

**IN THE NAME OF
GOD**



The role of Prebiotics And Probiotics In Allergy



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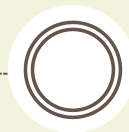
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- The **prevalence** of allergic diseases such as :
- **Asthma**

- Allergic rhinitis
- Atopic dermatitis increased sharply over the past two to three decades in many countries
- Allergies are now the most common chronic disease among children throughout the world
- Prevalence of Allergic rhinitis increased followed by an increase in
- Asthma prevalence and then Food Allergies
- Increasing in developing world related to a westernizing lifestyle, while decreasing in the industrialized world

Allergy risk factors



- **Environmental changes** , driving the allergy epidemic , not fully identified
- **Hygiene hypothesis** a strong case
- **Reduction in general microbial** exposure during early childhood
- Corresponding changes in **commensal microbial**
- **Early exposure** to pathogenic or nonpathogenic microbial products can either prevent or modify allergic responses
- **Antibiotics** , **inappropriate foods** disturb gut microbiota ,raise risk of allergy , especially in children

- Complex etiopathogeny



Multifactorial :

- Genetic factors
- Environmental factors and
- Immunological factors



Increasing risk of allergic diseases and AD :

- The composition of intestinal and cutaneous microbiome
- Maternal diet during pregnancy
- Mode of delivery
- Antibiotic treatment during pregnancy and early infancy
- Westernized lifestyle (chronic exposure to allergens)



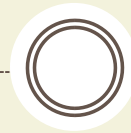
- **Microbial ecosystems** cover the surface of the **human body**
- It is clear that our **modern environment** has profound effects on **microbial composition and diversity**
- **Dysbiotic gut microbiota** associated with **allergic diseases**, **asthma** in cross-sectional, observational studies
- One of the main incriminated factors, alteration of the postnatal immune maturation due to **reduced microbial stimulations** caused by **modern life style**
- **Environmental factors** and an **aberrant gut microbiota** with a shift of the Th1/Th2 balance towards a **Th2** response

Cutaneous microbiome in AD



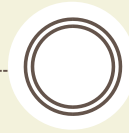
- Reduction of the cutaneous microbiome diversity in AD
- Early colonization with Staphylococcus aureus
- Cutaneous Staphylococcus epidermidis protective effect against AD
- Association between AD severity and Corynebacterium

- **Severity and chronicity** of **eczema** appear to be more important determinants of **skin microbiome** configuration



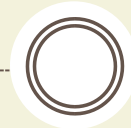
- Increase in **fungal diversity** : *Malassezia restricta*, *globosa* and *dermatis* in **~90%** of AD
- AD have **IgE mediated** sensitization to **Malassezia** species (positive skin prick tests)
- Correlates with **disease severity**

- **Demodex mites** (*Demodex folliculorum* and *Demodex brevis*) was not associated with an increased prevalence of AD



- Normal **immune homeostasis** is dependent upon **gut microbiota**
- Influenced by differences in colonization patterns
- The **intestinal microbiota** of **pregnant mothers** contributes greatly to the development of appropriate immune system and the health of the **new born**

Gut microbiome



- Numerous biological and metabolic functions • Alteration of the intestinal bacteria balance :
- **Inflammation** (LPS)
- Binding to the CD14/Toll-like receptor 4 (TLR-4) complex
 - Influence the **metabolism of the host** by :
- modulating the tissue composition of fatty acids
- Lactobacilli and Bifidobacteria produce bioactive isomers of conjugated linoleic acid with immunomodulating properties, **reducing the proinflammatory cytokines**
- Synthesizes of **glycosidic hydrolases**
- **Monosaccharides**

- Short chain fatty acids (SCFAs) (acetate, propionate, butyrate)

Short chain fatty acids (SCFAs)

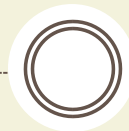


- Important role in energy metabolism;
- Butyrate (energy for colonic epithelial cells, IBD, intestinal disease)
- Propionate (lipogenesis and hepatic gluconeogenesis)
- Acetate (substrate for cholesterol synthesis)

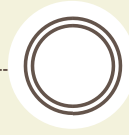


- Declining microbial exposure , increase of allergic disease

- Gut microbiota confer **specific immune-protective effects** through complex pathways , gut-associated lymphoid tissue (**GALT**), largest immune" organ" in humans
- These effects include :
- Local immunoglobulin A (**IgA**) production
- Induction of **tolerogenic dendritic cells**
- Regulatory T cell populations (**Treg**)
- Production of cytokines, (**IL**) **10** and transforming growth factor (**TGF**) **beta**
- **Inhibit** local **inflammation**
- **Improve** gut **barrier** mechanisms
- **Reduce inappropriate** immune responses



