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CurrentViews©

IN PEDIATRIC NUTRITION

Food Allergy in Infants and Young Children

Early Life Nutrition and the Role of Infant Formula

Nutrition, Microbiota and the Gut

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EDITOR'S NOTE

The world of Medicine has made great advances since its early days. In recent years we have had the privilege of witnessing developments in understanding the pathogenesis of many of the diseases burdening humankind. It is frustrating, though, to realize that most of this up-to-date knowledge does not reach its natural recipients, who are specialist in each specialty working in daily practice. Thus, we believe that the need for an informative journal is obvious and self-explanatory.

For this reason, CCM will fill the gap in continuing medical education to benefit every day clinical practice, by publishing this innovative series of Current Views. In every issue, readers will find a review article and several summary articles. *Current Views in Pediatric Nutrition* was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the CCM editorial team based on an ongoing review of the international literature, and articles are selected for review and citation on the basis of their relevance to clinical practice.

Current Views in Pediatric Nutrition provides specialists with an attractive means of continuing medical education that demonstrates the best of critical thinking and is a source of, and a catalyst for, new ideas and learning. The editors and medical advisors at CCM have made every effort to search the international literature to present the most current, interesting and cutting edge articles, in order to make *Current Views in Pediatric Nutrition* a respected and useful tool of physicians with one aim: to provide a good service to their patients. For this issue, we have retrieved information from several well respected peer reviewed journals:

Advances in Pediatrics
Ann Allergy Asthma Immunol
Br J Nutr
Cell Host Microbe
Clin Nutr
Curr Microbiol
Curr Opin Microbiol
Curr Probl Pediatr Adolesc
Front Immunol
Front Neurosci
Front Pediatr
Gut
Immunology and Allergy Clinics of North America
ISME J
J Allergy Clin Immunol
J Dev Orig Health Dis
J Nutr
J Pediatr
MEDICC Rev
mSphere
Nat Commun
Nature
Nutrients
Pediatr Allerg Immunol
Pediatr Gastroenterol Hepatol Nutr
Pediatric Clinics of North America
Pediatrics
PLoS One
Proc Natl Acad Sci
Rev Immunol
Seminars in Fetal and Neonatal Medicine

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A Note from the Regional Editors

Progress in Pediatric Nutrition has continued at a spectacular pace culminating in a rapid surge in the number of increasingly precise articles on information about the assessment of growth, the nutritional status assessment and feeding guidelines, biochemical evaluation of nutritional status, infant nutrition, enteral nutrition, parenteral nutrition, nutritional management in health as well as in disease for pediatric residents powered by research. The cumulative knowledge of the complexities of Pediatric Nutrition continues to be the foundation of new advances across the clinical care continuum.

Discoveries in the fields of metabolism, genomics and immunology have been particularly fruitful and have firmly established two new pillars of clinical care. These exciting fields of research also show immense promise for the future. Furthermore Clinical Medical Societies have been updating their Guidelines of Pediatric Nutrition.

Current Views in Pediatric Nutrition was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the Regional Editors based on an ongoing review of the international literature, and articles are selected and then summarized for citation and review on the basis of their relevance to clinical practice.

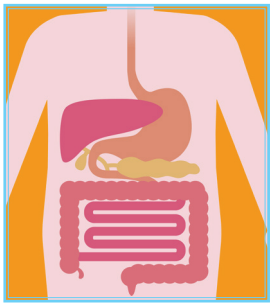
Current Views in Pediatric Nutrition mainly caters to the needs of the professionals, researchers, clinical practitioners and medical practitioners in the field of Pediatrics. Our content covers topics that advance clinical practice, and tackle issues related to global Pediatrics. The Regional Editorial Board's aim is to include the most complete and reliable sources of information and discoveries ongoing in Pediatrics and Nutrition research and treatment. The Regional Editors work as a distinguished team of experts to ensure the highest standards of selection. All relevant articles in the international literature are carefully considered and once selected all materials are promptly processed and published.

The stringency of selecting and voting on state of the art articles was done by our respected Regional Editorial team members who are listed within the journal. Our fundamental purpose is to advance clinically-relevant knowledge of Pediatric Nutrition, and improve the outcome of prevention, diagnosis and treatment of pediatric disease.

In this first issue, due to the spectacular developments seen lately, original research articles, early reports and review articles covering key points, potential pitfalls, and management algorithms which allow for rapid-reference, and link with the latest evidence, guidelines and protocols from ESPGHAN and NASPGHAN covering the major professional society recommendations for clinical practice have been included.

We believe that the readers will find many topics of interest related to their everyday practice.

The Regional Editorial Board

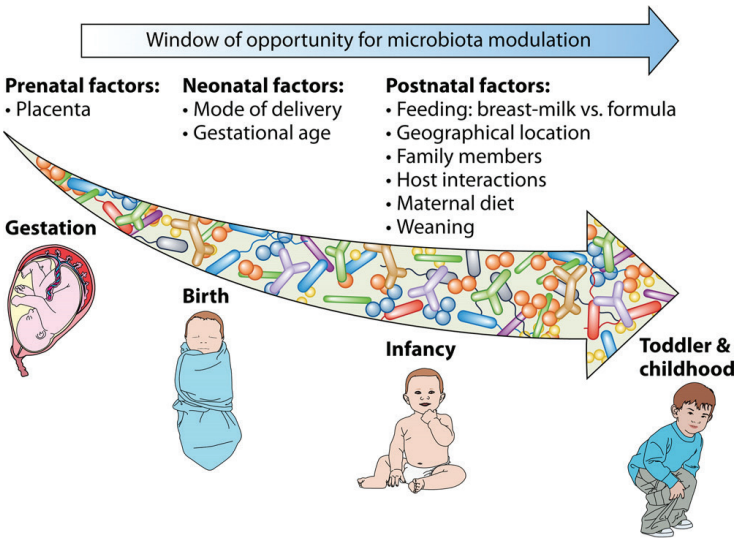


Feature Article

Early life nutrition and the role of infant formula

Nutrition, Microbiota and the Gut

Food Allergy in Infants and Young Children



Window of opportunity for microbiota modulation from gestation to childhood. The schematic representation shows a list of prenatal, neonatal, and postnatal factors that contribute to the bacterial gut composition in infants.

From: Milani C, Duranti S, Bottacini F, Casey E, Turroni F, Mahony J, Belzer C, Delgado Palacio S, Arboleya Montes S, Mancabelli L, Lugli GA, Rodriguez JM, Bode L7 de Vos W4,8, Gueimonde M, Margolles A, van Sinderen D, Ventura M. The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implicationsof the Infant Gut Microbiota. Microbiol Mol Biol Rev. 2017 Nov 8;81(4). pii: e00036-17. doi: 10.1128/MMBR.00036-17. Print 2017 Dec. Copyright © 2017 American Society for Microbiology. Used with Permission

Introduction

A food allergy is defined according to the National Institute of Allergy and Infectious Disease's expert panel as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food." Evidence suggests that the prevalence of food allergy is increasing, with reliable estimates of the number of children with food allergy as high as 8%. Food allergy has been a concern for a great many years.[1]

There is 'compelling evidence' for an increase in food allergy prevalence, and it has been hypothesized that changes in diet might be responsible for this increase. The changes in dietary intake that have been suggested to have a causal link with allergy development are a decreased intake of fruits and vegetables, a change in the types of fat in the diet, or both. This has led to an interest in the role of specific nutrients, foods, or both in allergy development and also the link between diet and existing allergic disease.[2]

The role of the infant diet in the development of food allergy has long been researched, with studies looking at the timing of important feeding events during infancy or the diet's content of particular nutrients, such as long-chain polyunsaturated fatty acids, vitamin D, and folic acid. However, a number of nutritional/dietary variables might be acting on the development of food allergy in infants, and therefore focusing on one nutrient or dietary characteristic (eg, timing of solid introduction) might be an oversimplification of the complex interactions taking place.[2]

Looking at the pattern of consumption as opposed to focusing on individual nutrients can take into account nutrient interactions of known or unknown effects, a process thought to be particularly useful when looking at disease etiology.[2]

Prevalence

Food is the most common trigger for anaphylaxis in children and studies show that annual rates for emergency department (ED) visits and hospital admissions for food induced anaphylaxis (FIA) have increased significantly. The current literature reports that infants constitute between 3% and 22% of anaphylaxis cases presenting to the ED.[3]

Food allergy is estimated to affect around 5% to 10% of infants and young children in developed countries. Data show that the incidence of food-induced anaphylaxis increased between the 1990s and 2010, particularly in children, although it remains unclear to what extent this is due to an increase in food allergy prevalence, an increase in severe reactions among allergic individuals, or an increased number of reactions in the same pool of allergic people. A recent acceleration in rates of adolescent anaphylaxis supports the concept of a cohort effect with children born in the early stages of the increase in food allergy prevalence in the early 2000s now reaching adolescence.[4]

There are increasing published reports on food allergy prevalence from around the world, which reveal emerging significant differences in the prevalence between countries, although the reasons for these differences are not yet established. The Europrevall birth cohort study was designed to compare food allergy prevalence between countries by using a standardized study protocol in multiple European centers. Around 12,000 infants from 9 countries were recruited into a series of birth cohorts in 2005 to 2010, with approximately 9000 infants followed up to 2 years of age. The prevalence of egg allergy was reported to range from 0.07% in Greece to more than 2% in Germany and the United Kingdom, whereas cow's milk allergy ranged from 0% in Greece to 1.3% in Lithuania. Outside of Europe, the HealthNuts study in Australia recruited 12-month-old infants around the same time as Europrevall (2007–2011). Of the 5300 participating infants, 3.0% were peanut allergic, 9.0% egg allergic, and 0.8% sesame allergic.[4]

Recently, there have been new publications reporting the prevalence of food allergy in infants in South Africa and China, both countries where food allergy was previously considered to be rare.[4]

IgE-Mediated and Non IgE-Mediated Food Allergy

IgE-Mediated Food Allergy

The best characterized food allergic reactions involve IgE antibodies that bind to high-affinity FcεRI receptors on mast cells and basophils as well as low-affinity FcεRII (CD23) receptors on macrophages, monocytes, lymphocytes, and platelets. When food allergens penetrate mucosal barriers and reach IgE antibodies bound to mast cells or basophils, mediators are released that induce vasodilatation, smooth muscle contraction, and mucus secretion, producing the symptoms of immediate hypersensitivity. The activated mast cells also release a variety of cytokines, which may contribute to the IgE-mediated late phase response. During the initial 4 to 8 hours, primarily neutrophils and eosinophils invade the site of response. These infiltrating cells are activated and release a variety of mediators, including platelet-activating factor, peroxidases, eosinophil major basic protein, and eosinophil cationic protein. In the subsequent 24 to 48 hours, lymphocytes and monocytes infiltrate the area and establish a more chronic inflammatory picture. With repeated ingestion of a food allergen, mononuclear cells are stimulated to secrete histamine-releasing factor (HRF), a cytokine that interacts with IgE molecules bound to the surface of basophils (and perhaps mast cells) and increases their releasability. The spontaneous generation of HRF by activated mononuclear cells in vitro has been associated with increased bronchial hyperreactivity in patients with asthma and increased cutaneous irritability in children with atopic dermatitis.[5]

IgE-mediated allergic reactions are associated with a variety of symptoms: generalized (e.g., hypotension, shock), cutaneous (e.g., urticaria, angioedema, pruritic morbilliform rash), oral and gastrointestinal (e.g., lip, tongue, and palatal pruritus and swelling, laryngeal edema, vomiting, diarrhea), and upper and lower respiratory systems (e.g., ocular pruritus and tearing, nasal congestion, pharyngeal edema, wheezing). A rise in plasma histamine has been associated with the development of these symptoms after blinded food challenges. In contrast, β-tryptase levels are usually not elevated.[5]

