal microbiota development
- Prolonged (initial) antibiotics
- Feeding: human milk may be protective…

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BENEFITS OF BREASTFEEDING

World Health Organization

EXCLUSIVE BREASTFEEDING FOR FIRST 6 MONTHS
CONTINUED BREASTFEEDING INCL. COMPLEMENTARY FEEDING UP TO 2 YEARS AND BEYOND

Term infants

- Protection against infection
- Oral tolerance
- Lower risk for allergies
- Lower risk for overweight
- Lower risk for diabetes
- Increased intelligence

Adapted from: Verhasselt, Mucosal Immunol, 2010

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HUMAN MILK COMPOSITION

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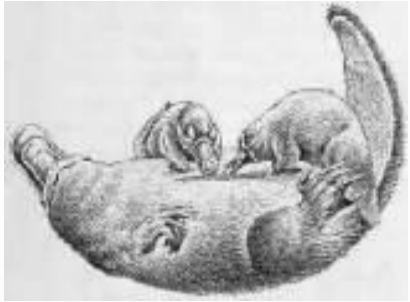
MILK EVOLUTION IN MAMMALS

First
Protective function

Second
Role in nutrition

Lactation may have its origin in the protection of young against microbial attacks by anti-infective secretions?



The egg-laying mammal platypus secrets milk from an incubation patch

Supplements of nutritive components during phylogeny gradually changed these secretions into a dual-purpose, highly protective/highly nutritive drink for the offspring: Human Milk.

Blackburn DG (1993) J Dairy Sci 76, 3195-3112; Blackburn DG et al. (1989) Mammal Review 19, 1-26; Vorbach C et al. (2006) Bioessays 28, 606-16.

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MILK IS VARIABLE ACCORDING TO OFFSPRING NEEDS

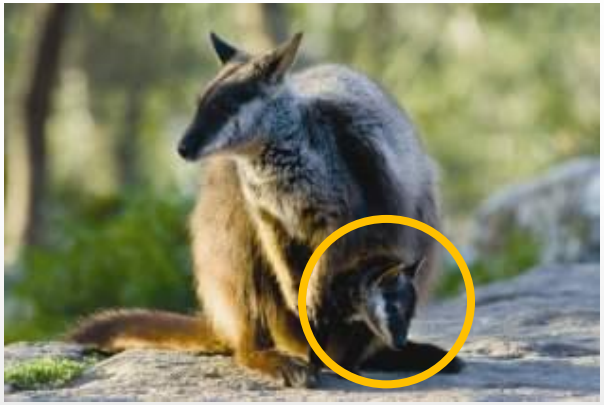
Extreme example: Wallabies

- **Wallabies Produce Two Different Kinds of Milk Types at Once**

  - Milk for the Developing Joey Inside the Pouch
  - Milk (e.g. higher fat) for the Developed Joey (Outside the Pouch)

- **Each Joey Suckles on a Different Teat in Order to Get the Right Milk!**

Closer to Preterm



Lefèvre C. M. et al, Genomics and Human Genetics, 11, 219-238 (2010).

AN ORCHESTRA OF COMPLEX FUNCTIONS IN A COMPLEX MATRIX

+ 88% Water

HMOS
Microbiota
Immunity

Bacteria
Microbiota
Immunity
Digestion

Fat / LCPUFA
Energy
Immunity
Brain
Growth

Hydration

Hormons
Growth
Mood

Vitamins
Growth
Immunity

Lactose
Energy

Living Cells
Immunity
…

Proteins
Growth
Immunity
Signaling

Nucleotides
Growth
Immunity
Brain

Minerals
Growth
Bone & Teeth
Blood

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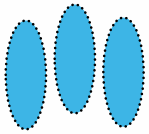
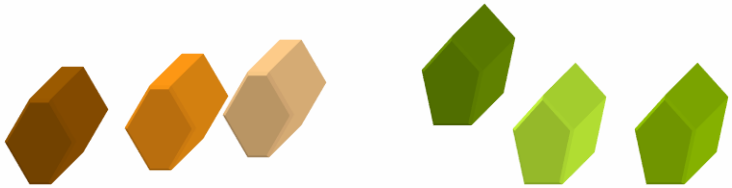
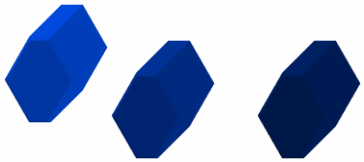
MILK COMPOSITION: BUILDING COMPLEX STRUCTURES

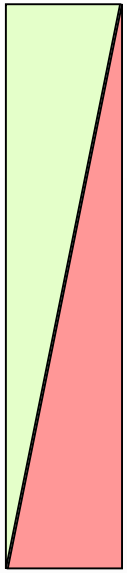
Building Block: ("wagons")



Monosaccharides **Fatty Acids** **Amino Acids** **Nutrition**

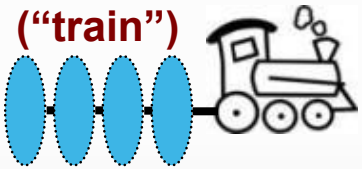






Synthesis & Digestion

Complex Biomolecule: ("train")



Prebiotics **Lipids** **Proteins** **Function**

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COMPOUNDS WITH IMMUNOLOGICAL PROPERTIES IN HUMAN MILK

Anti-microbial compounds
Immunoglobiuines: sIgA, SIgG, SIgM
Lactoferrin, lactoferrin B and H
Lysozyme
Lactoperoxidase
Nucleotide-hydrolizing
Antibodies
κ-casein and α-lactalbumin
Haptocorrin
Mucins
Lactadherin
Free secretory component
Oligosaccharides and pre-biotics
Fatty acids
Maternal leukocytes and Cytokines
sCD14
Complement and complement receptors
β-defensin-1
Toll-like receptors
Bifidus factor
Tolerance/priming compounds
Cytokines: Il10 and TGFβ
Anti-idiotypic antibodies

Immune development compounds
Macrophages
Neutrophils
Lymphocytes
Cytokines
Growth factors
Hormones
Milk peptides
Long-chain polyunsaturated fatty acids
Nucleotides
Adhesion molecules

Anti-inflammatory compounds
Cytokines: Il-10 and TGFβ
Il-1 receptor anatagonist
TNFα and Il-6 receptors
sCD14
Adhesion molecules
Long-chain polyunsaturated fatty acids
Hormones and growth factors
Osteoprotegerin
Long-chain polyunsaturated fatty acids
Hormones and growth factors

Field J Nutr 2005

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MEASUREMENT OF HUMAN MILK COMPONENTS