Prebiotics AND Probiotics



Prebiotics

- Non-digestible **carbohydrates**, **fatty acids**, **phenolic**, **phytochemical**
- Accepted prebiotics :
Fermentable oligosaccharides inulin, Fructo oligosaccharides (**FOS**),
Galacto oligosaccharides (**GOS**), **lactulose**
- Beneficially affect the host by ;
- Selectively stimulating growth or
- limiting some species of intestinal bacteria
- Improve the health of the host

Probiotics

- **living microorganisms** confer a health benefit on the host when administered in adequate amounts
- Commonly used probiotics : **lactobacilli**, **bifidobacteria** strains

The most known microorganism used as probiotics



Lactobacillus family:

- Acidophilus, sporogenes, lactis, reuteri RC-14, GG, L. plantarum 299v

Bifidobacterium:

- bifidum, longum, infantis, **Streptococcus group:** • thermophilus, lactis, fecalis

Non-bacterial organisms

- Non-pathogenic yeast Saccharomyces boulardii

• Lactobacillus and Bifidobacteria :

- Normal microbial flora
- Gram-positive
- Anaerobic bacteria
- Several types produce lactic acid

- hydrogen peroxide
- bacteriocins

Prebiotics - mechanism of action



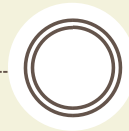
- Enhance the production of SCFAs (acetate, propionate, butyrate) anti-inflammatory effects
- Reduce the generation of toxic fermentation products
- Improve the Th1/Th2 ratio
- Increased lymphocyte and/or leucocyte numbers in gut-associated lymphoid tissues (GALT)
- Increased intestinal IgA secretion

Probiotics - mechanism of action



- Immunomodulatory effect
- Reduce the severity of AD
- Inhibiting T-helper 2 mediated response
- Improving the Th1/Th2 ratio
- Inhibiting cytokines IL-4, IL-5, IL-6 ,IL-13
- INF- γ decrease (cytokine released by Th1 cells)
- Phagocytosis
- Serum IgA is increased
- Stimulate the secretion of IL-10 and transforming growth factor- β (TGF- β)

- Reduce inflammation by reducing **proinflammatory** (cytokines IL-4, IL-6, TNF- α , INF- γ , hsCRP)



- Increasing expression :
- **IL-10**
- T Reg-related cytokines at mesenteric lymph nodes
- Inhibition of mature **dendritic cell differentiation**
- Inhibition transformation of **naive Tcells into Th2**
- Immunomodulation decreases the susceptibility to inflammatory and **allergic factors**
- Modulating the **intestine-skin axis**

- Modulate **intestine-brain axis**



- **In newborns**, the **distribution** of different **Bifidobacterium** species in the faeces influences the prevalence of allergic diseases
- In a study : **different** **Bifidobacterium** species in faeces of children with allergies compared to **healthy** ones,
- Significantly higher levels of **Bifidobacterium longum** **in healthy** children
- This strain **prevents** the occurrence of bronchial **asthma** and **allergic dermatitis**

Role of Probiotics in colon:



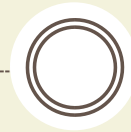
- Modulate the intestinal microbiome and immune status
- Improving the **intestinal barrier**
- **Reducing allergic** phenomenon and AD severity
- Intestinal permeability increased in AD
- Babies (caesarean section) have a lower colonization with Bacteroides and higher with Clostridium

- Early colonization with **Escherichia coli** has a **protective** role for AD

Modulating the human microbiome by pre- and probiotics

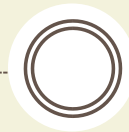
- **Gut microbiome** genetic material of all microbes:
- Bacteria , Fungi ,Protozoa and Viruses living inside digestive tract of humans and animals
- Composition of human microbiome varies depending on:
 - Age
 - Sex
 - Antibiotics

- **Bacteria** dominant microorganisms in the colon > 1,014 belonging to ~500-1,000 distinct species
- **Human intestinal microbiome is related to the host**
- **No two human beings with identical intestinal microbiome**



- Recently interest in the **use of probiotics** for the prevention and management of childhood **allergic** disease

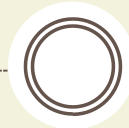
- **Selective probiotic strains** have ability to increase microbial stimulation and hence modulate the immune response
- Clinical and randomized clinical trials have proven the efficacy of a **limited number of probiotics**
- **Supplementation in pregnant women** for the prevention of some allergic disorders in **newborns**



- **Direct immune effect** appears by the **fermentation products** of prebiotics
- Gut microorganisms ferment prebiotics produce shortchain fatty acids (**SCFAs**):

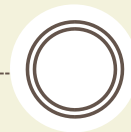
- Direct antiinflammatory effects
- Promote intestinal integrity through
- Epithelial cell proliferation , differentiation
- Affect both mucosal and systemic immunity
- **However, more studies are needed to confirm that these are clinically relevant effects**

Do probiotics affect allergies?



