Developing a Healthy Gut Flora in Children

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Agenda

• About myself
• How the microbiome develops from birth
  • What factors alter its development
• How the immune system develops and the interactions between the microbiome and immune system
• How the interactions of the microbiome and the immune system could have an affect on developing childhood conditions, such as:
  • Immune imbalances
  • Autism
  • Obesity/Type 2 diabetes
  • Fussy eaters
• Improving the developing microbiome in children – how probiotics could help
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How the microflora develops from birth

• Mode of birth
• Feeding method
• Gestational time
• Antibiotics
• Environment
• Weaning
Is there a Critical Phase of Infant Development?

• Recent studies have suggested that early microbiota imbalances are not reflected in adults, (Falony et al, 2016).

• Birth cohort studies have shown that alterations to an infants microbiome can have an affect on the immune system which may impact conditions later in childhood, (Hoskin-Parr et al, 2013, Sjögren et al, 2009).

• If the microbiome is altered within a critical phase, could it potentially have an affect on later immune conditions developing?

Possible critical phase of microflora and immune system development
Seeding the Infant Microbiome

• The reproductive tract was previously believed to be sterile, however recently experts have speculated that seeding of the infant's microbiome starts with the placenta.

• Studies have shown that newborns have complex microbial communities in the gut within the first few weeks, which then fluctuate in bacterial composition until a relatively mature diversity is reached around 1-3 years, (Biasucci et al, 2008).

• The first bacteria to establish in the newborn gut are usually aerobic, which then consume oxygen and change the environment of the intestines making it more suitable for anaerobic bacteria to thrive, (Alderberth, 2008).

How the microflora develops from birth

- Mode of birth
- Feeding method
- Gestational time
- Antibiotics
- Environment
- Weaning
Mode of Birth

- Infants born vaginally compared to caesarean show increased diversity in their intestinal microbiome.
- Biasucci et al, (2008) discovered an absence of Bifidobacterium in the intestinal microbiome of C-section infants on day 3 of life. Hill et al, (2017) suggest that caesarean infants are more often colonised with C difficile, compared to vaginal births.
  - Vaginal birth microbiomes = mothers vaginal microbiome
  - Caesarean birth microbiomes = skin microbiome
  - (Dominguez-Bello et al, 2010)
- Emergency C-section were found to have the highest species richness and diversity rather than those born by elective caesarean or vaginally, (Azad et al, 2013).
Mode of Birth

- C-section infants gradually progressed to harbouring a microbiota closely resembling vaginal delivery by week 8 of life, which was maintained at week 24, (Hill et al, 2017).
- Is the immune development of infants born by caesarean is altered within this early window of dysbioisis?
- Vaginal swabs have been shown to partially restore the microbiome of c-section infants, (Domínguez-Bello et al, 2016)
Poll Question

How many births in the UK were by caesarean section for the year 2013-2014?

a) 16%
b) 26%
c) 36%

https://www.nct.org.uk/professional/research/maternity%20statistics/maternity-statistics-england

Feeding Method

- Bifidobacteria dominated the microbiota of breast-fed infants, whereas formula-fed babies had significantly higher proportions of Bacteroides and members of the Clostridium coccoides and Lactobacillus groups, (Fallani et al, 2010).

- Exclusively formula-fed infants were more often colonised with E coli, C. difficile, Bacteroides, and lactobacilli, compared with breastfed infants, (Penders et al, 2006).
Feeding Method

• Breastfed infants have a lower bacterial richness and diversity. The unique oligosaccharides found in breast milk, serve as prebiotics for a limited number of gut microbes, (Azad et al, 2013)

• Five genera of bacteria were significantly more abundant in infants that were breastfed for longer than four months and four genera were more abundant in infants that were breastfed for a shorter duration, (Hill et al, 2017).

• The introduction of formula milk or solid food perturbs bacterial colonisation and the development of the neonatal immune system, (Hill et al, 2017).
Gestational Time

- The gut microbiota of preterm infants displays a significantly greater abundance of *Proteobacteria* compared to full term infants at week 1, (Hill, et al, 2017).