BREASTMILK

WATER

CARBOHYDRATES (energy source)
- Lactose
- Oligosaccharides (see below)

CARBOXYLIC ACID
- Alpha hydroxy acid
  - Lactic acid

PROTEINS (building muscles and bones)
- Whey protein
  - Alpha-lactalbumin
    - HAMLET (Human Alpha-lactalbumin Made Lethal to Tumour cells)
  - Lactoferrin
  - Many antimicrobial factors (see below)
- Casein
- Serum albumin

Alanine
Arginine
Aspartate
Glycine
Cysteine
Glutamate
Histidine
Isoleucine
Leucine
Lycine
Methionine
Phenylalanine
Proline
Serine
Taurine
Threonine
Tryptophan
Tyrosine
Valine
Carnitine (amino acid compound necessary to make use of fatty acids as an energy source)

Nucleotides (chemical compounds that are the structural units of RNA and DNA)
- 5'-Adenosine monophosphate (5'-AMP)
- 3'5'-Cyclic adenosine monophosphate (3'5'-cyclic AMP)
- 5'-Cytidine monophosphate (5'-CMP)
- Cytidine diphosphate choline (CDP choline)
- Guanosine diphosphate (UDP)
- Guanosine diphosphate - mannose
- 3'- Uridine monophosphate (3'-UMP)
- 5'-Uridine monophosphate (5'-UMP)
- Uridine diphosphate (UDP)
- Uridine diphosphate hexose (UDPH)
- Uridine diphosphate-N-acetyl-hexosamine (UDPAH)
- Uridine diphosphoglucuronic acid (UDPGA)
- Several more novel nucleotides of the UDP type

FATS
- Triglycerides
  - Long-chain polyunsaturated fatty acids
    - Docosahexaenoic acid (DHA) (important for brain development)
    - Arachidonic acid (AHA) (important for brain development)
    - Linoleic acid
    - Alpha-linolenic acid (ALA)
    - Eicosapentaenoic acid (EPA)
    - Conjugated linoleic acid (Rumenic acid)
- Free Fatty Acids
- Monounsaturated fatty acids
  - Oleic acid
  - Palmitoleic acid
  - Heptadecenoic acid
- Saturated fatty acids
  - Stearic
  - Palmitic acid

Plasmalogens

Sphingolipids
- Sphingomyelin
- Gangliosides
  - GM1
  - GM2
  - GM3
- Glucosylceramide
- Glycosphingolipids
- Galactosylceramide
- Lactosylceramide
- Globotriaosylceramide (GB3)
- Globoside (GB4)

Sterols
- Squalene
- Lanosterol
- Dimethylsterol
- Methosterol
- Lathosterol
- Desmosterol
- Triacylglycerol
- Cholesterol
- 7-dehydrocholesterol
- Stigma-and campesterol
- 7-ketocholesterol
- Sitosterol
- β-lathosterol
- Vitamin D metabolites
- Steroid hormones

VITAMINS
- Vitamin A
- Beta carotene
- Vitamin B6
- Vitamin B8 (Inositol)
- Vitamin B12
- Vitamin C
- Vitamin D
- Vitamin E
- a-Tocopherol
- Vitamin K
- Thiamine
- Riboflavin
- Niacin
- Folic acid
- Pantothenic acid
- Biotin

MINERALS

Copper
Manganese
Iodine
Selenium
Choline
Sulpher
Chromium
Cobalt
Fluorine
Nickel

METAL
- Molybdenum (essential element in many enzymes)

GROWTH FACTORS (aid in the maturation of the intestinal lining)
- Cytokines
  - Interleukin-1β (IL-1β)
  - IL-2
  - IL-4
  - IL-6
  - IL-8
  - IL-10
  - Granulocyte-colony stimulating factor (G-CSF)
  - Macrophage-colony stimulating factor (M-CSF)
  - Platelet derived growth factors (PDGF)
  - Vascular endothelial growth factor (VEGF)
  - Hepatocyte growth factor -α (HGF-α)
  - HGF-β
  - Tumor necrosis factor-α
    - Interferon-γ
  - Epithelial growth factor (EGF)
  - Transforming growth factor-α (TGF-α)
  - TGF-β1
  - TGF-β2
  - Insulin-like growth factor-I (IGF-I) (also known as somatomedin C)
  - Insulin-like growth factor- II
  - Nerve growth factor (NGF)
  - Erythropoietin

PEPTIDES (combinations of amino acids)
- HMGF I (Human growth factor)
- HMGF II
- HMGF III
- Cholecystokinin (CCK)
- β-endorphins
- Parathyroid hormone (PTH)
- Parathyroid hormone-related peptide (PTHrP)
- β-defensin-1
- Calcitonin
- Gastrin
- Motilin
- Bombesin (gastric releasing peptide, also known as neuromedin B)
- Neurotensin
- Somatostatin

HORMONES

Thyroid releasing hormone (TRH)
Prolactin
Oxytocin
Insulin
Corticosterone
Thrombopoietin
Gonadotropin-releasing hormone (GnRH)
GRH
Leptin (aids in regulation of food intake)
Ghrelin (aids in regulation of food intake)
Adiponectin
Feedback inhibitor of lactation (FIL)

Eicosanoids
- Prostaglandins (enzymatically derived from fatty acids)
  - PG-E1
  - PG-E2
  - PG-F2
- Leukotrienes
- Thromboxanes
- Prostacyclins

ENZYMES (catalysts that support chemical reactions in the body)
- Amylase
- Arysulfatase
- Catalase
- Histaminase
- Lipase
- Lysozyme
- PAF-acetylhydrolase
- Phosphatase
- Xanthine oxidase

ANTIPROTEASES (thought to bind themselves to macromolecules such as enzymes and as a result prevent allergic and anaphylactic reactions)
- a-1-antitrypsin
- a-1-antichymotrypsin

ANTIMICROBIAL FACTORS (are used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses.)
- Leukocytes (white blood cells)
  - Phagocytes
    - Basophils
    - Neutrophils
    - Eosinophils
  - Macrophages
  - Lymphocytes
    - B lymphocytes (also known as B cells)
    - mphocytes (also known as C cells)

retory immunoglobulin A) (the most
t antiinfective factor)

Complement C1
Complement C2
Complement C3
Complement C4
Complement C5
Complement C6
Complement C7
Complement C8
Complement C9
Glycoproteins
- Mucins (attaches to bacteria and viruses to prevent them from clinging to mucousal tissues)
- Lactadherin

