

GUT in FOCUS

**Symposium NOBEL FORUM, Karolinska Institutet,
February 2nd 2015, 10.00 -18.00**

Focus on development of intestinal microbiota (IM)

Lang Dennis: Challenges to the establishment and maintenance of a healthy intestinal microbiome in infants in developing countries.

The MAL-ED study is conducted at field sites in Peru, Brazil, S. Africa, Tanzania, India, Pakistan, Nepal and Bangladesh that have populations with historically high burdens of enteric diseases and malnutrition. It is an observational longitudinal birth cohort study that follows approximately 200 children at each site to determine the role of enteric infections, nutritional intake, and other environmental exposure variables on growth (length, weight, and head circumference), on cognitive development, and on immune responses to EPI vaccines. An important component of the project hypotheses is that one of the effects of frequent infection is impaired gut function and inflammation (enteropathy) that contributes to the development of malnutrition and that affects the aforementioned outcomes of interest. At these sites, we have observed frequent infection with enteric pathogens, sub-optimal breastfeeding, high rates of antibiotic use and sub-optimal diets in these resource poor settings. These factors will be discussed as obstacles to overcome in the establishment and maintenance of a healthy intestinal microbiome in individuals living in resource poor environments.

Eggesboe Merete: Factors affecting infant gut microbiota and possible consequences for health.

From once being employed as an extreme measure, to save the foetus after its mothers death, caesarean section is used increasingly more commonly as mode of delivery for entirely non-medical reasons. A sharp increase in caesarean delivery has been noted in most western countries during the last decades and in the US one third of all babies are now being delivered by a caesarean section. In Norway a 7-fold increase in caesarean rates took place between 1970s and 2001 (from 2% to 15%) and the incidence is still increasing. Focus so far has mainly been on short-term health consequences of caesarean delivery.

However, caesarean deliveries may have far more serious long term effects as it disrupts the natural transfer of microbes from one generation to the other. Instead of getting the ancient microbes that have co-evolved with humans, the infants gut is colonized with hospital acquired microbes, and skin microbes from the mother. Due to the cascading effects the first arriving microbes sets into motion, the consequence may be a disrupted final mature gut microbiota, which is not optimal for the human organism, and thus may cause adverse health effects. Maternal diet and use of antibiotics are other important factors that may disrupt gut microbiota during early infancy.

Even if the gut microbiota is corrected with time, the early disruptions may have long term effects due to the presence of developmental windows that relies on microbial stimulus from the gut, involving development of tolerance, angiogenesis and stress responses.

We present results from the NoMIC study of 450 infants in Norway where the effects of CS, antibiotics and diet on the gut microbiota composition (16sDNA Illumina) has been studied and related to health effects. We observed that neuropsychological development and high weight at 2 years shared features of a disrupted gut microbiota typically seen in CS babies.

Diaz-Heijtz Rochellys: The gut microbiota and developmental programming of the brain. A central question in the fields of neuroscience, psychology and psychiatry is one regarding the relative roles of genetic and environmental factors in shaping human behavior. Research over the last two years has revealed an influence of gut microbiota on the development of brain circuits that subserve motor *control*, *emotions*, and *learning* (Diaz Heijtz *et al.*, *PNAS*, 2011; Neufeld *et al.*, *Neurogastroenterol Motil*, 2011; Clarke *et al.*, *Mol Psychiatry*, 2012). The current challenge is to understand the precise mechanisms mediating these interactions. In her talk, Dr. Diaz Heijtz will present novel data supporting the notion that one of the mechanisms mediating the influence of gut microbiota on brain development and behavior involves the direct actions of gut-derived microbial molecules within the brain, as well as the long-term effects of antibiotic treatment during early brain development.

Raa Jan: β -glucan immune modulation by non-digestible and non-absorbable β -1,3/1,6-glucan particles. As they pass non-digested through the gastrointestinal tract, beta-1,3/1,6-glucan particles elicit biochemical mechanisms counteracting and preventing life-threatening infections, toxicity of bacterial endotoxins, mechanical organ damage, asthmatic and allergic reactions, and enhancing the efficacy of mucosal vaccines and injected anti-cancer monoclonal antibodies. Too good to be true?

MacFabe Derrick: Enteric short chain fatty acids: Microbial messengers of metabolism, mitochondria and mind: Implications in autism spectrum disorders. Clinical observations suggest that gut and dietary factors, transiently worsen, and in some cases appear to improve, behavioural symptoms in autism spectrum disorders (ASDs), but the reason of this is unclear. Recent evidence suggests ASD as a family of systemic disorders of increasing incidence manifesting altered immunity, metabolism and gene expression, and altered components of the gut microbiome. Pre or perinatal infection or hospitalization is emerging as a major risk factor for ASD. Can a common environmental agent link these disparate findings? Basic science and clinical evidence supports that enteric short chain fatty acids, present in diet and produced by the gut microbiome, particularly by opportunistic gut bacteria following carbohydrate ingestion, may be key triggers in ASD. Administration of propionic acid, a major fermentation product associated with ASD associated gastrointestinal bacteria, in rodents elicits behavioral, electrographic, neuroinflammatory, metabolic (lipid, mitochondrial, redox) and epigenetic changes closely resembling those found in ASDs. We hypothesize that ASDs are produced by

pre or post-natal antibiotic resistant bacterial infections in sensitive sub populations, which may have major implications in ASD cause, diagnosis and treatment. Collectively, this offers further support that gut microbiome metabolites, such as dietary or enteric bacterially produced short chain fatty acids, 1)are underappreciated modulators of brain development and behavior 2) may be plausible environmental agents that can trigger or exacerbate ASDs and 3)deserve further exploration in basic science, agriculture, and clinical medicine.

