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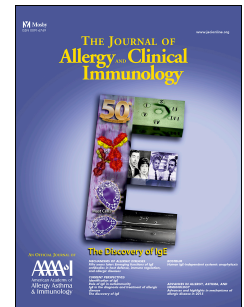
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The National Biome Initiative: An Allergy Perspective

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Abbreviations:

NMI- National Microbiome Initiative

iNKT- invariant Natural Killer T cell

In May 2016 the White House Office of Science and Technology in collaboration with private-sector stakeholders and federal agencies posted the “Fact Sheet for the National Microbiome Initiative” (NMI) for immediate release. The NMI was designed to meet 3 specific goals which collectively foster an understanding of the human symbiotic relationship with its microbial flora: 1) to support interdisciplinary research to answer fundamental questions of microbiome in diverse ecosystems; 2) to develop platform technologies for enhancing data sharing on microbiomes; and 3) to expand the microbiome workforce. The NMI, funded at more than \$121 million for fiscal years 2016 and 2017, is comprised of investments from multiple departments of the federal government including the Departments of Energy, Justice, Veteran’s Affairs, Offices of Research and Development, and Agriculture, the National Science Foundation, the Institutes of Health, Aeronautics and Space Administration, private stakeholders such as the Bill and Melinda Gates Foundation and the Juvenile Diabetes Research Foundation, and a number of academic institutions.

Early scientific publication on the manipulation of the microbiome to understand and intervene in human disease came as reports of self-infection by Dr. J.A. Turton with the hookworm *N. americanus* larvae. In 1976, Dr. Turton reported that hookworm infection decreased his allergic rhinitis symptoms during the pollen seasons of 1975 and 1976 and augmented his production of specific IgE (1). The case report was met with substantial controversy, skepticism, and generation of alternate hypotheses to explain the findings. For example, it was suggested that alterations in IgE antibody levels were not due to infection, but rather, to the use of levamisole to eradicate the initial infection prior to self-re-infection. Although current randomized controlled trials in Crohn’s disease and asthma have not borne out that hookworm infection is superior to placebo for controlling disease (2, 3) and popular media have run stories on the side effects and loss of effectiveness of infection, the observations of Turton along with the hypotheses of his skeptics were based in the immunologic reality that interventions which induce dysbiosis can have substantive effects on systemic diseases.

Shifts in the human microbiome are affected by developmental age, diet, and medication use (Figure 1). Underscoring the importance of the microbiome's development within its host is the fact that the infant microbiome is highly volatile and prone to changes that can be irreversible. Late developmental replacement of the microbiome in germ free infant mice fails to promote proper development of iNKT cell function and predisposes to development of asthmatic and colitic phenotypes (4). The presence of the commensal microbiome during the neonatal period increases regulatory T cells and decreases preferential B cell class switching to IgE (4). New data demonstrates that infants at risk for asthma have a microbiome depleted of a number of species including *Lactobacillus* and *Akkermansia* and that the metabolome of the asthma-prone infants decreases T regulatory cells while increasing CD4+/IL-4+ cells in vitro (5) (Table 1). Indeed, the gastrointestinal mucosal immune system is dependent on the microbiome for its genesis and gut associated lymphoid tissue does not develop in the absence of the intestinal flora. Diets can also induce dysbiosis and affect systemic immune responses. Foods found in the western diets that are high in salt and lipids can promote low grade systemic inflammation with elevated levels of peripheral IL-1 β , adiponectin, TNF α and Th17 cell accumulation (6). Just as the composition of the microbiome can be modified by the use of medications such as antibiotics, differences in the intestinal flora can alter how the host metabolizes drugs leading to complex interactions between the host, its flora, and its environment. The microbiome alters the metabolism of both acetaminophen and irinotecan (used in colon cancer chemotherapy) increasing drug side effects of liver toxicity and diarrhea, respectively (7).

The adaptive and innate immune systems may be influenced by the microbiome during health and disease (Table 1). For instance, *Enterobacteriaceae* IgA coated bacteria can contribute to the development of colitis whereas *Akkermansai muciniphilia* may offer protection from colitis. In humans, IgA deficiency has been associated with a more inflammatory microbiome but mice that lack IgA affinity maturation have more have dysbiosis (4). One unifying theme relates to the loss of bacterial diversity and commensal bacteria during an active

disease state. In active asthma, there is increased *Proteobacteria*, neutrophilic, therapy-resistant asthma associates with increased sputum concentrations of *Haemophilus*, *Streptococcus*, and *M. catarrhalis* and mechanistic studies suggest that the microbiome in active disease alters the response to corticosteroids (8). Although children with atopic dermatitis have more bacterial diversity than adults, both children and adults have an increased *Staphylococcus aureus* and decreased commensal bacterial load compared to those who do not have AD (9). Finally the microbiome of the esophagus of patients with active eosinophilic esophagitis has decreased bacterial diversity and less *Streptococcus*, a bacterium also seen in normal skin (10).