Alpha-lactoglobulin
Alpha-2 macroglobulin
Lewis antigens
Ribonuclease
Haemagglutinin inhibitors
Bifidus Factor (increases growth of Lactobacillus bifidus - which is a good bacteria)
Lactoferrin (binds to iron which prevents harmful bacteria from using the iron to grow)
Lactoperoxidase
B12 binding protein (deprives microorganisms of vitamin B12)
Fibronectin (makes phagocytes more aggressive, minimizes inflammation, and repairs damage caused by inflammation)
Oligosaccharides (more than 200 different kinds)

ANALYTICAL CHALLENGE

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HUMAN MILK COMPOSITION

QUANTITY

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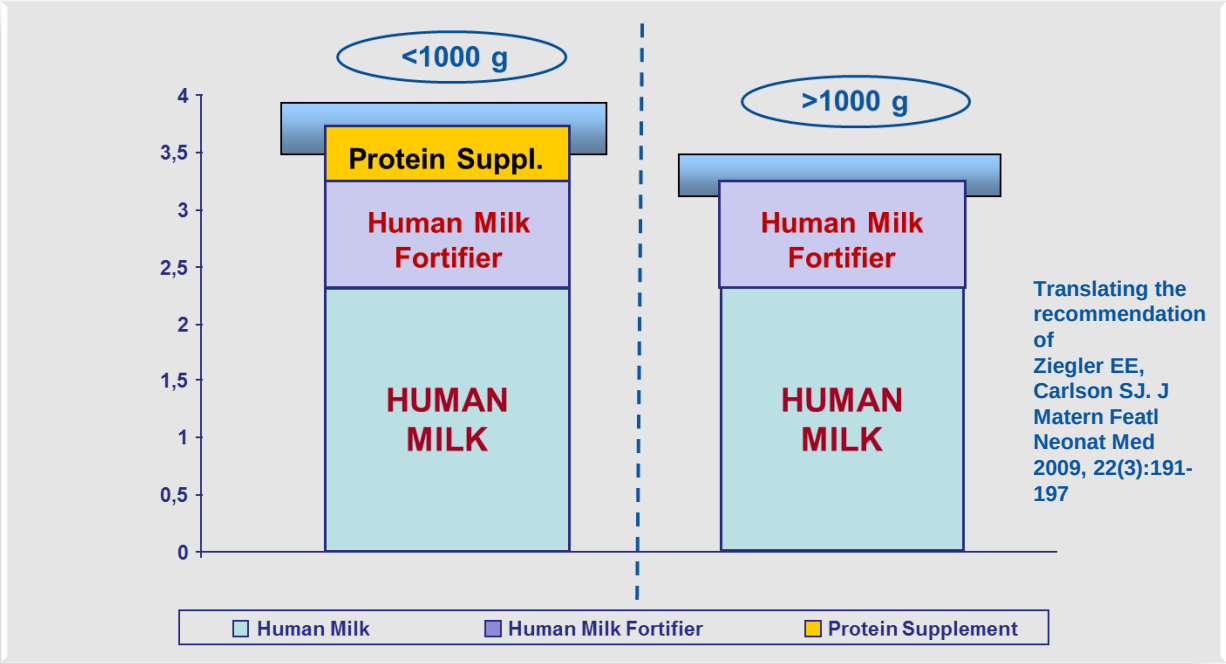
HUMAN MILK FOR PRETERM INFANTS



Translating the recommendation of Ziegler EE, Carlson SJ. J Matern Featl Neonat Med 2009, 22(3):191-197

XII. Human Milk in Feeding Premature Infants: Consensus Statement

Guido E. Moro, Sertac Arslanoglu, Enrico Bertino, Luigi Corvaglia, Rosario Montirosso, Jean-Charles Picaud, Staffan Polberger, Richard J. Schanler, Caroline Steel, Johannes van Goudoever, and Ekhard E. Ziegler

JPGN • Volume 61, Supplement 1

September 2015

1. All preterm infants with BW <1800 grams should be fed fortified HM (protein, vitamins & minerals to enable appropriate growth)
2. Start with standard fortification
3. If growth is not appropriate, individualized fortification is advisable:
   - targeted fortification (based on HM analysis)
   - adjustable fortification (based on BUN measurements)

Both are advisable depending on the NICU experience and facilities.

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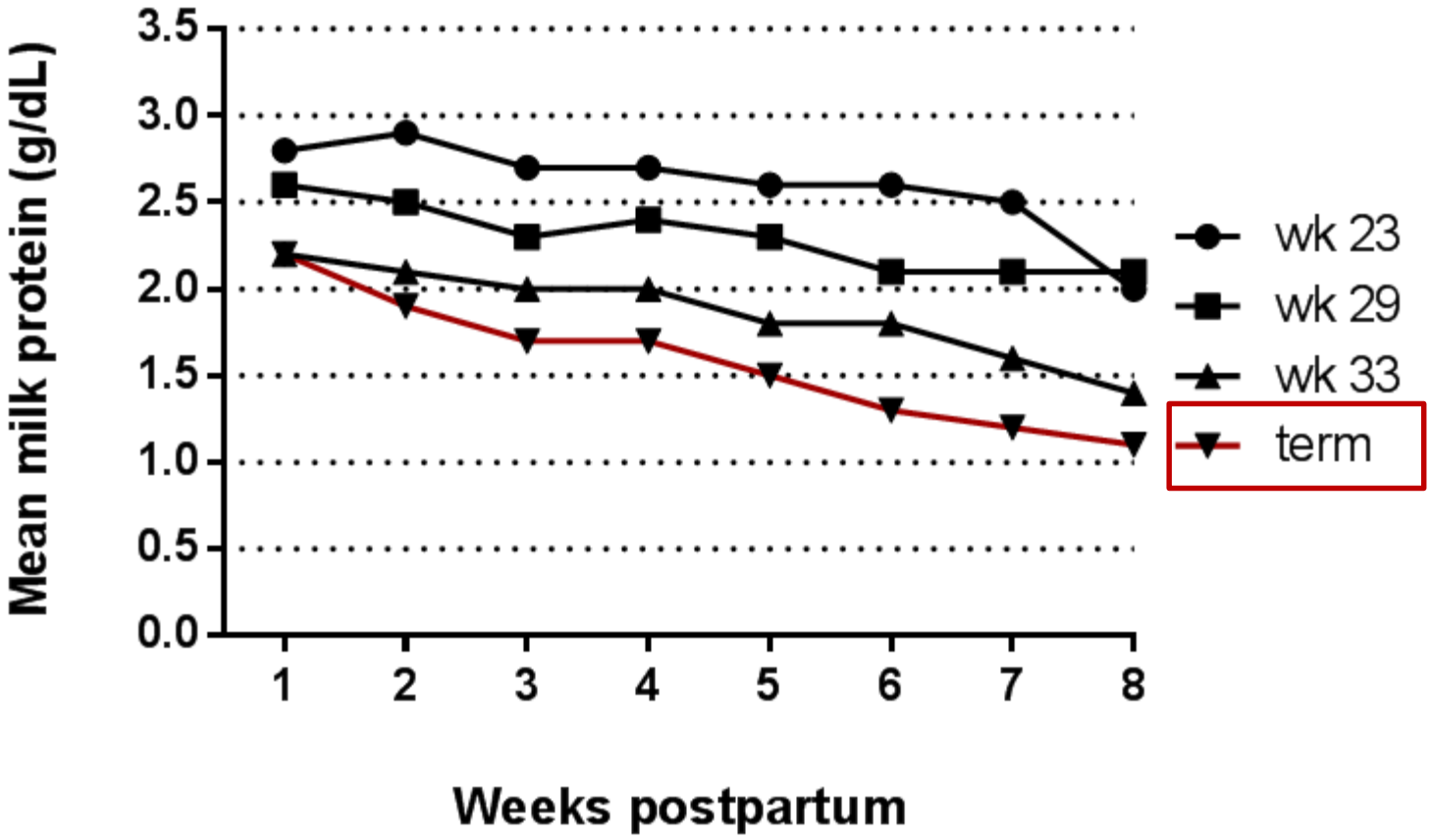
PROTEIN CONCENTRATION IN HUMAN MILK