Children possessing IgE antibodies directed at more numerous epitopes on major peanut or milk allergens had histories of more severe reactions than the children with IgE

antibodies directed at fewer epitopes. Greater diversity of recognized allergenic epitopes and increased IgE antibody affinity were associated with more efficient cross-linking of the IgE receptors and degranulation of effector cells.[5]

In IgE-mediated gastrointestinal reactions, endoscopic observation has revealed local vasodilation, edema, mucus secretion, and petechial hemorrhaging. Increased stool and serum PGE_2 and PGF_2 levels have been observed after adverse food reactions leading to diarrhea. Atopic dermatitis and chronic airway hyperreactivity (e.g., asthma) involve activation of other cell types (e.g., eosinophils) through IgE-mediated mechanisms.[5]

Non–IgE-Mediated Food Allergy

Type II antigen-antibody complex–dependent cytotoxic reactions occur when specific antibody binds to a surface tissue antigen or hapten associated with a cell and induces complement activation. Complement activation products promote the generation of various inflammatory mediators that lead to subsequent tissue damage. A few reports have implicated an antibody-dependent thrombocytopenia resulting from milk ingestion. However, little evidence supports any significant role for type II hypersensitivity in food-allergic disorders.[5]

Type III antigen-antibody complex–mediated hypersensitivity has been implicated in patients with a variety of complaints and elevated serum levels of food antigen-antibody complexes. However, food antigen-antibody complexes have been demonstrated in the sera of normal individuals and in patients with suspected food hypersensitivity. The complexes formed by the interaction of IgG, IgA, or IgM antibodies to β-lactoglobulin are found 1 to 3 hours after ingesting milk in normal children and adults. Although IgE-food antigen complexes are more commonly found in patients with food hypersensitivity, there are a few reports of antigen-immune complex–mediated vasculitis.[5]

Type IV and delayed type IV cell-mediated hypersensitivities have been implicated in food-allergic disorders for which the onset of clinical symptoms occurred several hours after the ingestion of a suspected food allergen. Ingestion of the sensitizing antigen may provoke mucosal lesions. In humans, a few investigators have found increased lymphocyte proliferation to food antigens in food-allergic individuals, but increased proliferation also is found in many asymptomatic subjects. Cell-mediated hypersensitivity reactions contribute to several gastrointestinal disorders, such as eosinophilic esophagitis, eosinophilic gastroenteritis, atopic dermatitis, and celiac disease. In several adverse food reactions, pathogenic factors are not well defined but are believed to involve immunologic mechanisms. Antigen-antibody complexes and cell-mediated reactions in part may be responsible for these pathogenic states.[5]

Clinical Manifestations of Food Allergy

Classification of food hypersensitivity disorders into those primarily involving IgE-mediated reactions, those not involving IgE-mediated mechanisms, and those that may involve IgE- and non–IgE-mediated mechanisms is most useful for clinical and diagnostic purposes.[5]

Risk Factors

Risk factors for the development of food allergy include a younger age, as the prevalence in children, especially young children under 3 years old, is higher than that in adults. A family history of atopic disease increases the risk of food allergy for an individual 4-fold. Familial atopic diseases, which place individuals at risk, include asthma, allergic rhinitis, atopic dermatitis, and food allergy. There are no particular genes known to be associated with food allergy and no genetic tests to identify persons at risk, but there is a higher concordance of peanut allergy for monozygotic twins than dizygotic twins (64% vs 7%). The sibling of a food allergic person has a 10-fold higher risk for the development of food allergy than the general population.

Natural History

The natural history of food allergy is not uniform and differs depending on the type of food, the allergenic proteins within the food, and the immunopathogenesis of the reaction. Development of food allergies occurs in the first year of life in 80% or more of children with food allergies. The peak prevalence of confirmed food allergy is at ~1 year of age. Children who begin with 1 food allergy, especially if it is an IgE-mediated allergy, have an increased chance of developing additional food and inhalant allergies.[6]

Prognosis of food allergy disease in young children allergic to cow's milk, egg, soybean, or wheat is very good with resolution being the most common outcome. Most cases of cow's milk allergy resolve by the age of 3 years old, with

Gastrointestinal Food-Allergic Disorders[5]				
Disorder	**Age Group**	**Characteristics**	**Diagnosis**	**Prognosis and Course**
IgE-Mediated Disorders				
Acute gastrointestinal hypersensitivity	Any	Onset: minutes to 2 h; nausea, abdominal pain, emesis, diarrhea; typically in conjunction with cutaneous and/or respiratory symptoms	History, positive SPT and/or serum food-IgE level; confirmatory OFC	Varies, food-dependent; milk, soy, egg, and wheat typically outgrown; peanut, tree nuts, seeds, and shellfish typically persistent
Pollen-food allergy syndrome (oral allergy syndrome)	Any; most common in young adults (50% of birch pollen–allergic adults)	Immediate symptoms on contact of raw fruit with oral mucosa: pruritus, tingling, erythema, or angioedema of the lips, tongue, oropharynx; throat pruritus/tightness	History, positive SPT with raw fruits or vegetables; OFC positive with raw fruit, negative with cooked	Severity of symptoms varies with pollen season; may improve in a subset of patients with pollen immunotherapy
IgE and non–IgE-Mediated Disorders				
Eosinophilic esophagitis	Any, but especially infants, children, and adolescents	*Children* : chronic or intermittent symptoms of gastroesophageal reflux, emesis, dysphagia, abdominal pain, and irritability *Adults* : abdominal pain, dysphagia, and food impaction	History, positive SPT and/or food-IgE level in 50% but poor correlation with clinical symptoms; patch testing may be of value; elimination diet and OFC; endoscopy or biopsy provides conclusive diagnosis and information about treatment response	Varies, not well established; improvement with elimination diet within 6-8 wk; elemental diet may be required; often responds to swallowed topical steroids
Allergic eosinophilic gastroenteritis	Any	Chronic or intermittent abdominal pain, emesis, irritability, poor appetite, failure to thrive, weight loss, anemia, protein-losing gastroenteropathy	History, positive SPT, and/or food-IgE level in 50% but poor correlation with clinical symptoms, elimination diet, and OFC; endoscopy or biopsy provides conclusive diagnosis and information about treatment response	Varies, not well established; improvement with elimination diet within 6-8 wk; elemental diet may be required

resolution in 56% at 1 year, 77% at 2 years, 87% at 3 years, 92% at 5 years, and 97% at 15 years of age, as seen in a prospective birth cohort study.[6,7]

Egg allergy, the second most common food allergy in young children, has a resolution rate of 16% at 12 months of follow-up, 28% at 24 months, 52% at 36 months, 57% at 48 months, and 66% at 60 months.[6,8]

Hypersensitivity to soybean is outgrown rapidly with 50%-83% of cases resolving in within 2 years. Two-thirds of children with atopic dermatitis and wheat allergy outgrow the hypersensitivity over 1-2 years. More severely atopic children with wheat allergy have resolution rates of 29% by 4 years, 56% by 8 years, and 65% by 12 years.[6]

Non-IgE-mediated reactions to cow's milk disappear sooner than IgE-mediated reactivity with the vast majority of children growing out of the reactivity by 1 year of age. Resolution of cow's milk and soy infantile food protein enterocolitis syndrome occurred in 27.3% and 75.0% at 6 months of age, 41.7% and 90.9% at 8 months, and 63.6% and 91.7% at 10 months, respectively, in a prospective study.[6]

The natural history of other food allergies is not as short-lived. Peanut, tree nut, fish, and shellfish allergies are more persistent than milk, soy, egg, and wheat allergy. Although traditionally it has been assumed that peanut allergy is never outgrown, actually 21.5% of peanut allergic children will outgrow their allergy. Recurrence can occur, in individuals who eat small or large amounts of peanuts after tolerance is confirmed by an oral challenge, with 8% of patients who outgrow peanut allergy suffering a recurrence. The vast majority of tree nut allergic people will not outgrow their allergy, with only 9 of 101 tree nut allergic individuals having resolution in a median time of 5.5 years.[6]

The natural history of fish and shellfish allergy has not been adequately studied. A case-control study among children

Gastrointestinal Food-Allergic Disorders[5] *(continued)*				
Disorder	**Age Group**	**Characteristics**	**Diagnosis**	**Prognosis and Course**
Non –IgE-Mediated Disorders				
Allergic proctocolitis	Young infants (<6 mo), frequently breastfed	Blood-streaked or heme-positive stools; otherwise healthy appearing	History, prompt response (resolution of gross blood in 48 h) to allergen elimination; biopsy conclusive but not necessary for most	Most able to tolerate milk or soy by 1-2 yr
Food protein-induced enterocolitis syndrome	Young infants	*Chronic* : emesis, diarrhea, failure to thrive on chronic exposure *Subacute* : repetitive emesis, dehydration (15% shock), diarrhea on repeat exposure after elimination period; breastfeeding protective	History, response to dietary restriction; OFC	Most have resolution in 1-3 yr; rarely persists into late teenage years
Dietary protein-induced enteropathy	Young infants; incidence has decreased	Protracted diarrhea, (steatorrhea), emesis, failure to thrive, anemia in 40%	History, endoscopy and biopsy; response to dietary restriction	Most have resolution in 1-2 yr
Celiac disease (gluten-sensitive enteropathy)	Any	Chronic diarrhea, malabsorption, abdominal distention, flatulence, failure to thrive or weight loss; may be associated with oral ulcers and/or dermatitis herpetiformis	Biopsy diagnostic, shows villous atrophy; screening with serum IgA antitissue transglutaminase and antigliadin; resolution of symptoms with gluten elimination and relapse on oral challenge	Lifelong
IgE , Immunoglobulin E; *OFC* , oral food challenge; *SPT* , skin-prick test.				

with food allergy showed that most children retained their allergy to fish over a 1-year follow-up and a study of 11 adult patients with shrimp allergy did not show any decrease in the shrimp-specific IgE levels over a 2-year period.[6]

