A NEW ERA IN INFANT NUTRITION

HUMAN MILK OLIGOSACCHARIDES

In collaboration with UNIVERSITY OF BARI

9TH & 10TH MARCH, 2018
ROME, ITALY

Information for medical profession only
## AGENDA

**9TH MARCH, 2018**

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.00-09.15</td>
<td>Mohamed Salah</td>
<td>Welcome &amp; Introduction</td>
</tr>
<tr>
<td>10.15-11.00</td>
<td>Prof. Hania Szajewska</td>
<td>Human milk and protection against infections</td>
</tr>
<tr>
<td>11.00-11.45</td>
<td>Prof. Flavia Indrio</td>
<td>Prebiotics and probiotics</td>
</tr>
<tr>
<td>11.45-12.00</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>12.00-12.45</td>
<td>Prof. Valerio Nobili</td>
<td>HMO basic science</td>
</tr>
<tr>
<td>12.45-13.30</td>
<td>Prof. Hania Szajewska</td>
<td>Infant formula supplemented with Human Milk Oligosaccharides: Where are we now?</td>
</tr>
<tr>
<td>13.30-14.00</td>
<td>Prof. Flavia Indrio</td>
<td>Wrap up</td>
</tr>
</tbody>
</table>
# Agenda

**10th March, 2018**

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.00-10.15</td>
<td>Prof. Flavia Indrio</td>
<td>Welcome</td>
</tr>
<tr>
<td>10.15-11.00</td>
<td>Prof. Valerio Nobili</td>
<td>Introduction to the history of the department (Repeated tour for the audience throughout the pediatric department)</td>
</tr>
<tr>
<td>11.00-11.45</td>
<td>Dr Fiammetta Bracci</td>
<td>Case study: All that glitters is not gold</td>
</tr>
<tr>
<td>11.45-12.00</td>
<td></td>
<td>Break</td>
</tr>
<tr>
<td>12.00-12.45</td>
<td>Dr. Alessandra Nicolardi</td>
<td>Case study: Crohn’s disease</td>
</tr>
<tr>
<td>12.45-13.15</td>
<td>Dr. Vanessa Dargenio</td>
<td>Case study: Recurrent abdominal pain: Case report</td>
</tr>
<tr>
<td>13.15-13.30</td>
<td>Prof. Flavia Indrio</td>
<td>Wrap up</td>
</tr>
</tbody>
</table>
Hania Szajewska, MD, is Professor and Chair of the Department of Paediatrics at the Medical University of Warsaw. Since March 2014, she has been the editor-in-chief (Europe) of the Journal of Pediatric Gastroenterology and Nutrition. Professor Szajewska has broad interests in paediatric nutrition but her research focuses on probiotics and prebiotics, the effects of early dietary interventions on later outcomes, acute and chronic diarrhoeal diseases and coeliac disease. She has been actively involved in several European Union-funded projects (e.g., PREVENTCD; NUTRIMENTHE; EarlyNutrition) and is an enthusiastic advocate for the practice of evidence-based medicine. Professor Szajewska served as a member of the Council of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and, more recently, as the general secretary of ESPGHAN. She also served as member and secretary of the ESPGHAN Committee on Nutrition. Currently, she is co-chair of the ESPGHAN Working Group on Probiotics and Prebiotics and Chair of the ESPGHAN Working Group on Outcomes in Nutrition Trials. Professor Szajewska has written more than 200 publications and 25 book chapters. (Citations 5144; Hirsch index 43 – Web of Science, February 2015.)
Prof. Flavia Indrio is currently senior consultant in pediatric gastroenterology in the Department of Pediatrics at the University of Bari, Italy. She teaches the pediatric gastroenterology course for residents at the University of Bari’s School of Medicine, and is a member of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee and various Italian societies including Pediatrics, Pediatric Gastroenterology and Neonatology.