- Hospitalisation and prematurity were associated with higher prevalence and counts of *C. difficile*, (Penders et al, 2006).


- The duration of gestation impacts the mother’s breast milk microbiome. The abundance of *Bifidobacterium* species is higher in breast milk from mothers who delivered at full term as compared with mothers of preterm infants, (Khodayar-Pardo et al, 2014).
Antibiotics

• Antibiotic use by the infant is associated with decreased numbers of bifidobacteria and Bacteroides, (Penders et al, 2006).

• Hussey et al, (2011) detected bifidobacteria in all control infants at both four and eight weeks, however only six out of nine antibiotic-treated infants had detectable bifidobacteria at four weeks.

• Greater diversity of *Bifidobacterium* spp. in the control group compared with antibiotic-treated infants, (Hussey et al, 2011)
Environment

- Many differing factors in the environment surrounding the newborn and even whilst in utero may have an effect on their developing microflora. The Old Friends Theory of interaction of the host with microbes is more relevant than the hygiene hypothesis, (Bloomfield et al, 2016).

- Infants with older siblings have shown to have slightly higher numbers of bifidobacteria, compared with infants without siblings, (Penders et al, 2006).

- Exposure to pets increases the abundance of two bacteria, Ruminococcus and Oscillospira, which have been associated with reduced atopic conditions and obesity, (Tun et al, 2017).
Environment

- Children living on farms were exposed to a wider range of microbes and this exposure explains the inverse relationship between asthma and growing up on a farm, (Ege et al, 2011).
- Traditional farming methods compared to industrialised farms are exposed to an environment rich in microbes, and show exceedingly low rates of asthma (Stein et al, 2016).
- Hand dishwashing = less allergic diseases in children, (Hesselmar et al, 2015).
Weaning

- Hill *et al*, (2017) suggests that the introduction of formula milk or solid food perturbs bacterial colonisation and the development of the neonatal immune system.
- Diet composition and nutritional status are the most critical modifiable factors regulating the gut microbiota at different time points across the lifespan and under various health conditions, (Sandhu *et al*, 2017).
The Developing Microbiome of the Infant

Natural childbirth, breast feeding, increased social exposure, less time spent indoors, diet and appropriate antibiotic use, may help restore the microbiome and perhaps reduce risks of allergic disease. Preventive efforts must focus on early life, (Bloomfield et al, 2016).

If the establishment of the stable adult microbiota is programmed in infancy, it may lead to a lifelong signature with significant effects on health, (Hill et al, 2017)
Poll question

Which of these statements do you believe is a good description of a newborns immune system?

a) A newborns immune system is fully developed from birth

b) A newborns immune system does not exist at birth

c) A newborns immune system requires microbial contact in order to develop
• The neonatal immune system is not fully developed at birth; newborns have adequate lymphocyte counts but these cells lack function, (Aquilano et al, 2016).

• The immune system is a learning device, and at birth it resembles a computer with hardware and software but few data. Additional data must be supplied during the first years of life, through contact with microorganisms from other humans and the natural environment. (Bloomfield et al, 2016).

• IgA is found in breastmilk and can prevent immune activation in infants by binding microbial antigens, (Tomkovich and Jobin, 2016).
How does the Microbiota and Immune System Interact?

• The immune system and microbiota develop and mature together, beginning at birth, or even potentially in the womb, (Aagaard et al, 2014).

• Germ-free mice have an underdeveloped immune system, (Tomkovich and Jobin, 2016).

• The microbiota impacts host immunity by limiting pathogen colonisation through niche occupation and resource use, (Tomkovich and Jobin, 2016).

• Components and metabolites of the microbiome affect immunity in the intestine. SCFAs increase serotonin production, which has an impact on host immunity. SCFAs also directly impact innate immune cells in the brain and central nervous system, (Tomkovich and Jobin, 2016).
How does the Microbiota and Immune System Interact?