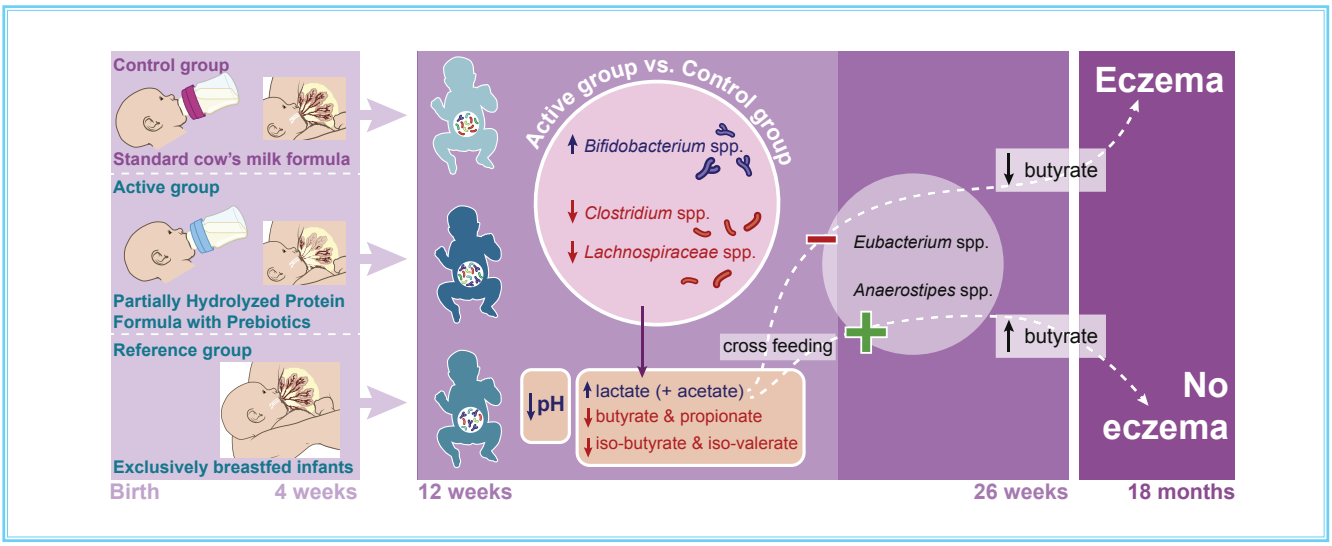
The proportion by which food-specific IgE levels decrease over time can predict development of tolerance. For a child with egg allergy below the age of 4 years, the probability of developing tolerance over the next 12 months was 52% for a decrease in the egg-specific IgE over 1 year of 50%, 65% for a decrease of egg-specific IgE of 75%, 78% for a decrease of egg-specific IgE of 90%, and 95% for a decrease of 99% in egg-specific IgE levels. For cow's milk allergy, the probability of developing tolerance over the next 12 months was 31% for a decrease of milk specific IgE over 1 year of 50%, 45% for a decrease of 70%, 66% for a decrease of 90%, and 94% for a decrease of 99% in the cow's milk-specific IgE levels. The probability of outgrowing the allergy in the next 5 years is less if the specific IgE values do not decrease significantly over a 1-year period.[6,9,10]

The Gut Microbiome and the Development of Food Allergy

It has been estimated that the human gut is populated with up to 100 trillion microbes. Rough estimates are that the microbiota (previously termed flora or microflora) contain on the order of 150-fold more genes than are encoded in the human genome. Although the composition of the microbiota changes substantially from infancy to adulthood, most organisms come from the four phyla Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria.[11]

The Microbiome and Immune Development

Early microbial colonization plays an important role the development of the innate and the adaptive immune systems,[11,12] and there are several proposed mechanisms to explain how alterations in microbiome could lead to the development of allergic disease. Experimental, germ-free (gnotobiotic) mouse models have demonstrated that gut-



A study by a group of scientists explored how the gut microbiota tracks eczema development in early life—and also whether gut microbiota composition was modulated by a prebiotic early-life dietary intervention.

Researchers analyzed the fecal samples of 138 vaginally-born infants at increased risk of allergy; the samples were collected from each infant at 4 and 26 weeks. Stool measurements of pH and lactate, as well as short-chain fatty acids, were also taken at 4, 12, and 26 weeks. The infants who were not breast-fed consumed either standard cow's milk formula (n=57) or a partially hydrolyzed formula containing specific oligosaccharides (pHF-OS) (n=51). These groups were compared with a reference group of breast-fed infants (n=30).

By 18 months, 52 of the 138 infants (about 38%) showed symptoms of eczema. The infants who went on to develop eczema by 18 months showed compositional differences in their gut microbiota compared to those not developing eczema: at 4 weeks, they showed decreased relative abundances of Parabacteroides and Enterobacteriaceae, while at 26 weeks they showed decreases in Eubacterium and Anaerostipes species, which are known to use lactate and to produce butyrate. So unsurprisingly, increased lactate and decreased butyrate were also observed at the 26-week mark in the stool of infants who would later develop eczema.

The researchers assessed the similarity in microbiota composition between the groups and found that the fecal microbiota composition, metabolites, and pH in infants who received the prebiotic-supplemented formula rather than the standard formula were closer to those of breast-fed infants.

From: Wopereis H, Sim K, Shaw A, Warner JO, Knol J, Kroll JS. Intestinal microbiota in infants at high risk for allergy: Effects of prebiotics and role in eczema development. J Allergy Clin Immunol. 2018 Apr;141(4):1334-1342.e5. doi: 10.1016/j.jaci.2017.05.054. Epub 2017 Sep 1. Available at https://www.jacionline.org/article/S0091-6749(17)31343-X/pdf. http://dx.doi.org/10.1016/j.jaci.2017.05.054

associated lymphoid tissues fail to develop when microbial colonization is delayed, leading to a Th2 skewed immune response. Secretory IgA produced by resident B cells in gut-associated lymphoid tissues may also promote oral tolerance by binding allergens in the gut and preventing their uptake. Microbial colonization has been shown to be important in the development of Th1 and regulatory T cells (Tregs), which are necessary to maintain immunologic balance and promote tolerance. Microbiota may also influence epigenetic modifications of genes. It is known that various forms of epigenetic changes, such as DNA methylation and histone modifications, play an important role in immune development and regulation, [32] and microbial metabolites butyrate and propionate have been shown to have inhibitory effects on histone deacetylases that may promote the development of peripherally induced Tregs. Lastly, the gut microbiota plays a significant role in the development and maintenance of barrier function and it is thought that a breakdown of this epithelial barrier may lead to allergic sensitization.[11]

The impact of the microbiome on human development, nutritional needs, and even psychological variations has become evident with advances in the ability to study these complex communities of microorganisms. There is also a growing appreciation for the role of the microbiome in immune regulation, and it is plausible that changes in the commensal microbiota may influence the development of

food allergy and other allergic diseases. When considering various determinants that may influence the unique bacterial families that constitute the microbiome, there are several factors to consider, including environmental setting, mode of delivery, birth order, antibiotic exposure, and diet. This article explores the relationship between the gastrointestinal microbiota and IgE-mediated food allergy and other allergic diseases.[11]

The Influence of the Microbiome in Allergic Disease

The potential impact of the microbiome on allergic disease was first studied in Europe using cross-sectional surveys to examine the prevalence of allergic diseases in children. The authors found that children living in farming environments had a significantly decreased frequency of hay fever, asthma, and eczema compared with children living in urban areas. This relationship was further explored in the GABRIELA and PARSIFAL cohorts, which confirmed previous observations that children living on farms had decreased rates of allergic disease compared with urban children. Although most studies have focused on the impact of postnatal environmental exposure, there is increasing evidence that prenatal exposure may also be important. Epidemiologic studies examining the effect of prenatal exposures on the development of allergic disease have shown that maternal exposure to farming environments during pregnancy is associated with decreased rates of asthma, allergic rhinitis, and eczema in their children.[11]

Establishment of the Microbiota during Early Life

Although the fetal compartment has long been considered sterile, colonization of the host by microbes seems to be initiated before birth. Maternally derived bacteria can be isolated from umbilical cord blood of healthy neonates born by means of cesarean section.[13,14] Bacteria are detected in the meconium of preterm human babies.[13,15]

Newborns are exposed to a large diversity of maternal bacteria during birth. Logically, the composition of the newborn microbiota is deeply influenced by the mode of delivery and exposure to bacteria. The microbiota composition of infants born by means of vaginal birth is similar to that of the maternal vaginal and gut microbiota,[13,16] whereas babies born by means of cesarean section harbor a microbiota resembling the human skin microbiota.[13,17] These differences in microbiota composition between infants born by means of vaginal birth and cesarean section are persistent, with microbes associated with cesarean section still detectable 2 years after birth.[13,18] The infant microbiota structure is highly unstable and has low diversity[13,19] compared with the adult microbiota.[13,20] The first major shift in intestinal microbiota composition was initially thought to be associated with the introduction of solid food.[13] The human intestinal microbiota further evolves with age and stabilizes after 3 years of life.[13,21] However, even at 5 years after birth, the gut microbiota might still not be definitely established.[13,22]

This period of microbiota evolution to an adult configuration during early life coincides with development of the immune system. It has also been shown that the immune influences induced by the microbiota during this specific window of time might be a determining factor in resistance or susceptibility to diseases, such as allergy, during infancy and potentially during adulthood.[13]

Early-Life Colonization and Allergic Diseases

Clinical studies have provided evidence for a link between bacterial composition in early life and allergy development. The composition of the lung microbiome has been identified as being altered in patients with allergic diseases and asthma in particular. A higher bacterial burden and diversity are observed in the lower airways of asthmatic patients compared with those of healthy subjects. Similar to the airway, early-life perturbations of the intestinal microbiota have also been shown to be associated with allergic diseases. An increased risk of allergic sensitization and allergic rhinitis, but not asthma, in the first 6 years of life is correlated with reduced bacterial diversity of the infant's intestinal flora.[13,23] Infants with atopic eczema exhibit a lower diversity of the gut microbiota.[13,24] Moreover, differences in the neonatal gut microflora might precede the development of atopy.[13,25] Together, these studies suggest that how the host is colonized by microbes during early life in different mucosal tissues can influence the later development of allergy.[13]

Conclusions

The perinatal period is an important developmental window that has the potential to define the child's trajectory of health and disease. Microbial colonization and the development of immune tolerance to commensal bacteria, at a time when immune cells – specifically Treg cells – are highly responsive to bacteria and bacterial metabolites is readily influenced by environmental exposures. Epidemiological studies and research in animal models have confirmed associations between perturbations in the overall diversity and, in some cases, specific microbial genera and adverse metabolic and immune diseases in genetically susceptible individuals. The high rates of elective cesarean delivery (CD), low rates of exclusive breastfeeding and widespread use of prescribed antibiotics have been associated with reduced intestinal bacterial diversity, and with increased abundance of potentially pathogenic species. Whereas elucidation of the complex mechanisms by which the microbiota modulates the regulatory functions of the immune system and metabolic health is still elusive, efforts should be dedicated to identify specific resident microbes that have either a pathogenic or a protective role in disease and to develop therapeutic strategies that optimize microbiota profile for health. In the meantime, medical practitioners and parents should support strategies that promote and protect the health of the gut microbiota and are consistent with public health recommendations from leading medical societies and health organizations, namely reduced use of elective CD, exclusive breastfeeding for the first six months of life, and judicious application of antimicrobials, especially those with broad-spectrum activities.[26]

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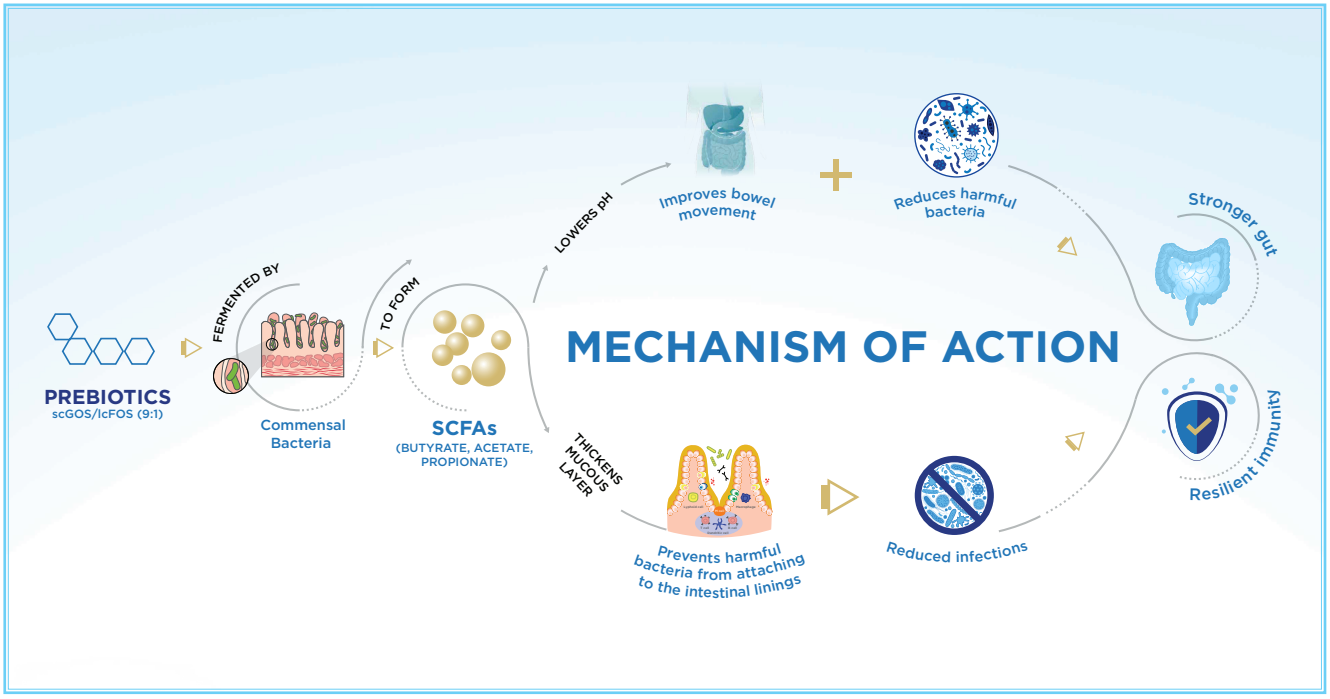
Early Life Nutrition and the Role of Infant Formula



Infant Formulae Supplemented with Prebiotics: Are they Better than Unsupplemented Formulae?