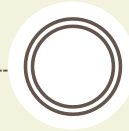
- Allergic children have a different intestinal flora from healthy children
- **Higher** levels of **Clostridia** and **lower** levels of **Bifidobacteria**

- **Bifidobacteria** and **Lactobacilli** are commonly in the intestinal flora of **non-allergic children**
- Human trials : **limited benefit** for the use of probiotics in **atopic dermatitis**
- Moderate benefit of probiotics for **eczema prevention**
- Whereas there is **less evidence** of a **benefit** for **other allergic disease**

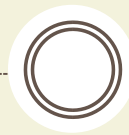


- Use in **allergic rhinitis** are **less robust**
- Currently, **no role** for probiotic therapy in the treatment of **bronchial asthma**

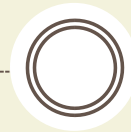
- Probiotics in the prevention of wheezing and asthma in infants have no outcomes
- No significant efficacy for reducing nasal symptom in
AR
- Related to the multiple factors:
- Environment, strain selection, dosage, moment of administration, genetic background



- Therefore there is insufficient evidence to recommend the administration of probiotics in the prevention and management of :
- Allergic rhinitis
- Asthma
- Future studies will be critical in determining the exact role of probiotics in allergic disorders

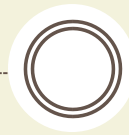


- Physicians have a **responsibility** to ensure the **efficacy** and **safety** of any products they prescribe or recommend
- There is still **insufficient evidence** to recommend probiotics for the **prevention of allergic diseases** or as part of standard **management** for any allergic conditions in **children**



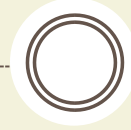
- The positive **effect of probiotics** related to:
- **Type** of probiotic strain
- Method of **administration**

- Onset time
- Dose size
- Duration of treatment
-



- Patient and parent therapeutic education represent an important element of the treatment plan
- Future of AD treatment belongs to novel biological therapeutic agents coming in the recent years.

Type of probiotics used in clinical trials



- Probiotic micro-organisms **must be appropriate** :
- **Non-pathogenic** and
- **Non-toxic** for human consumption
- **Toxicity tests**
- Must not affect **taste, texture**
- Must **survive** in the probiotic food in a sufficiently large concentration until they are consumed

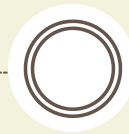
RECOMMENDATIONS FROM GUIDELINES



- Many experts bodies such as:
- The European Academy of Allergy and Clinical Immunology **(EAACI)**
- **Food Allergy and Anaphylaxis** Guidelines
- **Not recommend** using prebiotics, probiotics, or synbiotics for the **prevention** of any allergic condition
- because of great heterogeneity in the studies and variability in results • Others, such as :
- US National Institute of Allergy and Infectious Diseases **(NIAID)** have not given any recommendations



- World Allergy Organization **(WAO)** using prebiotics:
- **Only in infants** who are **not exclusively breastfed**
- **Pregnant** women
- **lactating** women when there is **high risk of allergy** in the **children** (presence of a biologic parent or sibling with asthma, allergic rhinitis, eczema, or food allergy)
- **Prevention of eczema**
- **Not any other allergic** disease
- Risk of adverse events was low



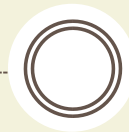
- Timing, duration, and choice of probiotic (strain and dose) are **not specified** in the WAO guidelines
- Given in the **last 4-6 weeks of pregnancy**
- Greater variability in timing and duration of **postnatal therapy** in the **infant** and/or **breastfeeding mother**
- Only probiotic strain with reproducible data is Lactobacillus rhamnosus GG (**LGG**)

Medical nutrition therapy



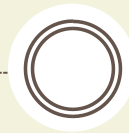
- Important role in modulation of the intestinal microflora
 - **‘functional food’ :**
- Prebiotics
- Probiotics
- Natural antioxidant
- Good metabolic effects
- Improving digestion and absorption of food , minerals, vitamin synthesis
- Improving overall nutritional status and **health**

Conclusion



- Improving nutritional status
- High nutrient digestion
- Specific and non-specific immune response
- Beneficial effects on the GI and skin

Supporting the use of pre- and probiotics in patients with Atopic dermatitis



- No enough data in the literature to respond to questions regarding :
- Optimal dosing

- Optimal time to start treatment
- **Duration**
- **Personalized use** of probiotics
- Most randomized controlled trials and meta-analyzes
- Probiotics for **at least 8 weeks**
- Beneficial effects in improving **SCORAD** of AD