Preterm vs. Term



Bauer J, Gerss J. Clin Nutr 2011;30:215–20.

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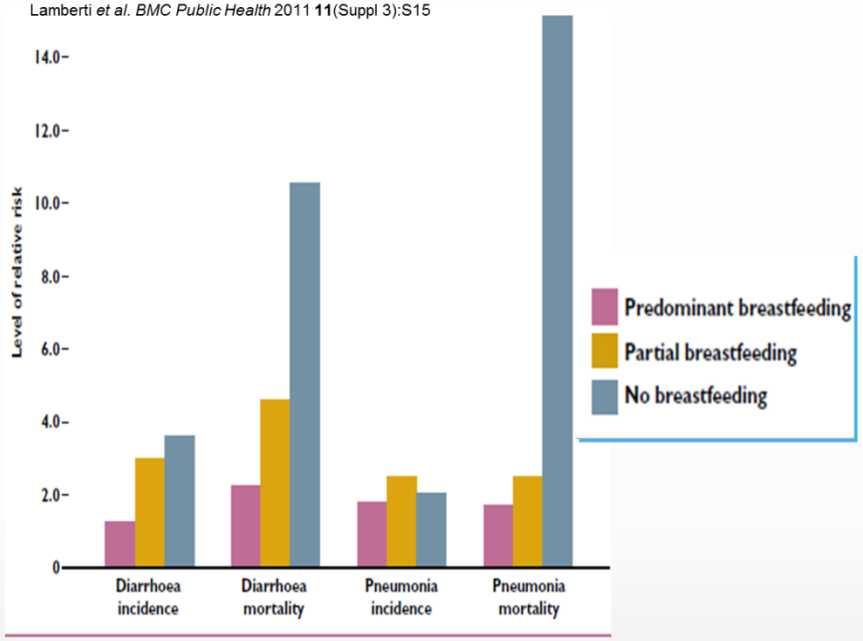
DOSE RESPONSE OF BREAST FEEDING TERM INFANTS

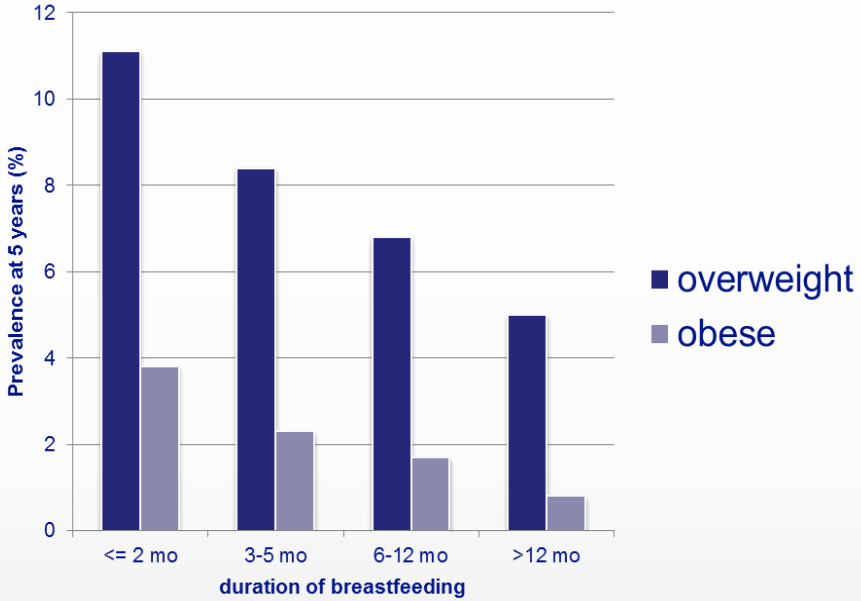
INFECTIONS (IMMUNITY)

Lamberti *et al. BMC Public Health* 2011 **11**(Suppl 3):S15



OVERWEIGHT OBESITY

Von Kries et al 1999 BMJ (319): 147-150



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EARLY NUTRITION STUDY

MULTICENTER STUDY IN PRETERM INFANTS

- **RCT First 10 days donor milk vs preterm formula if own mother's milk was not (sufficiently) available**
- **Primary outcome parameter: cumulative incidence of LOS/Meningitis, NEC or death in first 60 days**
- **No difference in primary outcome**
- **However 89 vs 84,5% received own mother's milk in first 10 days!**
- **>50% own mother's milk associated with lower risk in primary outcome compared to <50% own mother's milk**

Corpeleijn et al JAMA Pediatr 2016;170:654-61

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HUMAN MILK COMPOSITION

QUALITY

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HUMAN MILK QUALITY

Impact of Pasteurization on Growth of Preterm Infants

- 17% **higher fat absorption** and **more weight gain and linear growth** in infants fed mother's own raw milk compared to mother's own pasteurized milk (Andersson, 2007).
  Probable reason: **deactivation of BSSL** by pasteurization.

- **Improved weight gain** and a **decreased risk for NEC** was found in premature infants fed with mother's own raw milk compared with pasteurized donor milk (Montjaux-Régis, 2011).