Skórka A, Pieścik-Lech M, Kołodziej M, Szajewska H. Infant formulae supplemented with prebiotics: Are they better than unsupplemented formulae? An updated systematic review. Br J Nutr. 2018 Apr;119(7):810-825. doi: 10.1017/S0007114518000120. Epub 2018 Feb 19.

In 2011, the Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) systematically reviewed published evidence related to the safety and health effects of the administration of formulae supplemented with pro- and/or prebiotics compared with unsupplemented formulae.

With regard to probiotics, in line with the 2011 ESPGHAN document(1), the recent updated systematic review of Skórka A et al., concluded that the available scientific data suggest that the administration of currently evaluated probiotic-supplemented formulae to healthy infants does not raise safety concerns with regard to growth and adverse effects. Some beneficial clinical effects are possible; however, there is no existing robust evidence to recommend their routine use. The latter conclusion may reflect the small amount of data on a specific probiotic strain(s) and outcomes, rather than a genuine lack of an effect. The efficacy and safety should be considered for each probiotic(s)-supplemented formula.

With regard to prebiotic-supplemented formulae, in 2011 the ESPGHAN Committee concluded that the administration of currently evaluated prebiotic-supplemented formulae to healthy infants does not raise safety concerns with regard to growth and adverse effects. The Committee did not support the routine use of prebiotic-supplemented formulae in infants. Subsequent to the Committee review, new evidence

on the effects of supple- mentation of infant formulae with prebiotics was published. Skórka A et al., aimed to update the 2011 evidence on the effects of the administration of prebiotic-supplemented infant formulae to find out whether there is a need to revise current recommendations.

The authors updated evidence on the effects of the administration of prebiotic-supplemented infant formulae (IF) compared with unsupplemented IF. Five databases were searched up to March 2017 for randomized controlled trials. In all, forty-one publications were identified, including twenty-five new publications. The administration of currently evaluated prebiotic-supplemented formulae to healthy infants does not raise safety concerns with regard to growth and adverse effects.

Thus, in line with the 2011 ESPGHAN document, the available scientific data suggest that the administration of currently evaluated prebiotic-supplemented formulae to healthy infants does not raise safety concerns with regard to growth and adverse effects. Some favorable clinical effects are possible, primarily stool softening, which may be beneficial in some infants.

Long-Term Sex-Differential Effects of Neonatal Vitamin A Supplementation on in *vitro* Cytokine Responses

Jensen KJ, Søndergaard MJ, Andersen A, Martins C, Erikstrup C, Aaby P, Flanagan KL, Benn CS. Long-Term Sex-Differential Effects of Neonatal Vitamin A Supplementation on in vitro Cytokine Responses Br J Nutr. 2017 Dec;118(11):942-948. doi: 10.1017/S0007114517002938. Epub 2017 Nov 23.

Vitamin A and its metabolites are essential for the functioning of the immune system. Vitamin A supplementation (VAS) is recommended for children from 6 months to 5 years of age in populations with high risk of vitamin A deficiency (VAD) to reduce VAD-related morbidity and mortality. High-dose VAS in the neonatal period (NVAS) is not WHO policy but has been tested in several randomized controlled trials (RCT) and is currently being considered as a policy, at least for sub-groups.

Jensen KJ et al., in Guinea-Bissau conducted several of the NVAS trials, and found that NVAS had sex-differential effects on mortality, being associated with slightly lower mortality in males, but higher mortality in females. The negative effect in females increased with increasing length of follow-up, and other studies have indeed corroborated this pattern; in all existing trials with follow-up to 12 months of age, females who had received NVAS had higher mortality than females who had received placebo at birth from 6 to 12 months of follow-up. The investigators hypothesized that this could be due to a negative interaction between NVAS and subsequent diphtheria–tetanus–pertussis (DTP) vaccination (recommended in three doses at 6, 10 and 14 weeks of age) in females.

In this study, the authors analyzed the long-term immunological effects of neonatal vitamin A supplementation (NVAS) in 247 children, who had been randomly allocated to 50 000 or 25 000 IU vitamin A (15mg and 7·5mg retinol equivalents, respectively) or placebo at birth. At 4-6 months of age, they assessed bacille Calmette-Guérin (BCG) scarification, and analyzed in vitro responses of TNF-α, IL-5, IL-10, IL-13 and IFN-γ in whole blood stimulations to phytohaemagglutinin (PHA), purified protein derivative (PPD), tetanus toxoid and lipopolysaccharide. There were no differences between the two doses of NVAS, and thus they were analyzed combined as NVAS (any dose) v. placebo. All analyses were performed unstratified and by sex. NVAS increased the chance of having a scar after BCG vaccination in females (NVAS v. placebo: 96 v. 71 %, proportion ratio: 1·24; 95 % CI 1·09, 1·42), but not in males ($p_{\text{for interaction}}$=0·012). NVAS was associated with significant sex-differential effects on the pro- to anti-inflammatory cytokine ratios (TNF-α:IL-10) to PPD, tetanus toxoid and medium alone, which were increased in females but decreased in males. In addition, IL-17 responses tended to be increased in NVAS v. placebo recipients in males but not in females, significantly so for the PHA stimulation.

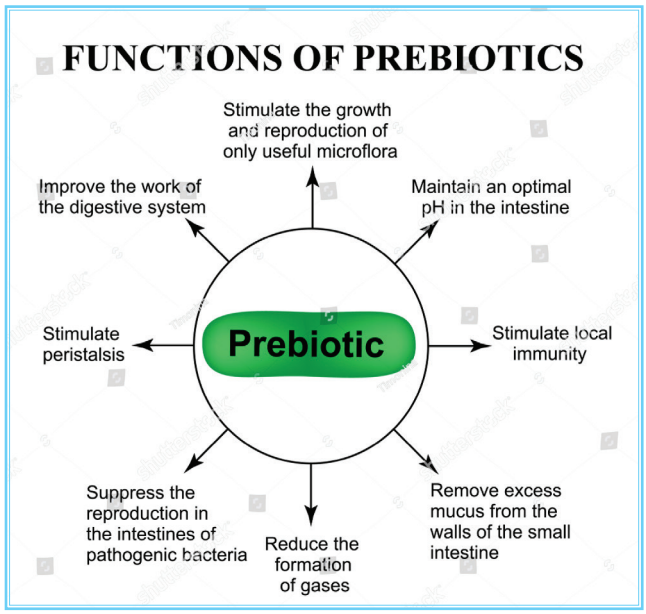
This study indicates long-lasting effects of NVAS on responses to BCG vaccination and immunological responsiveness of peripheral blood cells persisting at 4–6 months of age in a sex-dependent manner. NVAS v. placebo was as-

sociated with increased frequency of BCG scars in females, making scar frequencies in NVAS-receiving females comparable to those of boys in general. NVAS was also associated with more pro-inflammatory cytokine responses in females, whereas the opposite tendency was seen in males. Sex differences in NVAS effects were found for responses to several recall antigens and for baseline secretion in non-stimulated cells, suggesting generalized sex-dependent immune-modulatory properties of NVAS. Except for IL-1Ra, plasma inflammatory markers were not associated with NVAS, indicating that the effects observed for in vitro responses were not due to differences in systemic inflammation at the time of bleeding.

Effects of Infant Formula Composition on Long-Term Metabolic Health

Lemaire M, Le Huërou-Luron I, Blat S. Effects of Infant Formula Composition on Long-Term Metabolic Health.J Dev Orig Health Dis. 2018 Feb 5:1-17. doi: 10.1017/S2040174417000964. [Epub ahead of print]

Quality and quantity of early nutrition plays a crucial role since it can have a great influence on developing infants' metabolism, impacting weight gain, adiposity and energy metabolism on the short and long-term through physiological and behavioral pathways. Breast milk is recognized as the ideal nutrition for the full-term newborn. An exclusive breastfeeding for the first six months of life is therefore recommended by the World Health Organization. However, despite these recommendations, breastfeeding rates remain low. In 2013 in the United States, 81.1% of infants were breastfed at birth but only 22.3% were exclusively breastfed at the age of 6 months. The same occurs in Europe, despite large disparities between countries, with breastfeeding rates beyond 4-6 months well below optimum levels. When breastfeeding is not possible or wanted, the only alternatives are infant formulas (IF). Despite obvious improvements over the past 50 years, IF remain perfectible to better approach the physiologic effects of breast milk. The objective of this review was to summarize differences between breastfed and formula-fed infants on long-term metabolic health, focusing on vaginal, term-born, healthy infants.



Improvements such as reducing the protein content, modulating the lipid matrix and adding prebiotics, probiotics and symbiotics, are discussed regarding metabolic health. Early nutrition plays a predominant role in health and well-being of the newborn and in later life by modulating its metabolism. Improving the functional effects of IF to reduce the gap between breastfed and formula-fed infants is crucial and has been the topic of great research over the past years. Yet, numerous questions remain to be answered about which components should be added to IF and in which quantity depending on their metabolic fate and outcomes. Indeed, when it comes to human milk composition and infant nutrition in general, there is no "one-size-fits-all construct". Regarding metabolic health of infants, an improved IF would consist in modulating all macronutrients: proteins (to decrease the quantity but mostly improve their quality), lipids (to resemble the size, structure and composition of the fat globule by the addition of dairy lipids, cholesterol and MFGM, and also a balanced ω3:ω6 LC-PUFA ratio) and to supplement with prebiotics, probiotics or synbiotics. However, further studies are needed to improve IF composition and gain comprehension on how it may modulate the interplay between host metabolism and gut microbiome and exert long-term health benefits. Gut microbiota development plays a key role but due to its complexity, the underlying pathways impacting the

infant biology remain largely unknown. Animals such as the nonhuman primate and the neonatal piglet, excellent preclinical models for the human infant, proved to be useful to control and account for some confounding factors found in human studies and to investigate the mechanisms involved in the long-term effects of early nutrition. They allow for the screening of potential nutritional factors and the selection of the most promising ones. Yet there is still a need for a standardized model for infant growth and development. Besides, they remain models and additional well-designed longitudinal human studies are needed to investigate the effects of the IF composition on host metabolism beyond infancy.