• Three way interaction between mucosal immune cells, the intestinal epithelium and the microbial communities (Powell and MacDonald, 2017).

• An important function of the intestinal immune system is to control the exposure of bacteria to host tissues, thereby lessening the potential for pathological outcomes, (Hooper et al, 2012).

• Intestinal goblet cells secrete mucin glycoproteins that create a thick viscous coating at the intestinal epithelial cell surface.
  • **Colon**: two distinct mucus layers, the outer layer contains large numbers of bacteria whilst the inner mucus layer is resistant to bacterial penetration.
  • **Small intestine**: lacks a clearly distinct inner and outer mucus layer.
    • (Hooper et al, 2012).
How does the Microbiota and Immune System Interact?

Immune Development Th1/Th2 Balance

- Homeostasis in the gut mucosa is maintained by a system of checks and balances between Th1, Th2, Th17 and Treg cells, (Hooper, 2012).
- A naïve T cell (Th0) becomes a Th1, Th2 or a Th17 depending on the cytokines in the environment, which is influenced by antigen.
- Newborn's tend to be biased towards Th2 dominance, which can be switched off quickly after birth through microbial exposure, (Berger, 2000).
Immune Development Th1/Th2 Balance

- **Th1-type cytokines**: produce the pro-inflammatory response. Responsible for killing intracellular parasites and for perpetuating autoimmune responses.
- **Th2-type cytokines**: more of an anti-inflammatory response. Promotion of IgE and eosinophilic responses in atopic conditions.
  - The optimal scenario would therefore seem to be that humans should produce a well balanced Th1 and Th2 response, suited to the immune challenge, (Berger, 2000).
- Over-activation of either pattern can cause disease, and either pathway can down-regulate the other, (Kidd, 2003).
Inadequate Colonisation and Inappropriate Immune Programming

First year of life: Maternal immune protection will decrease, own immune system is immature

Immune vulnerability to infection

Antibiotics

Dysbiosis and gastrointestinal disorders may occur

Vicious circle between immune system impairment and increasing dysbiosis

Leaky gut

How the interactions of the microbiome and the immune system could have an affect on developing childhood conditions
Microbiota, Immune Development and Allergy

• A more diverse gut microbiota early in life might prevent allergy development, (Sjögren et al, 2009).

• The epidemic of allergy and asthma results from reduced exposure to natural environments with rich microbiota, changed diet and sedentary lifestyle, (Haahtela et al, 2015).

• Studies have identified mode of birth, pet exposure, and having older siblings as being significant risk modifying factors in the development of food allergy, (Blázquez and Berin, 2017).

• Children reported to have taken antibiotics during infancy were more likely to have asthma at 7.5 years, (Hoskin-Parr et al, 2013).

• Younger gestational age at birth was associated with childhood asthma outcomes, (Sonnenschein-van der Voort et al, 2014).
Microbiota, Immune Development and Allergy

- Secretory IgA produced by resident B cells in GALT bind allergens in the gut and prevent their uptake.
- Microbial colonisation has been shown to be important in the development of Th1 and regulatory T cells, which are necessary to maintain immunologic balance and promote tolerance.
- 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 sensitisation.

(Prince et al, 2015).
Abnormalities in gut permeability have been linked to the development of type 1 diabetes mellitus. A larger proportion of the phylum Bacteroidetes has been observed in children with T1DM, (Uusitalo *et al*, 2016).

- Microbes can be protective, neutral or provocative for the development of autoimmunity.
- The diversity of microbiota was reduced in diabetic patients. (Yurkovetskiy *et al*, 2015).
Microbiota, Immune Development and Autism

- Recent studies have made links between particular bacteria from the indigenous gut microbiota and phenotypes relevant to Autism Spectrum Disorder (ASD) raise the important question of whether microbial dysbiosis plays a role in the development or presentation of ASD symptoms, (Vuong and Hsiao, 2017).