MILK QUALITY – FUNCTIONAL MILK PROTEINS

Frozen Human Milk

Host Defense Proteins
Activity lowered up to 70%

Pathogens* applied to HM

grow up to 3.6 fold in 6h

** S aureus, P aeruginosa, E coli*

Pasteurised Human Milk

Host Defense Proteins
Activity lowered up to 90 %

Pathogens* applied to HM

grow up to 4.6 fold in 6 h

Akinbi et al JPGN 2010

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HUMAN MILK PROCESSING: A SYSTEMATIC REVIEW OF INNOVATIVE TECHNIQUES TO ENSURE THE SAFETY AND QUALITY OF DONOR MILK

- Holder pasteurisation is currently the most used method
- But affects several of the active ingredients
- Data about safety for microbiological control are still scarce for most of the novel technologies
- consensus on processing conditions is necessary for non-thermal technologies, before any conclusions on the qualitative and nutritional advantages of these techniques can be drawn.

Peila C, Emmerik NE, et al, JPGN 2016 (accepted for publication)

HUMAN MILK COMPOSITION

Maternal factors:

- Diet & health condition of the mother

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HUMAN MILK COMPOSITION

OTHER NEW INSIGHTS

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DIFFERENT HUMAN MILK FOR SONS & DAUGHTERS

Energy content of breast milk for boys is higher

HM for boys had 25% greater caloric content than HM for girls

Boys grow faster than girls, thus, have an increased energy demand.

Breastfed boys consume more milk

How gender-specific milk is physiological regulated is yet unknown.

- Hinde K (2007): Current Biology 17, R958–R959
- Landete-Castillejo T et al. (2004): Behav Ecol Sociobiol 57, 749–799
- Michaelsen KF et al. (1994): Am J Clin Nutr 59, 600–611.
- Powe CE et al. (2010): American Journal of Human Biology 22, 50–54

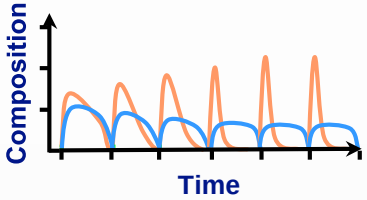
HUMAN MILK IS VARIABLE ⇔ CONSISTENCY IN BENEFITS

- Mums Diet and Local Environment, Lifestyle

- Mums & Babies Health Conditions

- Genetic Background

- Compositional Changes during Lactation



- Human milk composition in different regions of the world

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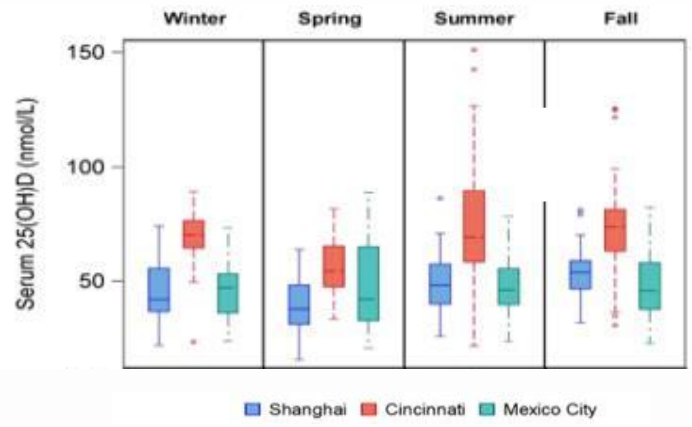
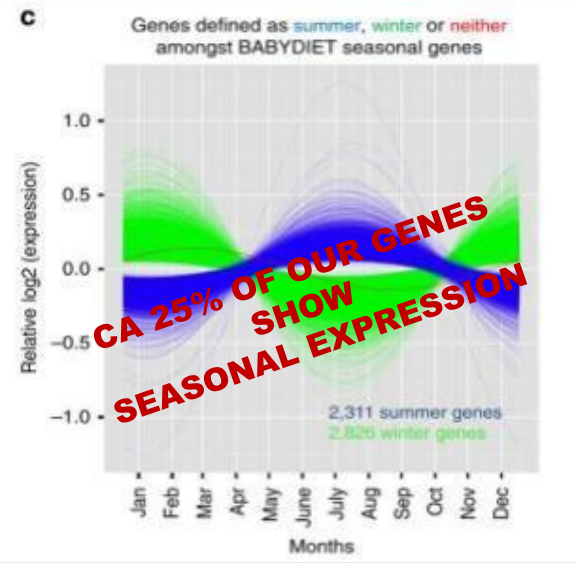
HUMAN MILK: QUATTRO STAGIONI

Giuseppe *Arcimboldo*
(* 1526; † 11. July 1593 in Milano)



Maternal vitamin D status by season and site, $p < 0.001$ by ANOVA,



Widespread seasonal gene expression in the immune system

23% of the genome (5,136 unique genes out of 22,822 genes tested) show significant seasonal differences in gene expression


ARTICLE

Received 9 Sep 2014 | Accepted 23 Mar 2015 | Published 12 May 2015 OPEN

Widespread seasonal gene expression reveals annual differences in human immunity and physiology

Xaquin Castro Dopico[1,*], Marina Evangelou[1,*], Ricardo C. Ferreira[1], Hui Guo[1], Marcin L. Pekalski[1], Deborah J. Smyth[1], Nicholas Cooper[1], Oliver S. Burren[1], Anthony J. Fulford[2], Branwen J. Hennig[2], Andrew M. Prentice[2], Anette-G. Ziegler[3], Ezio Bonifacio[4], Chris Wallace[1,5,**] & John A. Todd[1,**]

Dawodu A et al, Nutrients. 2015; 7: 1081–1093; Ala-Houhala M et al Am J Clin Nutr. 1988;48:1057-60.

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HM REFLECTS HEALTH STATUS OF THE INFANT


Articles | Clinical Investigation

Pediatric RESEARCH Volume 71 | Number 2 | February 2012

Changes in immunomodulatory constituents of human milk in response to active infection in the nursing infant

Arieh Riskin[1], Meital Almog[2], Regina Perl[2], Katy Halasz[2], Isaac Srugo[2] and Aharon Kessel[2]


OPEN

ORIGINAL ARTICLE

Maternal and infant infections stimulate a rapid leukocyte response in breastmilk

Fotini Hassiotou[1,2], Anna R Hepworth[1], Philipp Metzger[2,3], Ching Tat Lai[1], Naomi Trengove[1,4], Peter E Hartmann[1] and Luis Filgueira[2]

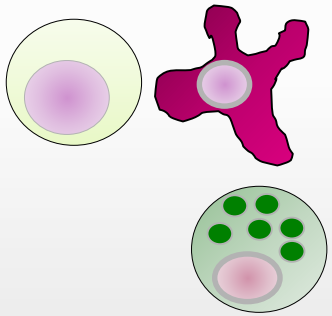
- During active infection in the infant, total number of white blood cells, specially number of macrophages, and TNFα levels in breast milk increase.
- Dynamic immunological connection between lactating mothers and their infants

- Baseline level of leukocytes (0-2%) in mature milk unless the mother and/or her infant became infected, when leukocyte numbers significantly increased up to 94% leukocytes out of total cells ($P < 0.001$).