The Effect of Early Limited Formula on Breastfeeding, Readmission, and Intestinal Microbiota

Flaherman VJ, Narayan NR, Hartigan-O'Connor D, Cabana MD, McCulloch CE, Paul IM. J Pediatr. 2018 May;196:84-90.e1. doi: 10.1016/j.jpeds.2017.12.073. Epub 2018 Mar 14.

Increasing enteral volume by supplementing breastfed newborns with formula could ameliorate morbidity, especially for those with pronounced weight loss, but has been discouraged by guidelines as the result of several concerns. First, numerous studies have demonstrated that receiving both breast milk and formula in the first few days after birth increases the risk of breastfeeding cessation. Second, some evidence suggests that the use of formula along with breastfeeding reduces the health benefits associated with breastfeeding, perhaps by altering the abundance of beneficial intestinal microbiota such as Lactobacillus and Bifidobacterium, which have been associated with reduced risk of infectious and allergic disease. Some studies have also reported that the use of formula increases the abundance of taxa such as Clostridia that are associated with increased risk of eczema. Third, the use of formula to supplement breastfeeding can impact maternal experience.

Flaherman VJ et al., conducted this study in order to determine whether using 10 mL formula after each breastfeeding before copious maternal milk production affects breastfeeding duration, readmission, and intestinal microbiota through 1 month of age.

In this randomized controlled trial, the researchers enrolled 164 exclusively breastfeeding newborns, 24-72 hours old, whose weight loss was ≥75th percentile for age, and whose mothers had not yet begun mature milk production. Enrolled newborns were assigned randomly to either supplement breastfeeding with early limited formula (ELF), 10 mL of formula after each breastfeeding stopped at the onset of copious maternal milk production (intervention), or to continue exclusive breastfeeding (control). Outcomes assessed through 1 month included breastfeeding duration, readmission, and intestinal microbiota.

> *In this population of healthy newborns with weight loss ≥75th percentile, ELF did not interfere with breastfeeding at 1 month, breastfeeding without formula at 1 month, or intestinal microbiota. ELF may be an important therapeutic option for newborns with the potential to reduce readmission rates.*

At 1 week of age, 95.8% of infants receiving ELF and 93.5% of control infants were still breastfeeding ($p > .5$); readmission occurred for 4 (4.8%) control infants and none of the infants receiving ELF ($p = .06$). At 1 month of age, 86.5% of infants receiving ELF and 89.7% of control infants were still breastfeeding ($p > .5$); 54.6% of infants receiving ELF and 65.8% of controls were breastfeeding without formula ($p = .18$). ELF did not lead to decreased abundance of Lactobacillus or Bifidobacterium and was not associated with expansion of Clostridium.

This randomized trial of 164 newborns did not demonstrate improved outcomes for infants receiving exclusive breastfeeding compared with limited formula supplementation using the ELF strategy. Furthermore, ELF did not affect breastfeeding duration or formula use in the first month and did not impact microbial diversity or lead to decreased abundance of Lactobacillus or Bifidobacterium or expansion of Clostridium. These findings are important because increasing enteral intake for newborns with pronounced weight loss might reduce morbidity from jaundice and dehydration and could lead to reduced newborn readmissions. We also found that ELF was used for a median (IQR) of

21-4 days; during the first week, there were no readmissions for newborns assigned to ELF, and 4 readmissions occurred for control newborns.

Growth, Stool Consistency and Bone Mineral Content in Healthy Term Infants Fed sn-2-Palmitate-Enriched Starter Infant Formula

Béghin L, Marchandise X, Lien E, Bricout M, Bernet JP, Lienhardt JF, Jeannerot F, Menet V, Requillart JC, Marx J, De Groot N, Jaeger J, Steenhout P, Turck D. Growth, stool consistency and bone mineral content in healthy term infants fed sn-2-palmitate-enriched starter infant formula: A randomized, double-blind, multicentre clinical trial. Clin Nutr. 2018 Jun 1. pii: S0261-5614(18)30200-0. doi: 10.1016/j.clnu.2018.05.015. [Epub ahead of print]

Infant formulae using structured triacylglycerols (structured lipids) were developed in order to increase the proportion of palmitate at the sn-2 position and to test possible beneficial effects on lipid and mineral balance. These studies demonstrated that palmitic acid and calcium absorption are improved by introduction of structured lipids. A number of studies have reported an 8-40% reduction in fecal total fatty acid-calcium soaps or palmitate-calcium soaps when formulae containing structured lipids are fed while some studies reported softer stools in infants fed formulae with an increase in sn-2 palmitate and a concomitant reduction in sn-1 and sn-3 palmitate.

Two studies assessed bone maturation with formulae containing structured lipids in two studiesand reported significally higher values of bone mineral content and bone speed of sound in infants fed formulae with a high sn-2 palmitate content compared to infants fed a low sn-2 palmitate formula.

This study was a randomized, double-blind, controlled, multicenter trial which compared three infant formulae with differing content of sn-2 palmitate. The main purpose was to evaluate weight gain and stool consistency during the first 4 months of life. The authors hypothesized that stools would be softer in the groups receiving formulae enriched with sn-2 palmitate, whereas weight gain would be comparable among all groups. Secondary objectives were an evaluation of bone mineral content, body composition, digestive tolerance and safety of the three formulae.

This large (n = 488) randomized, double-blind, multicenter trial investigated whether increasing the sn-2 palmitate content of infant formula improves stool consistency and bone mineral content (measured by dual-energy x-ray absorptiometry), without affecting growth or health. From ~1 week to 4 months of age, infants were exclusively fed one of three formulae: i) control formula (CF; 16% of total palmitate at sn-2; n = 162), (ii) experimental formula 1 (EF1; 43% of total palmitate at sn-2; n = 166) or (iii) experimental formula 2 (EF2; 51% of total palmitate at sn-2; n = 160).

Intention-to-treat analysis showed softer stools in both EF groups (vs. CF) at ages 2 weeks and 1 and 2 months ($p \leq 0.01$), but not 3 and 4 months. At 4 months, all groups had similar growth outcomes while bone mineral content was significantly higher in EF1 ($p = 0.0012$) and EF2 ($p = 0.0002$) compared with CF. Comparison of reported adverse events up to 12 months revealed no differences among groups. All 3 infant formulae exhibited equally good digestive tolerance.

The study, reporting weight gain, stool consistency, and bone mineral content in healthy full-term infants, is the largest (n = 488) reported randomized, controlled trial to date investigating the comparative effects of infant formulae with differing palmitate positional distribution. The authors assessed three formulae which differed in their content of sn-2 palmitate: 16%, 43% and 51% of total palmitate content. In a reciprocal manner, the palmitate present at triacylglycerol positions sn-1 and sn-3 was substantially reduced in the formulae containing structured lipids compared to the control formula.

In conclusion, this study demonstrates that feeding infant formulae with increased levels of sn-2 palmitate and a concomitant decrease in sn-1 and sn-3 palmitate supports normal infant growth, results in softer stools during the first 2 months of life and increased bone mineral content at 4 months of age, and is well tolerated. Thus, feeding formulae containing high sn-2 palmitate is safe and provides positive outcomes to infants in terms of stool consistency and bone mineralization.

Amino Acid-Based Formula in Premature Infants with Feeding Intolerance: Comparison of Fecal Calprotectin Level

Jang HJ, Park JH, Kim CS, Lee SL, Lee WM. Amino Acid-Based Formula in Premature Infants with Feeding Intolerance: Comparison of Fecal Calprotectin Level. Pediatr Gastroenterol Hepatol Nutr. 2018 Jul;21(3):189-195. doi: 10.5223/pghn.2018.21.3.189. Epub 2018 Jun 28.

Calprotectin is an antimicrobial protein found in neutrophils, monocytes, macrophages, and some squamous epithelium cells and known to increase especially in gastrointestinal (GI) inflammation. Its presence in stool indicates neutrophil migration to the GI mucosa and can suggest the severity of mucosal inflammation. According to a systemic review, fecal calprotectin (FC) level was elevated in infants with necrotizing enterocolitis (NEC) and was useful as a noninvasive prognostic marker of NEC. However, high FC levels in healthy infants are related to the physiological response of the gut, such as intestinal permeability, gut microbiota, and response to alimentary allergens.

Jang HJ et al., investigated FC levels in preterm infants with and without feeding intolerance (FI), and compared the FC levels after changing to AAF.

The medical records of 67 premature infants were reviewed retrospectively. The fully enterally-fed infants were classified into two groups; the FI group (29 infants) and the control group (31 infants). Seven infants with necrotizing enterocolitis, sepsis, and perinatal asphyxia were excluded. If breast milk (BM) or preterm formula (PF) could not be tolerated by infants with FI, amino acid-based formula (AAF) was tried temporarily. Once FI improved, AAF was discontinued, and BM or PF was resumed. We investigated the FC levels according to the type of feeding.

Significant differences were found in gestational age, birth weight, age when full enteral feeding was achieved, and hospital stay between the FI and control group ($p<0.05$). The FC levels in the FI group were significantly higher than those in the control group ($p<0.05$). The FC levels in the AAF-fed infants with FI were significantly lower than those in the BM- or PF-fed infants ($p<0.05$). The growth velocities (g/d) and z scores were not significantly different between the FI and control group ($p>0.05$).

Therefore, in this preliminary study it was demonstrated that the FC levels in the FI group were significantly higher than in the non-FI group. And the FC levels in AAF-fed infants with FI were significantly lower than BM- or PF-fed infants with FI. No significant differences in postnatal growth parameters were observed between the FI and control groups, which might be associated with the temporary use of AAF.

The authors concluded that the FC levels in AAF-fed infants with FI were significantly lower than those in the BM- or PF-fed infants with FI. The mitigation of gut inflammation through the decrease of FC levels in AAF-fed infants with FI could be presumed.

Nutrition, Microbiota and the Gut

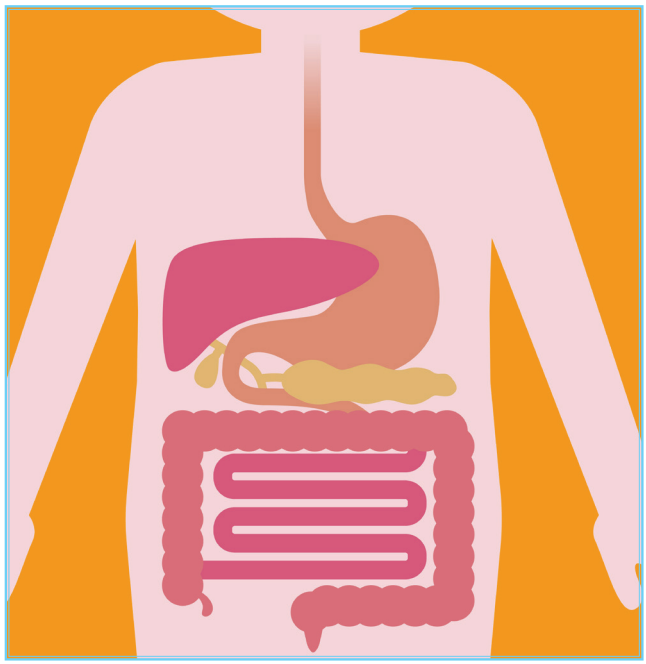
The Microbiome and Metabolome of Preterm Infant Stool Are Personalized and Not Driven by Health Outcomes, Including Necrotizing Enterocolitis and Late-Onset Sepsis.

Wandro S, Osborne S, Enriquez C, Bixby C, Arrieta A, Whiteson K. mSphere. 2018 Jun 6;3(3). pii: e00104-18. doi: 10.1128/mSphere.00104-18. Print 2018 Jun 27.