Bakken Johan: Feces transplantation - US recommendations & experience.

Patients who have failed to respond to repeated antibiotic treatment for recurrent *Clostridium difficile* infection (RCDI) present a particularly difficult challenge. Recent investigations of patients with RCDI have demonstrated significant disruption of the intestinal microbiome diversity as well as bacterial richness. Following the initial report on fecal microbiota transplantation (FMT) published by Eiseman in 1958, instillation of stool collected from a healthy donor into the intestinal tract of patients with RCDI has been used increasingly and with a high degree of success to correct the intestinal dysbiosis brought about by repeated courses of antibiotic treatment. By now, multiple case reports and case series describing the outcome of FMT for more than 700 patients from around the Western world have been published. FMT treatment success rates are high and have ranged between 77 and 98%; the highest success rates have been observed with instillation of stool via the lower GI tract. A prospective randomized controlled trial was recently conducted in Holland, demonstrating superior treatment outcomes with FMT when compared to conventional therapy with oral vancomycin. FMT has been universally well accepted by patients and represents a low cost alternative treatment approach to an increasing clinical problem, with unlimited supply of the raw material (human stool). FMT appears to be safe, as no report of severe adverse events directly attributed to the instillation procedure itself has been reported so far. However, possible long term consequences of FMT are unknown, and the US Food and Drug Administration currently considers FMT to be investigational therapy.

Norén Torbjörn: Feces transplantation - EU recommendations.

Recurrent *Clostridium difficile* infection (CDI) exhibit a disrupted diverse gut microbiome where recolonization decides final outcome of this often challenging course of disease. Clinical trial and error treatment with fecal microbiota transplant (FMT) have until recently produced limited grade of scientific data. Lack of standardized procedure and obscure declaration of product content have also made data evaluation difficult. Lately a randomized controlled study has proven FMT superior to standard vancomycin therapy and this has inspired several ongoing studies. Current evidence has further more introduced FMT as an accepted treatment in recent European guidelines published by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID 2014). This talk will update on the current position of FMT in treatment and the slowly emerging consensus of different procedures in practice, as well as concerns still present.

Norin Elisabeth: On-going treatment of CDI-patients in Sweden.

Recurrent *Clostridium difficile* infections, (CDI) following use of antibiotics, is an increasing problem, in spite of use of some new antibiotic drugs. Fecal microbiota transplant (FMT), i.e. utilization of stool from a healthy donor (close relative/donor pool) is often in use today. When administering FMT, the major risk is the possibility of transferring potential pathogens/contagious agents from the donor to the recipient, implying a time- and cost-consuming screening before treatment initiation. We are working with cultivated microbiota

transplant (CMT), an anaerobic cultivated human intestinal microbiota which over a period of almost 20 years has been recultivated and given to a substantial number of patients without occurrence of any significant complications. The risk of transfer of any contagious agents from the donor to the recipient when using FMT is discussed as when applying CMT, we know that the donor still is in good condition, the treatment cost is significantly reduced, risk of development of further antibiotic resistance is reduced and it is a significant improvement of the life conditions for the patients.

Kjelstad Garborg Kjetil: ACHIM as first line treatment for Clostridium difficile infection. Clostridium difficile infection (CDI) is a disease most often resulting from an antibiotic-induced disturbance of the healthy intestinal microbiota. Up to one third of patients with CDI treated with first line antibiotics (Metronidazole or Vancomycin) experience recurrent or relapsing infection within few weeks, and multiple recurrences are common. Reconstitution of a healthy intestinal microbiota by fecal microbiota transplantation (FMT) is significantly more effective than vancomycin in the treatment of recurrent CDI. We hypothesize that the instillation of a healthy intestinal microbiota will be more effective in inducing a durable cure than Metronidazole for primary CDI.

An anaerobically cultivated human intestinal microbiota (ACHIM), derived from a stool sample from a healthy individual and extensively tested for pathogens, has been used in hundreds of patients with recurrent CDI with cure rates comparable to FMT with fresh feces.

In a multi-center randomized controlled trial we will compare the effect of a 10-day course of Metronidazole 500 mg tid versus rectal instillation of ACHIM with regard to cure without recurrence of CDI within 70 days after treatment.

For a disease caused by antibiotics, the use of more antibiotics is counterintuitive. Reconstitution of a healthy intestinal microbiota as first line treatment for CDI may represent a paradigm shift in the management of this increasingly common and serious infection.

Benno Peter: Is Irritable Bowel Syndrome (IBS) a Dysbiotic Bowel Syndrome (DBS)? Two cases of post-infectious IBS, were successfully treated with transplantation of a cultivated intestinal microbiota. This suggests that a dysbiosis of the intestinal microbiota could be the culprit at least in some cases of IBS. Resetting the gut microbiota might be a possible solution for these patients that otherwise may face a life-long quality of life reduction. Studies have suggested that conditions as varied as chronic constipation, metabolic syndrome, autoimmunity, asthma, cardiovascular disease and Crohn's disease may be caused by intestinal dysbiosis. If this is the case we would like to suggest a new term: Dysbiotic Bowel Syndrome (DBS).

Midtvedt Tore: Summary and concluding remarks

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