HUMAN MILK .....  3D...IS...

Cells

- Macrophages
- Neutrophils
- T cells
- DC
- Epithelial cells

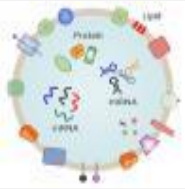


Milk fat globules

- Origin: breast epithelial cells
- Plasma membrane enveloped lipid droplet
- Lipid trilayer enclosed
- Main fat storage units in milk
- 0,2 – 15 µm in size

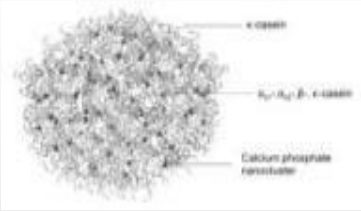
Extracellular vesicles

- Origin: various cell types
- Lipid bilayer enclosed
- Mediators of intercellular communication
- <0,2 µm in size



Casein micelles

- a-casein, b-casein, k-casein
- Non-globular proteins with a micellar structure
- Human milk micelles ~43 nm



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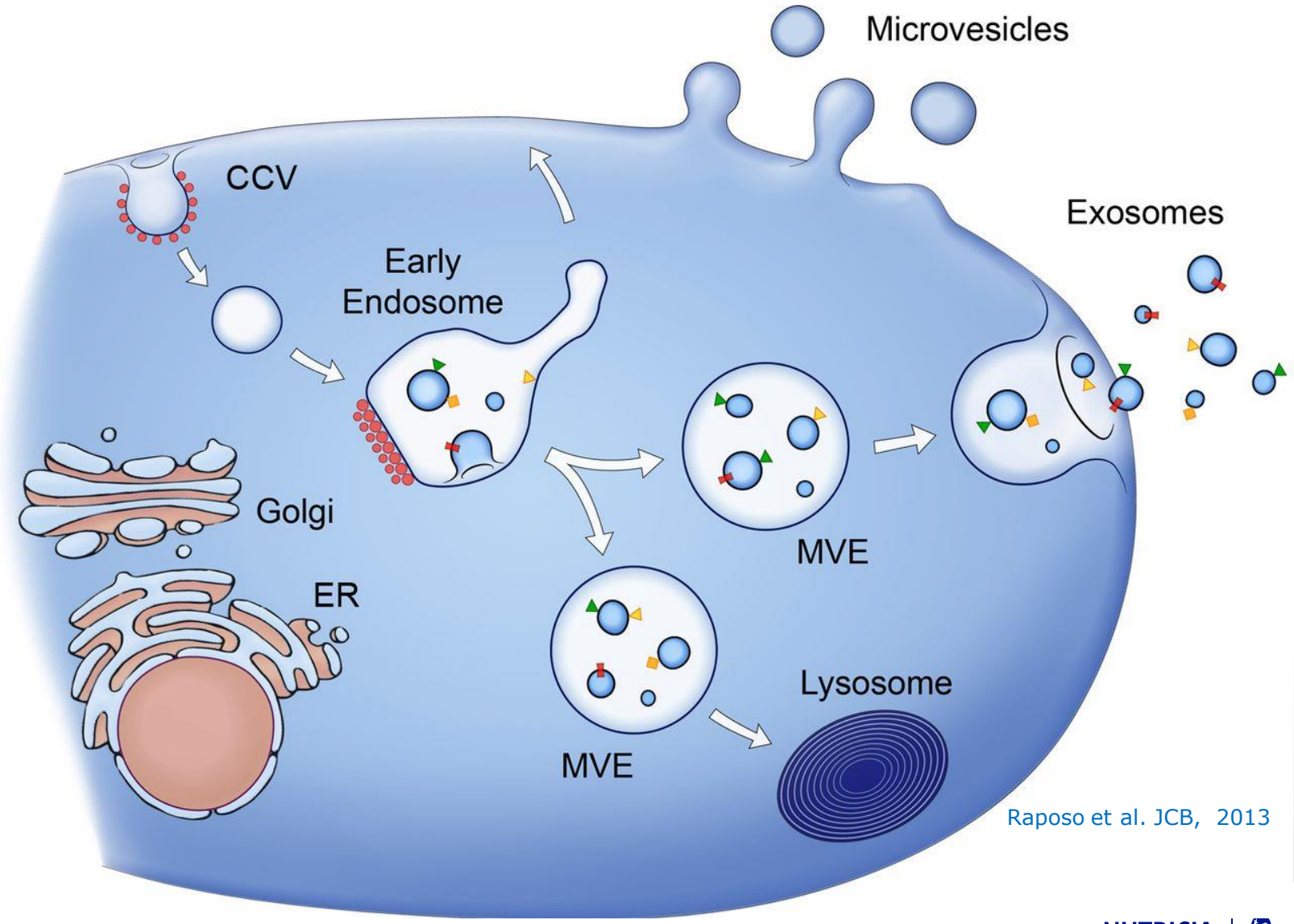
EV FORMATION