The assembly and development of the gut microbiome in infants have important consequences for immediate and long-term health. Preterm infants represent an abnormal case for bacterial colonization because of early exposure to bacteria and frequent use of antibiotics. To better understand the assembly of the gut microbiota in preterm infants, fecal samples were collected from 32 very low birth weight preterm infants over the first 6 weeks of life. Infant health outcomes included health, late-onset sepsis, and necrotizing enterocolitis (NEC). Wandro S et al., characterized bacterial compositions by 16S rRNA gene sequencing and metabolomes by untargeted gas chromatography-mass spectrometry.

Preterm infant fecal samples lacked beneficial Bifidobacterium spp. and were dominated by Enterobacteriaceae, Enterococcus, and Staphylococcus organisms due to nearly uniform antibiotic administration. Most of the variance between the microbial community compositions could be attributed to the baby from which the sample derived (permutational multivariate analysis of variance [PERMANOVA] $R^2 = 0.48$, $p < 0.001$), while clinical status (health, NEC, or late-onset sepsis) and overlapping times in the neonatal intensive care unit (NICU) did not explain a significant amount of variation in bacterial composition. Fecal metabolomes were also found to be unique to the individual (PERMANOVA $R^2 = 0.43$, $p < 0.001$) and weakly associated with bacterial composition (Mantel statistic $r = 0.23 \pm 0.05$, $p < 0.05$). No measured metabolites were found to be associated with necrotizing enterocolitis, late-onset sepsis, or a healthy outcome. Overall, preterm infant gut microbial communities were personalized and reflected antibiotic usage.

Therefore, the authors measured bacterial compositions and metabolomic profiles of 77 fecal samples from 32 preterm infants to investigate the differences between microbiomes in health and disease. Rather than finding microbial signatures of disease, they found that both the preterm infant microbiome and the metabolome were personalized and that the preterm infant gut microbiome is enriched in microbes that commonly dominate in the presence of antibiotics. These results contribute to the growing knowledge of the preterm infant microbiome and emphasize that a personalized view will be important to disentangle the health consequences of the preterm infant microbiome.



Immunological Effects of Human Milk Oligosaccharides

Triantis V, Bode L2, van Neerven RJJ. Immunological Effects of Human Milk Oligosaccharides. Front Pediatr. 2018 Jul 2;6:190. doi: 10.3389/fped.2018.00190. eCollection 2018.

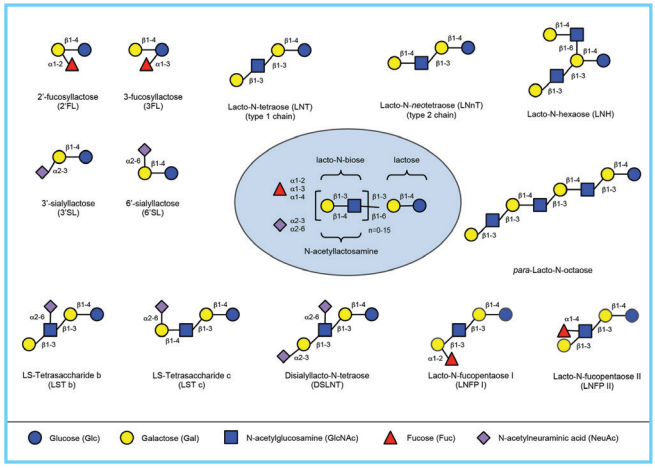
Based on its richness in immune-related components like human milk oligosaccharides (HMOs), milk proteins and lipids, breastmilk can be seen as the first functional food humans encounter during their life. HMOs comprise a group of structurally complex, unconjugated glycans found in human breastmilk. Although the amount and precise composi-

tion of HMOs varies depending on time of lactation and the genetic makeup of each woman as well as potential environmental exposures, human breast milk contains an average of 5–15 g of oligosaccharides per liter, making HMOs the third most abundant solid component of breast milk after lactose and lipids. Each oligosaccharide is built on a lactose backbone expanded by the addition of galactose, N-acetylglucosamine, fucose or sialic acid, branched and elongated in different ways, generating approximately 200 different structures identified to-date. As they are only minimally digested in the gastrointestinal tract, HMOs reach the colon intact or are absorbed in small quantities, reach the systemic circulation and are excreted in urine. In this way, they may exert a plethora of functions at multiple sites throughout the body and beyond the intestinal lumen and intestinal mucosal surfaces, including the urinary tract or the immune system. HMOs were first described as prebiotic substrates for the infant gut microbiota, promoting the establishment of bifidobacteria and lactobacilli, based on striking differences in microbiota composition between breastfed and bottle fed infants.

This review summarizes the current knowledge of the effects HMOs can have on infections, allergies, auto-immune diseases and inflammation, and will focus on the role of HMOs in altering immune responses through binding to immune-related receptors.

HMOs contribute to the development of the microbiota and the immune system of newborn infants.

However, despite many in vitro- and animal experiments, HMOs have not been tested extensively in placebo controlled infant studies. It is clear that several HMOs will be introduced in the near future into infant nutrition to supplement or replace non-human prebiotics like galactooligosaccharides and/or fructooligosaccharides. Prebiotics have been added to infant nutrition in the early 2000's as non-digestible oligosaccharides in an attempt to mimic some of the function of HMOs. With these prebiotics a large number of studies have shown effects on intestinal infection, respiratory infection and allergy. As the selection of prebiotics is based on functional similarities with HMOs, and extrapolating from in vitro and animal experiments with HMOs, it is to be expected that inclusion of HMOs to infant formula will have additional benefits to infant health, and may supplement the functionality of the prebiotics that are already used. Still more research is needed to clarify whether HMOs may also



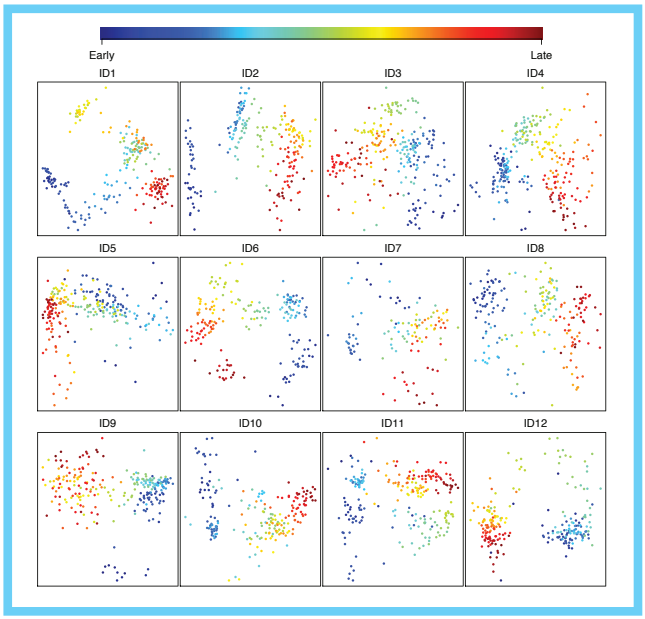
Human milk oligosaccharide composition blueprint. HMO composition follows a basic blueprint shown in the center.

have a therapeutic rather than a protective effect in human immune disorders. The emerging evidence for the beneficial effects of HMOs once again provide a powerful rationale to encourage women to breastfeed their infants to provide the full scope of benefits that stem from a diverse composition of HMOs that is provided through mother›s milk and could potentially be personalized to match the genetic context and environmental exposures of the mother-infant dyad.

Individuality and Convergence of the Infant Gut Microbiota During the First Year of Life

de Muinck EJ, Trosvik P. Individuality and convergence of the infant gut microbiota during the first year of life. Nat Commun. 2018 Jun 8;9(1):2233. doi: 10.1038/s41467-018-04641-7.

The human gut microbiota plays a vital role in health and disease, and microbial colonization is a key process in infant development. de Muinck EJ et al., provide a high-resolution view of the microbial colonization process of 12 infants, using fecal samples obtained on a near daily basis during the first year of life, including one pair of dizygotic twins and one pair of siblings born 16 months apart. Although developmental trajectories are highly individual, they all show pronounced temporal structure and non-linear dynamics. Furthermore, the authors observe a period of accelerated convergence, between ~60 and 130 days after birth, when the microbiotas of the infants become much more similar to one another.



Development of the infant GI microbiota is highly structured in time. Each panel shows a non-metric multidimensional scaling (nMDS) plot based on Bray–Curtis distances, for each of the 12 infants

This period coincides with a bloom of Bifidobacterium spp. and a decline in several groups within the phylum Firmicutes, and concludes roughly at the time of introduction of solid food. The twins' GI microbiotas track each other closely throughout, despite of one receiving intensive antibiotics treatment towards the end of the first month of life.

Findings were largely in accordance with previous reports, e.g., phylum level colonization patterns and gradual increase in diversity. However, the non-linear properties of these processes have, to our knowledge, not been described previously and would not have been observable without high-frequency sampling. Convergence of the infant gut microbiota towards decreasing beta-diversity, over time scales from months to years, has also been reported. The defined period of accelerated convergence reported here demonstrates a pattern, general across the cohort, of fine-scale temporal dynamics, and the potential importance of dense longitudinal sampling in order to describe important phenomena in the infant gut colonization process.

Although antibiotic treatment has been shown to disrupt the infant gut microbiome, both immediate and long term effects are not well understood. For example, one study of the gut microbiota in preterm infants found that administration of antibiotics in the neonatal intensive care unit did not significantly affect the long term development of the GI microbiota. It is possible, although this would need to be substantiated in a larger study with proper controls, that the apparent lack of effect on the GI microbiota in the case of the twins in this study could be the result of near constant re-seeding through contact with an age-matched sibling.

These results emphasize the importance of longitudinal sampling, of an appropriate resolution, in order to properly describe and compare microbiotas of human infants. Similar studies, of wider scope in terms of sampling duration, cohort size, locations and lifestyles, should be undertaken in order to gain an even more profound understanding of the human developmental process. This would allow for rational design of studies linking individual developmental trajectories to relevant health outcomes.

Microbial and Nutritional Programming-The Importance of the Microbiome and Early Exposure to Potential Food Allergens in the Development of Allergies

Cukrowska B. Microbial and Nutritional Programming-The Importance of the Microbiome and Early Exposure to Potential Food Allergens in the Development of Allergies. Nutrients. 2018 Oct 18;10(10). pii: E1541. doi: 10.3390/nu10101541.

The "microbiota hypothesis" ties the increase in allergy rates observed in highly developed countries over the last decades to disturbances in the gut microbiota. Gut microbiota formation depends on a number of factors and occurs over approximately 1000 days of life, including the prenatal period. During this period the microbiota helps establish the functional immune phenotype, including immune tolerance. The development of immune tolerance depends also on early exposure to potential food allergens, a process referred to as nutritional programming. This article elaborates on the concepts of microbial and nutritional programming and their role in the primary prevention of allergy.

Allergies are one of the key medical problems in highly developed countries, where the proportion of those affected exceeds 30% and continues to grow. The observed increase in allergy rates is associated with the type of lifestyle and involves excessive cleanliness and antibiotic use, small families, increased Cesarean section (CS) rates, altered dietary habits (increased use of processed foods, ready meals), rapid urbanization, and increasingly limited contact with nature.

These factors immensely affect the composition of the gut microbiota, which is currently believed to be essential for immune system functioning and the development of immune tolerance. The gut microbiota establishes itself over approximately 1000 initial days of life. During this time, the microbiota programs the baby's immature immune system. Another key factor determining the composition of gut microbiota is nutrition. The baby's diet affects the composition of microbiota (e.g., in the breastfed infants, predominantly bifidobacteria occur) and is a source of exposure to potential allergens. Studies show that the diet of both the mother (during pregnancy and lactation) and the baby influence the development of allergies later in life.