- Disturbances of microbiome composition coupled with the influence of host genetics can result in long-term effects on physiology and behaviour, (Dinan and Cryan, 2017).
Microbiota, Immune Development and Obesity

- Germ-free mice colonised with faecal microbes obtained from an obese human exhibited excessive weight and fat mass gain whereas mice whose gut microbiome originated from a lean individual remained lean. Ridaura et al (2013)

- Cassidy-Bushrow et al, (2015) reported a twofold higher risk of obesity at the age of 2 in caesarean delivered infants with no household pets compared to those born vaginally.
Microbiota, Immune Development and Fussy Eaters

• Diet has profound effects on microbiota composition and metabolite production, both of which influence host immunity, (Tomkovich and Jobin, 2016).

• Dietary iron depletion at weaning imprints low diversity in the microbiota that is not easily recovered, (Pereira et al, 2015).

• SCFA production depends on two interdependent factors: dietary fibre and microbiota composition.

• The addition of GOS/FOS to solid foods increases the faecal proportion of bifidobacteria in the intestinal microbiota of fully formula-fed infants in the weaning period, (Scholtens et al, 2006).
Improving the developing microflora in children – how probiotics could help

• The aim of the probiotic approach is to repair the deficiencies in the gut flora and restore the protective effect, (Bezirtzoglou and Stavropoulou, 2011).


• Certain probiotic strains or multi strain mixtures have potent immunomodulatory activity in diverse disorders including allergic asthma, atopic dermatitis and rheumatoid arthritis, (Kang and Im 2015).
Improving the developing microflora in children – how probiotics could help

• Probiotics have a strain-dependent capability to endow T cells with regulatory properties (Tregs), (Farid, et al 2011).

• The influence of commensal bacteria on the balance of T cell subsets is now known to extend well beyond the intestines, (Hooper, 2012).

• Live probiotics or their metabolites could interact with B and T cells and confer them to have immunoregulatory functions. Through this interaction, probiotics could contribute to maintaining immune homeostasis by balancing pro-inflammatory and anti-inflammatory immune responses, (Kang and Im 2015).
Improving the developing microflora in children – how probiotics could help

- Our own Protexin study provides evidence that a mixture of seven strains of probiotics and Fructooligosaccharide can clinically improve the severity of Atopic Dermatitis in young children, (Farid et al, 2011).

- Early probiotic supplementation (at the age of 0-27 days) was associated with a decreased risk of islet autoimmunity when compared with probiotic supplementation after 27 days or no probiotic supplementation, (Uusitalo et al, 2016).

http://www.protexin.com/research
Improving the developing microflora in children – how probiotics could help

‘Protecting and repairing the developmental processes of the healthy infant microbiome is the modern medical frontier’,
(Meropol and Edwards, 2015).
Bio-Kult
Bio-Kult Infantis

- 7 different strains
- 1 billion CFU/sachet
- Omega 3
- Vitamin D
- Preplex
- Sachets
Bio-Kult Infantis Studies

- Studies using 7 strains of live probiotic bacteria with the prebiotics
  - reduced diarrhoea
  - improved constipation
  - improved eczema
  - improved colic
These specific 7 probiotic strains used in this trial can be found in Bio-Kult Infantis.
Colic Study

**Outcomes after 7 days of Treatment**
- Placebo Group
- Synbiotic Group

- % Treatment Success (p < 0.005): 35.7% vs. 82.6%
- % Complete Resolution of Symptoms (p < 0.03): 7% vs. 39%

**Outcomes after 30 days of Treatment**
- Placebo Group
- Synbiotic Group

- % Treatment Success (p < 0.01): 46% vs. 87%
- % Complete Resolution of Symptoms (p = 0.24): 36% vs. 56%

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**IMPROVED THE SEVERITY OF ATOPIC DERMATITIS (ECZEMA) IN 40 INFANTS AND CHILDREN AGED 3 MONTHS TO 7 YEARS**

Mean Reduction in SCORAD Index (The Severity Scoring of Atopic Dermatitis)

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References


Any questions?
Any further queries?

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