Prof. Indrio is President of the scientific board for the Continuous Medical Education of Family Pediatricians, and has been awarded the Ivan Casas Prize for research on probiotics. She is also a scientific coordinator of a research group studying functional gastrointestinal disorders in the Middle East and North Africa region.
Prof. Valerio Nobili is Associate Professor of Pediatrics at the University “La Sapienza” in Rome, Italy. He is the Head of Hepatology, Gastroenterology, and Nutrition Unit and the Chief of Liver and Gut Research Unit at the Bambino Gesù Children Hospital in Rome. He is also a member of the ESPGHAN (European Society Gastro Hepatology Nutrition Pediatric) and member of the Board of MEDSCAPE Gastroenterology. He is a reviewer for the following medical journals: Hepatology, GUT, Journal Gastroenterology and Hepatology, Journal Pediatric Gastroenterology and Nutrition, World Journal Gastroenterology, Journal of Hepatology, Liver International, Pediatric Transplantation, Expert Review of Molecular Diagnostics, Journal of Hematology, Journal of Internal Medicine, Journal of Clinical Rheumatology, Clinical Endocrinology. For the Pediatric Obesity Journal, he’s an Associate Editor. He has published more than 350 works in international reviews and has attended numerous national as well as international Congresses as reporter.
Dr. Dargenio Vanessa Nadia graduated in Medicine from the medical school of the University of Bari in July 2015 with a 110/110 cum laude. Currently, she’s a second-year resident at the Department of Pediatrics, ‘Policlinico’ Bari University Hospital in Italy. During her training, she’s been actively collaborating in study groups in the field of pediatric gastroenterology focusing mainly on probiotics, Coeliac Disease and Inflammatory Bowel Disease. Dr. Dargenio Vanessa Nadia participated as delegate at the Young Investigator Forum of Bergen, The Netherlands, in September 2017.
Dr. ALESSANDRA NICOLARDI

Dr. Alessandra Nicolardi graduated in Medicine at the medical school of the University of Bari in October 2015 with a 110/110 cum laude. Currently, she’s a second-year training doctor at the Pediatrics Department of the “Policlinico Bari University Hospital”, Italy. In the last two years, under the supervision of the head of the department, she has actively collaborated in study groups in the field of pediatric gastroenterology and has conducted a very interesting clinical trial on Inflammatory Bowel Disease. Dr. Alessandra Nicolardi is also very interested in Coeliac Disease. She participated as delegate at the Espghan’s Summer School “Beyond the nutrients” in June 2017.
Dr. Fiammetta Bracci is a pediatric gastroenterologist from Rome. She has a PhD in Gastroenterology from the University "La Sapienza". Dr. Fiammetta has been with the Children’s Hospital “Bambino Gesù” for the last 20 years. She has her focus mainly on inflammatory bowel diseases (IBD), however her daily activities include pediatric gastroenterology as a whole. She believes IBD in children is quite challenging and doctors must carefully handle the disease and help children and their families go through the chronic bowel illness with care.
HUMAN MILK AND PROTECTION AGAINST INFECTIONS

As written in a 2008 BMJ article, ‘Formula milk is just a food, whereas breast milk is a complex living nutritional fluid that contains antibodies, enzymes, and hormones, all of which have health benefits’ (Hoddinott et al. BMJ 2008;336:881-7). Exclusive breastfeeding for around 6 months is a desirable goal, but partial breastfeeding as well as breastfeeding for shorter periods of time are also valuable. A 2016 Lancet systematic review concluded that breastfeeding provides protection against child infections and malocclusion, increases in intelligence, and probable reductions in overweight and diabetes (Victora et al. Lancet 2016; 387: 475-90). Here, evidence on the effects of breastfeeding on the risk of infections is summarized.

Otitis media. Evidence has shown that breastfeeding is associated with a significant reduction in the risk of acute otitis media. Comparison of ever breastfeeding with exclusive bottle-feeding yielded a pooled odds ratio for acute otitis media in infants younger that 2 years of age, mostly from high-income settings, of 0.67 (11 trials, 95% CI 0.62 - 0.72). No effect was seen in children older than 2 years (5 trials, OR 1.21, 95% CI 0.60–2.45).

Gastrointestinal infections. Evidence from a large number of studies, mostly from low- or middle-income settings, is available. There is strong evidence that breastfeeding reduces the risk of diarrhea incidence in infants younger than 6 mo of age (23 trials, RR 0.37, 95% CI 0.27–0.50), as well as in children 6 mo to 5 years (11 trials, RR 0.46, 95% CI 0.28–0.78). Breastfeeding also reduced the risk
of admissions to the hospital for diarrhea, particularly in children <5 years of age (9 trials, RR 0.28, 95% CI 0.16–0.50). Of note, not all trials adjusted for potential confounders.

Respiratory tract infections. Breastfeeding for 4 or more months was associated with a reduction in both the incidence or prevalence of lower respiratory tract infections (16 trials, RR 0.68, 95% CI 0.60–0.77) and the risk of hospitalization secondary to respiratory tract infections (17 trials, RR 0.43, 95% 0.33–0.55) in children younger than 2 years.