Raposo et al. JCB, 2013

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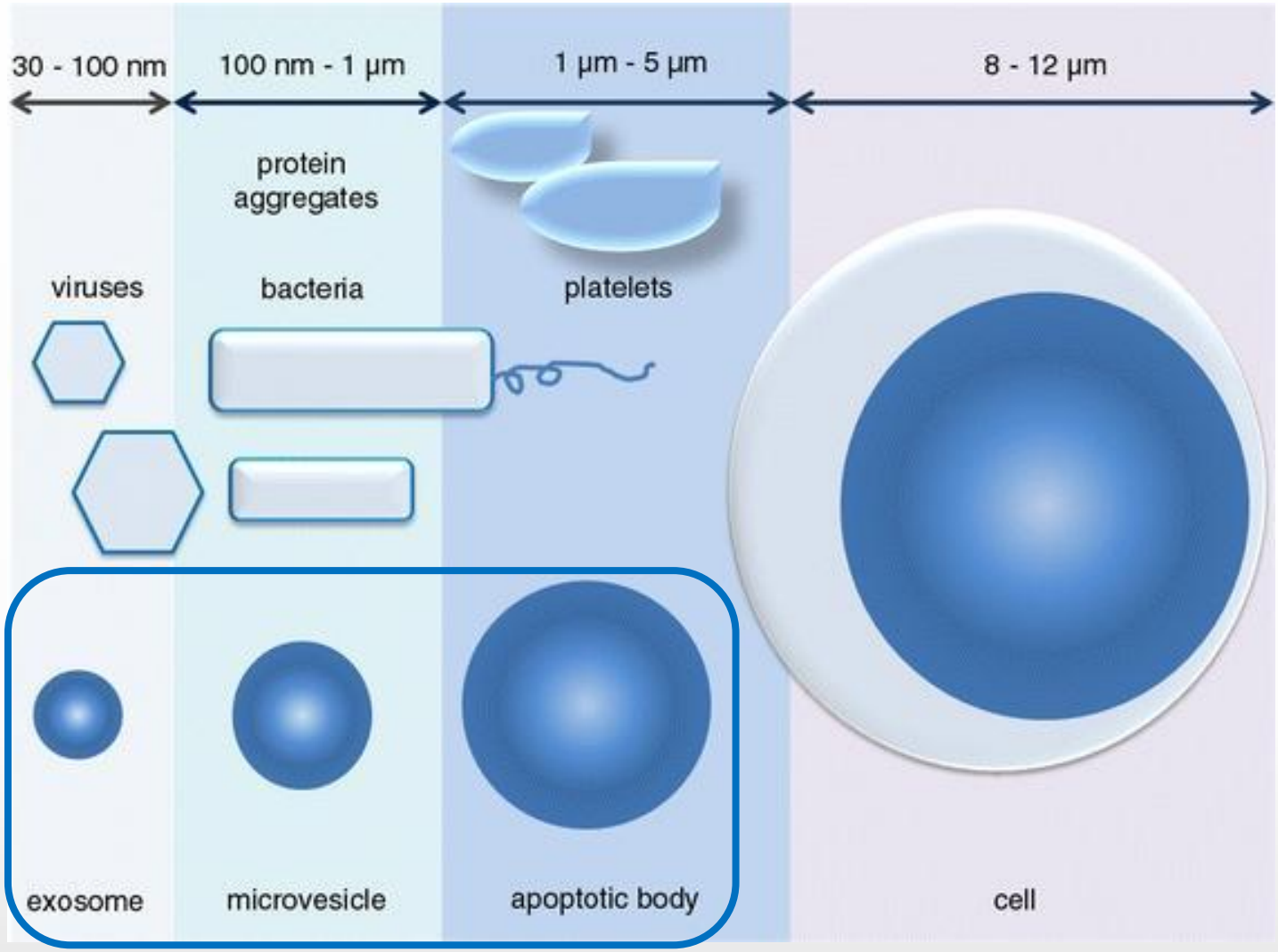
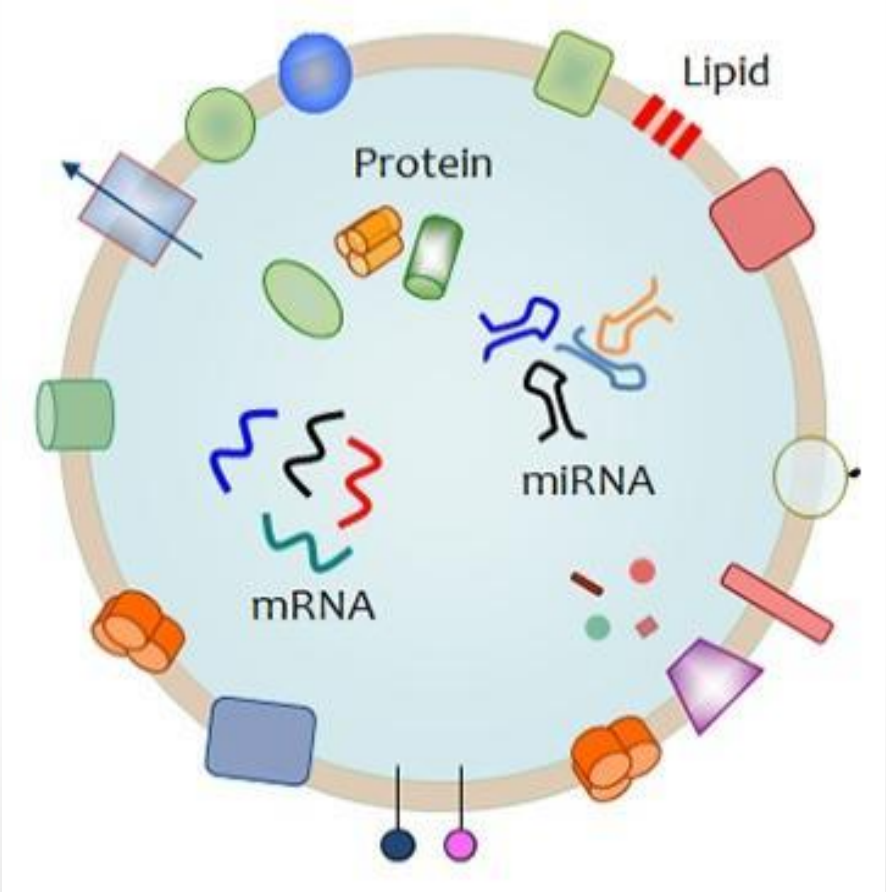
EXTRACELLULAR VESICLES (EV)



György et al. Cell Mol Life Sci, 2011

EV CARGO



Lipids

-Ceramide

-Cholestrol

-Phosphatidylserine

Proteins

-MHC class I/II

-Co-stimulatory molecules

-Cytokines (e.g., IL-1β, TGF-β)