This article presents the role of the gut microbiota and controlled exposure to food allergens in allergy development as well as the possible preventive measures intended to stem the rise in allergy rates.

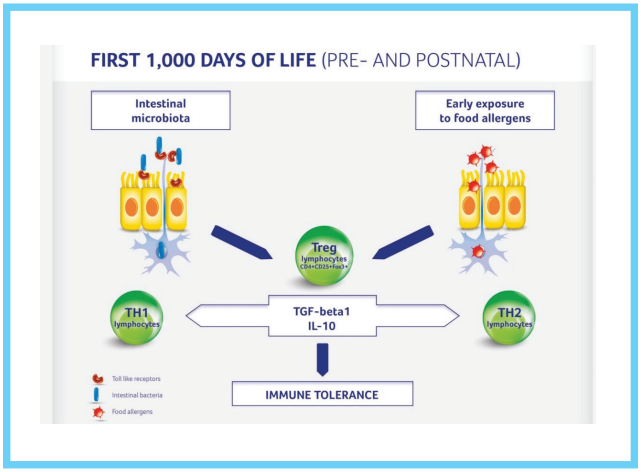
Infant Formulas Supplemented with Prebiotics and Probiotics in Allergy Prevention

In particular, the point is made that formula-fed or mixed-fed children are more prone to developing allergy. Infant formulas are based on cow's milk, whose composition is fundamentally different from that of human breast milk. This is why, manufacturers supplement infant formulas with bioactive ingredients present in human breast milk, including substances directly affecting the baby's microbiome, such as oligosaccharides with prebiotic properties or probiotic bacteria derived from human breast milk (e.g., *Bifidobacterium breve*). There are also synbiotic formulas containing both oligosaccharides and probiotic bacteria.

The most thoroughly studied oligosaccharides are a mixture of short-chain galacto-oligosaccharides (scGOS) and long-chain fructo-oligosaccharides (lcFOS) in a 9:1 ratio, at a dose of 8 g per liter. It was demonstrated that supplementation of infant formulas with a scGOS/lcFOS mixture shifts the microbiotic profile in formula-fed infants towards the profile observed in breastfed infants. Consequently, these infants were shown to bear an increased number of bacteria from the genera Bifidobacterium and Lactobacillus. In addition, formula supplementation with scGOS/lcFOS helped resolve post-antibiotic-therapy dysbiosis, lowered stool pH (the pH reached the values similar to those observed in breastfed infants), and made the short-chain fatty acid profile similar to that present in breastfed infants. The use of a synbiotic formula supplemented with scGOS/lcFOS and the probiotic bacteria Bifidobacterium breve M-16V in infants born via CS induced elimination of dysbiosis by increasing the number of bifidobacteria. In older, healthy children aged 1–3 years, a 3-month-long diet of synbiotic formula also resulted in an increase in bacteria of the genus Bifidobacterium

The Effect of Nutritional Programming on Allergy Development

A baby's diet affects the development of allergies by acting at least bi-directionally. On the one hand food influences the composition of the gut microbiota influencing the development and functioning of the immune system. On the other hand an induction of immune tolerance can be achieved by direct exposure to potential allergens during pregnancy, lactation, and weaning. The contact of the immune system with small doses of allergens activates the formation of Treg lymphocytes. The advent of the 21st century completely altered our attitudes toward exposure to potential allergens. The PASTURE study (Protection against Allergy: Study in Rural Environments) of 2014 demonstrated that the less varied the diet during the first year, the higher the risk of developing food allergy at the age of 4, 5, and 6 years. This study also showed a significant reduction of 26% for the development of asthma, with each additional food item introduced in the first year of life. Likewise, a study called LEAP (Learning Early about Peanut Allergy) demonstrated that introducing a potential allergen (in this case: peanuts) at small doses into



Immune tolerance development in children. Regulatory (Treg) T lymphocytes are activated by the gut microbiota and contact with potential food allergens.

the diet early (at the age of 4–6 months) reduced the incidence of allergy to this allergen by 80%.

Early Life Colonization of the Human Gut: Microbes Matter Everywhere

Korpela K, de Vos WM. Early life colonization of the human gut: microbes matter everywhere. Curr Opin Microbiol. 2018 Aug;44:70-78. doi: 10.1016/j.mib.2018.06.003. Epub 2018 Aug 4.

Microbes colonizing the infant intestine, especially bacteria, are considered important for metabolic and immunological programming in early life, potentially affecting the susceptibility of the host to disease. Korpela K et al., combined published data to provide a global view of microbiota development in early life. The results support the concept that the microbiota develops with age in an orchestrated manner, showing common patterns across populations. Furthermore, infants are colonized at birth by specific, selected maternal fecal bacteria and likely their bacteriophages. Therefore, infants are adapted to receiving specific bacterial signals, partly derived from the maternal microbiota, at successive immunological time windows during early development. Birth by caesarean section compromises the initial vertical transmission of microbes whereas antibiotic use shifts the microbiota away from the normal developmental pattern. These disruptions alter the microbial signals that the host receives, potentially affecting child development.

Microbiota and Derived Parameters in Fecal Samples of Infants with Non-IgE Cow's Milk Protein Allergy under a Restricted Diet

Díaz M, Guadamuro L, Espinosa-Martos I, Mancabelli L, Jiménez S, Molinos-Norniella C, Pérez-Solis D, Milani C, Rodríguez JM, Ventura M, Bousoño C, Gueimonde M, Margolles A, Díaz JJ, Delgado S. Microbiota and Derived Parameters in Fecal Samples of Infants with Non-IgE Cow's Milk Protein Allergy under a Restricted Diet. Nutrients. 2018 Oct 11;10(10). pii: E1481. doi: 10.3390/nu10101481.

Cow's milk protein allergy (CMPA) is the most common food allergy in infancy. Non-IgE mediated (NIM) forms are little studied and the responsible mechanisms of tolerance acquisition remain obscure.

This study was designed to evaluate intestinal microbiota and fecal associated parameters in infants with NIM-CMPA, under a milk elimination diet, compared to healthy infants, on an unrestricted diet, in an effort to establish potential links among microbiota and its metabolites, main feeding sources, and tolerance acquisition.

Seventeen infants between one and two years old, diagnosed with NIM-CMPA, were recruited. They were all on an exclusion diet for six months, consuming different therapeutic protein hydrolysates. After this period, stool samples were obtained and tolerance development was evaluated by oral challenges. A control group of 10 age-matched healthy infants on an unrestricted diet were included in the study. Microbiota composition, short-chain fatty acids, calprotectin, and transforming growth factor (TGF)-β_1 levels were determined in fecal samples from both groups. Infants with NIM-CMPA that consumed vegetable protein-based formulas presented microbiota colonization patterns different from those fed with an extensively hydrolyzed formula. Differences in microbiota composition and fecal parameters between NIM-CMPA and healthy infants were observed. Non-allergic infants showed a significantly higher proportion of Bacteroides compared to infants with NIM-CMPA. The type of protein hydrolysate was found to determine gut microbiota colonization and influence food allergy resolution in NIM-CMPA cases.

The importance of formula selection for the management of infants with CMPA (both IgE and non-IgE mediated) and the acquisition of tolerance has been previously stated in studies by Berni Canani and colleagues, who demonstrated that an EHF supplemented with a probiotic (Lactobacillus rhamnosus GG) was able to accelerate tolerance acquisition in infants with CMPA. However, the microbiota was not analyzed in these works. In this study, the authors observed that only those infants who were consuming rice hydrolyzed formulas did not develop clinical tolerance after six months of an exclusion diet, and presented significant differences in their microbiota with respect to those who outgrew their CMPA.

The results indicate that the type of formula consumed in early life can determine the composition and diversity of the microbiota established. These preliminary data on NIM-CMPA still have to be taken with caution due to the high inter-individual variability in the microbiota among infants in this age period. Although, with the present data, the authors hypothesize that differences in a child's main diet may influence the intestinal microbiota and its metabolic products, and, ultimately, influence tolerance acquisition, which has an important impact on clinical practice in NIM-CMPA.

The Effect of Long Chain Polyunsaturated Fatty Acid Supplementation on Intelligence in Low Birth Weight Infant during Lactation

Song Y, Liu Y, Pan Y, Yuan X, Chang P, Tian Y, Cui W, Li D. The effect of long chain polyunsaturated fatty acid supplementation on intelligence in low birth weight infant during lactation: A meta-analysis. PLoS One. 2018 Apr 10;13(4):e0195662. doi: 10.1371/journal.pone.0195662. eCollection 2018.

The growth and development of LBWIs are closely related to their nutritional status. First, LBWIs require 110–150 calories daily, with additional milk supplementing that ingested from nursing in order to increase the carbohydrate intake. Second, LBWIs require higher protein intake than normal newborns and need special formulas. Since humans cannot synthesize n-3 and n-6 polyunsaturated fatty acids in vivo, they must get them from their diet, and LBWIs cannot effectively convert the precursor fatty acids, resulting in less capacity for fat storage. LBWIs may lack long chain polyunsaturated fatty acids (LCPUFA) after birth, including docosahexaenoic acid (DHA) and arachidonic acid (AA). DHA and AA are essential for the development of the brain and central nervous system, and they quickly accumulate in the foetal anaphase and affect the development of the nervous system. Previous reports studying whether supplementing breastfeeding with LCPUFA can improve LBWI intelligence were not conclusive. Some reports showed that supplementation with DHA and AA can improve infant intelligence. However, other studies showed that LBWIs supplemented with DHA and AA led to no significant improvement in neurodevelopment or in levels of intellectual, language, and motor development. The LCPUFA supplement dose, duration, ratio of different fatty acids, supplementation scheme and feeding patterns may impact the nervous system development and intelligence of LBWIs. Therefore, whether LCPUFA supplementation can improve neurodevelopment and intelligence, also, the duration and appropriate dose of LCPUFA supplementation require further investigation.

In this study, Song Y et al., conducted a meta-analysis to explore whether long chain polyunsaturated fatty acid supplementation can improve the intellectual level of LBWIs and to identify the most effective intervention duration.

The authors performed a comprehensive search of multiple databases in order to identify studies focused the association between intelligence and long chain polyunsaturated fatty acid supplementation in LBWIs. Studies that compared the Bayley Scales of Infant Development (BSID) or the Wechsler Abbreviated Scale of Intelligence for Children (WISC) scores between LBWIs who were supplemented and controls that were not supplemented with LCPUFA during lactation were selected for inclusion in the meta-analysis.

The main outcome was the mean difference in the mental development index (MDI) and psychomotor development index (PDI) of the BSID and the full scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) of the WISC between LBWIs and controls. The findings indicated that the mean BSID or WISC scores in LBWIs did not differ between the supplemented groups and controls.

This meta-analysis does not reveal that LCPUFA supplementation has a significant impact on the level of intelligence in LBWIs.

In summary, although long-chain polyunsaturated fatty acids were reported to be essential for fetal infant mental and visual development, the impact of DHA, AA, EPA or DPA supplementation on level of intelligence of LBWIs could not be proven. Therefore, whether long-chain polyunsaturated fatty acids supplements are beneficial for LBWIs has not been shown conclusively.

Food Consumption Patterns of Infants and Toddlers: Findings from the Feeding Infants and Toddlers Study (FITS) 2016

Roess AA, Jacquier EF, Catellier DJ, Carvalho R, Lutes AC, Anater AS, Dietz WH. Food Consumption Patterns of Infants and Toddlers: Findings from the Feeding Infants and Toddlers Study (FITS) 2016. J Nutr. 2018 Sep 1;148(suppl_3):1525S-1535S. doi: 10.1093/jn/nxy171.