The protection provided by human breast milk is, in part, due to the unique composition of immunologic factors that have the ability to overcome the immature immune responses of an infant. Among others, these include growth factors for protective bacteria; oligosaccharides, glycoconjugates, and glycolipids that block the adherence of pathogens to the mucosa and thereby protect the breastfed infant against invasive infections; lysozymes that lyse certain bacteria; lactoferrin that via its iron-binding capacity interferes with the proliferation of siderophilic bacteria and fungi; and secretory IgA antibodies that bind to adherence sites, virulence factors, or toxins of microorganisms. Those protective factors are able to resist enzymatic digestion in the gastrointestinal tract of the infant and are supplied when the infant’s immune system is still immature. Presence of immunologic factors is one of the most important features of human milk. Knowledge on these factors is needed to reduce the gap in health outcomes in breast-fed and formula fed infants.
PREBIOTIC AND PROBIOTIC

Increasingly, the gut microbiome is implicated in the development of intestinal function, not only as a microbiological agent but also by altering exposure to dietary compounds that influence intestinal maturation. Whereas the composition and metabolism of the gut microbiome is influenced by diet, the gut microbiome can also modify dietary exposures in ways that are beneficial or detrimental to the human host. The colonic bacteria metabolize macronutrients, either as specialists or in consortia of bacteria, in a variety of diverse metabolic pathways. Early postnatal nutrition may also represent a vital determinant of adult health by making an impact on the development and function of gut microbiota. An inadequate gut microbiota composition and function in early life seems to account for the deviant programming of later immunity and overall health status. In this regard, probiotics, which have the potential to restore the intestinal microbiota balance, may be effective in preventing the development of chronic immune-mediated diseases. Recently the increasing knowledge on functional components changed the nutritional approach in different periods of life. A comprehensive review of prebiotic and probiotic will be addressed.
HMO BASIC SCIENCE

The composition of human milk is the biologic norm for infant nutrition. Human milk also contains many hundreds to thousands of distinct bioactive molecules that protect against infection and inflammation and contribute to immune maturation, organ development, and healthy microbial colonization. Some of these molecules, e.g., lactoferrin, are being investigated as novel therapeutic agents. A dynamic, bioactive fluid, human milk changes in composition from colostrum to late lactation, and varies within feeds, diurnally, and between mothers. The most important worldwide institution recommend exclusively breast feeding your baby for the first six months of life - after that you can continue to breast feed alongside the introduction of your baby’s first “solid food. Feeding infants with adapted formula milk is increasing. Many milk proteins are degraded by heat treatment and freeze-thaw cycles may not have the same bioactivity after undergoing these treatments. Also the role of IgF1 will be discussed both in breastfeeding compared to formula feeding. Moreover, particular infant population such as SGA (small gestational age) will be followed during the follow-up and their used milk.
RECURRENT ABDOMINAL PAIN: CASE REPORT

INTRODUCTION
The term ‘recurrent abdominal pain’, or RAP, refers mainly to the duration of a painful period and to the frequency of pain. The commonly accepted duration is at least three months, and over this three-month period there must be at least three episodes of pain severe enough to impair the daily activities of the affected patient. Over the years, with advances in medical technology and a better understanding of the pathophysiology of abdominal pain, more and more organic causes have been identified. Yet, the most common causes of RAP in children are still functional.

CASE STUDY
Luca, 5 years old, comes to our observation for recurrent abdominal pain in the last six months. The parents reported an access to the emergency room for abdominal pain not associated with vomiting one month earlier. The near and remote pathological anamnesis were unremarkable. At admission he underwent blood tests, abdominal ETG, ECG with cardiological examination and surgical consultation, all within the normal range. During hospitalization he showed a sudden confusional state with spatio-temporal disorientation, gait disturbances and unset of archaic reflexes (suction). Neurological counseling showed no focal deficits except for a positive Romberg; a ideo-motor slowdown was described and a negative urgent CT scan was recommended. The
vigilant EEG highlighted clear-cut figures on the fronto-center-temporal derivations of the right regions; the EEG performed after hypnotic deprivation confirmed slowing of brain electrical activity on the right F-C-T regions, with a tendency to affect the analogous contralateral regions. Brain and spinal-cord MRI substantially highlighted "Slight thinning of the right hippocampus at the level of the head and the body with widening of temporal horn of the ipsilateral ventricle". Neuropsychological evaluation showed an undetectable IQ, dissociative disorders, auditory hallucinations and confusional state. The following diagnosis was made: "Suspected temporal crises in hippocampal sclerosis and psychological disorder". Carbamazepine, Omeprazole and neurological follow-up were undertaken.