-Heat shock proteins

Genetic material

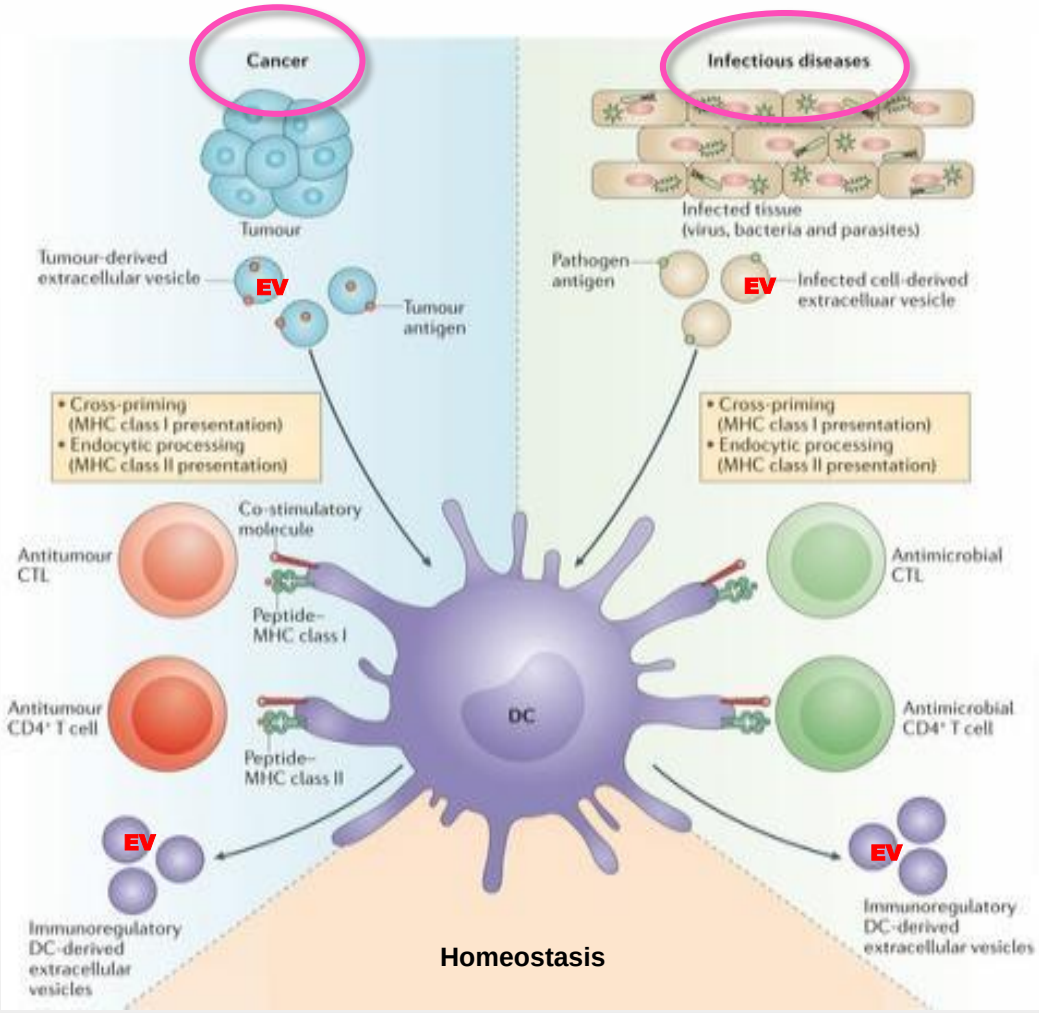
-miRNA

-mRNA

-Small non-coding RNA

Adapted from EVpedia

BIOLOGICAL ROLE OF EV



Adapted from: Robbins et al. Nat Rev Imm, 2014

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THE COMPOSITION & BENEFITS OF HUMAN MILK

…there are different orchestra…

…and even one orchestra can play very different music!

No WW reference Value for HM composition

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NEC AND HUMAN MILK

NEC AND PROBIOTICS

Pubmed search 2016:

- **NEC and human milk: 219 hits**

- **NEC and Probiotics: 181 hits**
- **First publication 2002**
- **One of the first publications by Kate Costeloe (2003)**

POTENTIAL NUTRITIONAL THERAPIES FOR NEC

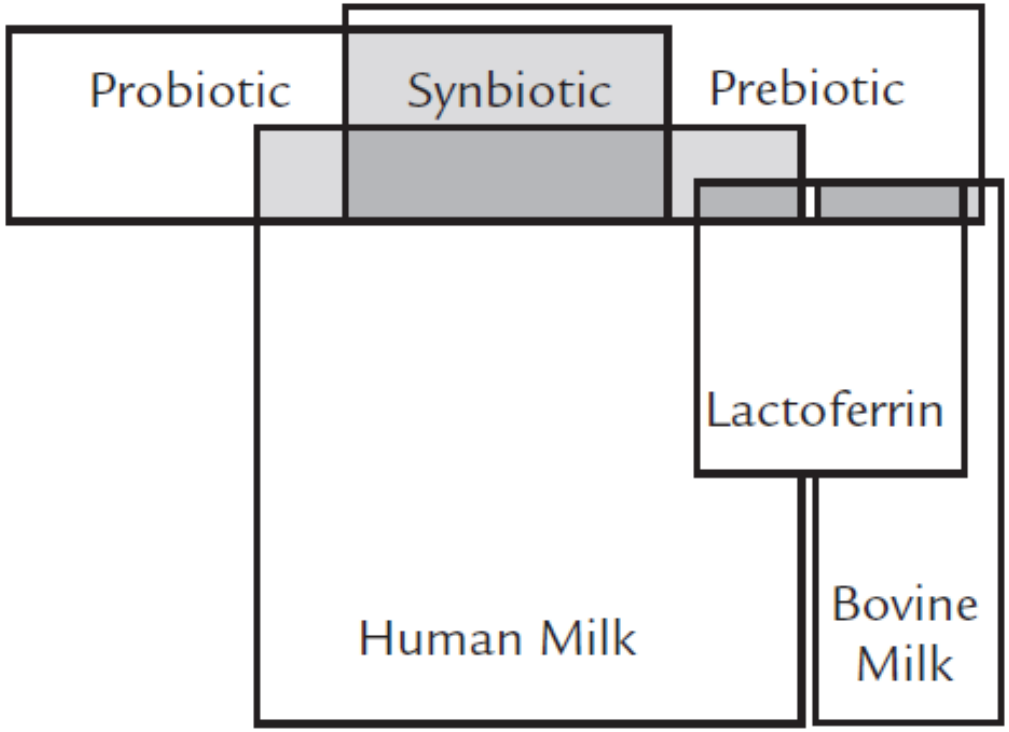

Fig. 1. Dietary and supplemental strategies for altering the intestinal microbiota of the premature infant. Shading represents areas of overlap.

Vongbhavit et al. Prevention of necrotising enterocolitis through manipulation of the intestinal microbiota in the premature infant. Clin Ther 2016;38:716-32.

NEW INSIGHTS IN HUMAN MILK COMPOSITION AND BENEFITS FOR PRETERM INFANTS

CONCLUSIONS

- No worldwide standard for human milk composition
- Quantitative and qualitative aspects of human milk are important for the benefit of preterm infants
- Freezing and processing have major impact on bioavailability of ingredients of human milk
- Human milk & supplements (eg prebiotics, probiotics, synbiotics, lactoferrin) may have protective effect for the development of NEC in preterm infants

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