The prevalence of obesity and type 2 diabetes continues to increase. These conditions disproportionately affect minorities and are associated with poor nutrition early in life. Current food-consumption patterns can inform pending dietary guidelines for infants and toddlers.

The aim of this study was to describe infant feeding, complementary feeding, and food and beverage consumption

patterns of 0- to 23.9-mo-olds in the general population.

The Feeding Infants and Toddlers Study 2016 is a cross-sectional survey of caregivers of children aged <4 y. Dietary data were collected from a national random sample by using a 24-h dietary recall (n = 3235). The percentage of children consuming foods from >400 food groups was calculated. Differences in the percentage consuming between Hispanic, non-Hispanic white, and non-Hispanic black children aged 0-23.9 mo were evaluated with the use of ORs and 95% CIs.

Eighty-three percent of 0- to 23.9-mo-olds (n = 2635) were ever breastfed, 34% of 0- to 3.9-mo-olds (n = 305) and 15% of 4- to 5.9-mo-olds (n = 295) were exclusively breastfed, and 24% of 12- to 14.9-mo-olds (n = 412) consumed breast milk on the day of the recall. Complementary foods were more likely to be introduced before 4 mo in formula-fed infants (27%) than in infants who did not consume formula (5%). Half of 4- to 5.9-mo-olds consumed iron-fortified infant cereal, but few consumed iron-rich meats. Among toddlers (12-23.9 mo; n = 1133), >20% consumed no servings of fruit or vegetables on the day of the recall, approximately half consumed 100% fruit juice, and one-quarter to one-third consumed a sugar-sweetened beverage (SSB).

The authors concluded that breastfeeding initiation and duration have improved, but exclusivity remains low. Low consumption of iron-rich foods, fruit, and vegetables and lack of variety in vegetable consumption are problems. Efforts to reduce the consumption of SSBs and 100% fruit juice are warranted in early childhood.

Infant Colic Represents Gut Inflammation and Dysbiosis

Rhoads JM, Collins J, Fatheree NY, Hashmi SS, Taylor CM, Luo M, Hoang TK, Gleason WA, Van Arsdall MR, Navarro F, Liu Y. Infant Colic Represents Gut Inflammation and Dysbiosis. J Pediatr. 2018 Aug 31. pii: S0022-3476(18)30947-8. doi: 10.1016/j.jpeds.2018.07.042. [Epub ahead of print]

Sequential calprotectin measurements in babies with colic have consistently showed a reduction as the crying improved, but some have suggested that this is a normal developmental phenomenon. One of the confounding factors in the dysbiosis-gut inflammation hypothesis for colic is that babies who are fed breast milk may have higher levels of fecal calprotectin than those fed formula, although this has not been found consistently. The same authors have previously reported that calprotectin levels in breast milk were about 1% of the fecal levels. Infants taking human milk may have a different microbial population with reduced alpha-diversity (number of species) compared with those on infant formula, complicating conclusions about colic and microbial diversity. In this current report, Rhoads JM et al addressed 2 questions: (a) Is colic associated with gut inflammation and dysbiosis? Or, (b) alternatively, are elevated fecal calprotectin and abnormal microbiota artifacts produced by the effects of milk type and an incompletely developed neonatal microbiome?

A nested case-control design of 3 of the authors' studies was used to analyze clinical and laboratory data at presentation, comparing babies with colic with controls. All investigators other than the biostatistician were blinded during data analysis. Subjects were recruited based on their age and crying + fussy time. The investigators screened 65 infants, 37 with colic, as defined by Barr diary (crying + fussing time >3 hours daily), who were compared with 28 noncolicky infants.

Fecal calprotectin was elevated in babies with colic. For each mode of infant feeding (breast milk, formula, or breast + formula), infants' fecal calprotectin was higher in babies with colic. Infants with colic had similar levels of fecal alpha diversity (richness) when compared with controls, and alpha diversity was lower in breast-fed babies. Beta diversity at the phylum level revealed significant differences in microbial population. A phylum difference resulted from reduced Actinobacteria (95% of which are Bifidobacilli) in babies with colic. Species significantly associated with colic were Acinetobacter and Lactobacillus iners.

In summary, although long-chain polyunsaturated fatty acids were reported to be essential for foetal infant mental and visual development, the impact of DHA, AA, EPA or DPA supplementation on level of intelligence of LBWIs could not be proven. Therefore, whether long-chain polyunsaturated fatty acids supplements are beneficial for LBWIs has not been shown conclusively.

Seeking Biomarkers of Early Childhood Malnutrition's Long-term Effects

Valdés-Sosa PA, Galler JR, Bryce CP, Rabinowitz AG, Bringas-Vega ML, Hernández-Mesa N, Taboada-Crispi A. Seeking Biomarkers of Early Childhood Malnutrition's Long-term Effects. MEDICC Rev. 2018 Apr;20(2):43-48.

Globally, malnutrition continues to impact large numbers

of children aged less than five years in low-resource settings. While low weight-for-age levels have been reduced to 22.9% over the past decade, 155 million children aged <5 years have low stature for age, and 52 million have low weight for age, with more than half of these children living in South Asia. PEM not only causes physical and metabolic changes, it also causes long-term cognitive and behavioral problems that can persist over the lifespan and across generations. Thus, it is important to study its effects on the central nervous system using the latest technologies and to develop targeted interventions that can reverse or reduce these adverse consequences.

This 45-year study—ongoing—was made possible by collaboration among Barbadian, Cuban and US scientists. It is the first to use quantitative EEG to assess early childhood malnutrition's long-term neurocognitive effects and identify biomarkers of increased risk for related sequelae, supporting improved targeting of preventive efforts. Since EEG is relatively inexpensive and available, this is particularly promising for developing countries.

Protein-energy malnutrition affects one in nine people worldwide and is most prevalent among children aged less than five years in low-income countries. Early childhood malnutrition can have damaging neurodevelopmental effects, with significant increases in cognitive, neurological and mental health problems over the lifespan, outcomes which can also extend to the next generation. This article describes a research collaboration involving scientists from five centers in Barbados, China, Cuba and the USA. It builds on longer-term joint work between the Barbados Nutrition Study (which, over a 45-year span, has extensively documented nutritional, health, behavioral, social and economic outcomes of individuals who experienced protein-energy malnutrition in the first year of life and healthy controls from the same classrooms and neighborhoods) and the Cuban Neuroscience Center (which has developed low-cost brain imaging methods that can be readily used in low income settings to identify biomarkers for early detection and treatment of adverse consequences of childhood malnutrition). This collaboration, which involved Barbadian, Cuban and US scientists began in the 1970s, when quantitative EEG techniques were applied to EEG data collected in 1977-78, at which time study participants were aged 5-11 years. These EEG records were never fully analyzed but were stored in New York and made available to this project in 2016.

These data have now been processed and analyzed, comparing EEG findings in previously malnourished and control children, and have led to the identification of early biomarkers of long-term effects of early childhood protein-energy malnutrition. The next stage of the project will involve extending earlier work by collecting EEG recordings in the same individuals at ages 45-51 years, 40 years later, and comparing findings to earlier data and to these individuals' behavioral and cognitive outcomes. Quantitative EEG biomarkers of the effects of protein-energy malnutrition may help identify children at greatest risk for early malnutrition's adverse neurodevelopmental effects and inform development of targeted interventions to mitigate the long-term adverse effects of protein-energy malnutrition in developing countries.

Advocacy for Improving Nutrition in the First 1000 Days to Support Childhood Development and Adult Health

Schwarzenberg SJ, Georgieff MK; COMMITTEE ON NUTRITION. Advocacy for Improving Nutrition in the First 1000 Days to Support Childhood Development and Adult Health. Pediatrics. 2018 Feb;141(2). pii: e20173716. doi: 10.1542/peds.2017-3716. Epub 2018 Jan 22.

Healthy, normal neurodevelopment is a complex process involving cellular and structural changes in the brain that proceed in a specified sequence.

The most active period of neurologic development occurs in the first 1000 days of life, the period beginning at conception and ending at the start of the third postnatal year. Rapid change occurs from the first development of a structure recognizable as the brain (postconception day 18) to age 2 years.

The period of fetal life and the first 2 years postpartum may be seen as a time of tremendous opportunity for neurodevelopment and a time of great vulnerability.

Maternal prenatal nutrition and the child's nutrition in the first 2 years of life (1000 days) are crucial factors in a child's neurodevelopment and lifelong mental health. Child and adult health risks, including obesity, hypertension, and diabetes, may be programmed by nutritional status during

this period. Calories are essential for growth of both fetus and child but are not sufficient for normal brain development. Although all nutrients are necessary for brain growth, key nutrients that support neurodevelopment include protein; zinc; iron; choline; folate; iodine; vitamins A, D, B_6, and B_{12}; and long-chain polyunsaturated fatty acids. Failure to provide key nutrients during this critical period of brain development may result in lifelong deficits in brain function despite subsequent nutrient repletion. Understanding the complex interplay of micro- and macronutrients and neurodevelopment is key to moving beyond simply recommending a "good diet" to optimizing nutrient delivery for the developing child. Leaders in pediatric health and policy makers must be aware of this research given its implications for public policy at the federal and state level. Pediatricians should refer to existing services for nutrition support for pregnant and breastfeeding women, infants, and toddlers. Finally, all providers caring for children can advocate for healthy diets for mothers, infants, and young children in the first 1000 days. Prioritizing public policies that ensure the provision of adequate nutrients and healthy eating during this crucial time would ensure that all children have an early foundation for optimal neurodevelopment, a key factor in long-term health.

The Immune Consequences of Preterm Birth

Melville JM, Moss TJM. The immune consequences of preterm birth. Front Neurosci. 2013; 7: 79.

Preterm birth occurs in 11% of live births globally and accounts for 35% of all newborn deaths. Preterm newborns have immature immune systems, with reduced innate and adaptive immunity; their immune systems may be further compromised by various factors associated with preterm birth. The immune systems of preterm infants have a smaller pool of monocytes and neutrophils, impaired ability of these cells to kill pathogens, and lower production of cytokines which limits T cell activation and reduces the ability to fight bacteria and detect viruses in cells, compared to term infants. Intrauterine inflammation is a major contributor to preterm birth, and causes premature immune activation and cytokine production. This can induce immune tolerance leading to reduced newborn immune function. Intrauterine inflammation is associated with an increased risk of early-onset sepsis and likely has long-term adverse immune consequences. Requisite medical interventions further impact on immune development and function. Antenatal corticosteroid treatment to prevent newborn respiratory disease is routine but may be immunosuppressive, and has been associated with febrile responses, reductions in lymphocyte proliferation and cytokine production, and increased risk of infection. Invasive medical procedures result in an increased risk of late-onset sepsis. Respiratory support can cause chronic inflammatory lung disease associated with increased risk of long-term morbidity. Colonization of the infant by microorganisms at birth is a significant contributor to the establishment of the microbiome. Caesarean section affects infant colonization, potentially contributing to lifelong immune function and well-being. Several factors associated with preterm birth alter immune function. A better understanding of perinatal modification of the preterm immune system will allow for the refinement of care to minimize lifelong adverse immune consequences.

In conclusion, advances in obstetric and neonatal medicine have enabled profound reductions in perinatal mortality in recent years but this benefit has not come without cost. With increased rates of survival of preterm infants has come growing numbers of babies with illness and long-term disability, even for those born close to term. The consequences for immune development and function of preterm birth are largely unknown. We need to better understand the impact of preterm birth and associated factors, including obstetric and neonatal management, on immune function in order to improve health outcomes for the increasing number of individuals born preterm.