**CONCLUSIONS**

Hippocampal sclerosis (HS) is considered one of the major pathogenic factors of drug-resistant temporal lobe epilepsy. HS is characterized by selective loss of pyramidal neurons – especially of sectors CA1 and CA3 of the hippocampus – pathological proliferation of interneuron networks, and severe glia reaction. These changes occur in the course of long-term and complex epileptogenesis. Rare cases of HS in pediatrics and poor literature in this regard.
CASE STUDY: CROHN’S DISEASE

Crohn’s disease (CD) is an immune mediated inflammatory condition that can cause chronic inflammation of the gastrointestinal tract and can have a long-lasting impact upon nutrition. Therapy is designed to induce prolonged remission, which can often be achieved by a combination of corticosteroids and immunosuppressants. Unfortunately most of these treatment options, though effective, come at a significant cost to the patient in terms of adverse effects. Due to its excellent safety profile and its equipotential to corticosteroids in inducing remission, EEN is now considered a first-line agent to induce remission and improve malnutrition in children with active CD in many parts of the world. I describe a clinical case in which an infant presenting Crohn’s disease achieved clinical remission using exclusive enteral nutrition, which has been shown to induce remission in older children with active Crohn’s disease.
ALL THAT GLITTERS IS NOT GOLD

Five years old child. Born at term, breast fed for 12 months, good weight and height gained. Started having constipation at the age of 3 years when toilet training started. He also had retentive behavior, pain at defecation, hard and dry stools, loss of appetite, failure to thrive. The child showed partial response to a small dose of macrogol and was referred to our paediatric gastroenterology outpatient clinic. At examination he had hard stools palpable in the left lower abdominal quadrant and a perianal fissure. Macrogol dose was increased and topical treatment for the anal fissure was prescribed. He initially responded but one month later started again to have hard stools, loss of appetite and weight loss. He was seen by his GP who prescribed a cow’s milk protein free diet with improvement of his appetite and bowel habits but not of his weight. The child was sent back to our outpatient clinic for further evaluation. We did blood test for CBC, RCP, total IgE, food allergy, autoantibodies for coeliac disease. Bingo! He had positive anti TTG antibodies with a value >200, positive EMA in two consecutive samples, and positive DQ2; coeliac disease was diagnosed according to the ESPGHAN criteria. He started a strict gluten free diet with great clinical improvement, he could stop macrogol therapy, gained weight, recovered energy. 1 year later………. started having diarrhea, weight loss, asthenia, tachycardia. Poor compliance to the gluten free diet was suspected but blood tests showed negative anti TTG antibodies. Fortunately… he did the whole blood samples expected for CD follow-up and after few days a picture of hyperthyroidism was diagnosed! The child started endocrine therapy and finally definitely recovered and enjoyed his gluten free meal!
INFANT FORMULA SUPPLEMENTED WITH HUMAN MILK OLIGOSACCHARIDES: WHERE ARE WE NOW?

Human Milk Oligosaccharides (HMOs) are the third largest component of human milk, with contents ranging from 1–10 g/L in mature milk to 15–23 g/L in colostrum. They are complex carbohydrates composed of five monosaccharides (galactose, glucose, fucose, N-acetylglucosamine, and the sialic acid derivative N-acetylmuraminic acid). The lower incidence of gastrointestinal and other infections found in breastfed infants, as well as other benefits of breastfeeding such as the establishment of beneficial gut microbiota, promotion of intestinal development, and stimulation of immune maturation, may, in part, be related to the presence of HMOs. Approximately 150-200 HMOs have been described. Among others, postulated effects of HMOs include: (1) prebiotic effects (HMOs serve as metabolic substrates for beneficial bacteria, support their growth, and provide them with a growth advantage over potential pathogens); (2) antiadhesive antimicrobials (HMOs serve as glycan receptor decoys and prevent pathogen attachment); (3) intestinal epithelial cell modulators (HMOs affect intestinal epithelial cells and modulate their gene expression, which leads to changes in cell surface glycans and other cell responses); and (4) immune modulators (HMOs modulate lymphocyte cytokine production, potentially leading to a more balanced Th1/Th2 response).
Current interest in HMOs is driven by three major factors. These include: (1) advances in analytical methods of HMO; (2) progress in biotechnology which allows nowadays the production of at least some HMOs though processes such as chemoenzymatic synthesis, microbial metabolic engineering, and isolation from human donor milk or dairy streams; and (3) formal approval by the European Food Safety Authority and Food and Drug Administration of the safety of 2’-fucosyllactose (2’-FL) and lacto-N-neotetraose (LNnT) when added alone or in combination to infant, follow-on, and young child formula.

Indeed, these two HMOs, 2’-FL and LNnT, have recently been added to infant formula, either alone or in combination with other prebiotics. Current evidence suggests that compared with the administration of unsupplemented infant formula, supplementation of formula with 2’-FL and LNnT is safe, well tolerated, and supports age-appropriate growth. Preliminary data suggest that formula with 2’-FL and LNnT reduced bronchitis and medication use (antipyretics and antibiotics). Formula supplemented with 2’-FL (in various concentrations) and galactooligosaccharides (GOS) compared with GOS-supplemented formula alone is safe, well tolerated, and supports age-appropriate growth. Effects on immune functions are possible. More studies are needed to decide which compound(s) would be most suitable for supplementation, which concentrations and combinations should be used, and how long HMOs should be given. In future, when more HMOs become available, other HMOs may be added to infant formula.