As the current data shows, putting the microbiome and its complexities into context can be astounding. The human microbiome has been estimated to have at least 100 genes for every one human gene. While the human has 10 trillion cells, the microbiome has 100 trillion cells. Since the microbiome itself is diverse in its bacterial composition, alterations in the type of microbiotic load changes the range of genomic diversity. As such, microbial genome wide association studies have to account not only for higher numbers and diversity of genes but also for the relative abundance of any given taxa (7). Given the complexities of the immune response to bacterial products and metabolites, the need for understanding the microbiome, its interaction with the host and its constituents, its temporal and developmental fluctuations, and its metabolomics become daunting tasks requiring interactions between clinical and basic specialists and systems biologists. To this end, combining the NMI with other initiatives such as the international initiative on the developmental origins of health and disease (DoHad), the metabolomics standards initiative, and the human exposome project could push our understanding of the human microbiome, its mechanisms of interaction with the immune system, and how it is influenced by the environment.

A vast number of questions remain regarding the effects, importance, and consequences of the microbial exposome, perhaps more than can be answered even by the

NMI. These outstanding inquiries include how the microbiome interacts with its own members, for example how viruses, bacteria, and fungi could alter one another's functional differences, which changes in the microbiome are causal to versus an effect of the disease state or therapeutic intervention, and the mechanisms by which the microbiome alters structural and/or inflammatory cell function and vice versa. In addition, it is not always clear if live bacteria, their metabolome, or just bacterial components are required to induce immunologic alterations. Through a herculean and integrated effort our improved understanding of the microbiome and its influences on the human immune system could lead to insights that are pivotal for understanding how to improve disease states.

Figure Legend. The Microbiota of Allergic Diseases. Environmental exposures alter bacterial diversity and increase inflammation. The result is a tissue and gut dysbiosis with decreased bacterial diversity, changes in the microbiome of target organs. The alterations in normal flora likely interacts with increased inflammation to alter patient phenotypes such as disease response.

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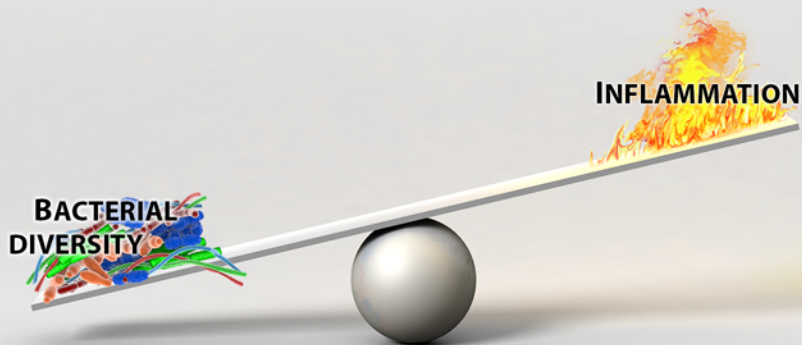
Table 1. Associations of Microbiota with Allergic Diseases

Article	Topic	Associations with Microbiota
Chen et al, Archives of Internal Medicine, 2007 Dellon et al, Gastroenterology 2011	Association of H. pylori with allergic diseases	H. pylori acquisition associates with reduced allergy and asthma risk in children EoE associates with decreased odds of H. pylori infection EoE
Marri et al, JACI 2013	Association of microbiome with asthma severity	Asthmatics had an increase in Proteobacteria. Mild asthmatic microbiome is more similar to severe asthma than healthy controls
Prince et al, Pediatric Clinics of North America, 2015	Review article on the species of bacteria and risk of allergy	Children who developed allergy had lower loads of Bacteroides, Bifidobacteria, Enterococci, and more Clostridia. C sections are associated with less microbial diversity and lower Bacteroides, Bifidobacteria, E. Coli, and increased Klebsiella, Enterobacter, Enterococcus, and clostridia. Similar effects were seen with birth order and antibiotic use. Food allergy data relies largely on animal models. One study with proven egg allergy showed decreased risk with a dog or older siblings in the home. Cow's milk allergy subjects had higher more Clostridium and Atopobium.
Benitez et al, Microbiome 2015	Study of microbiome in EoE and controls	EoE subjects had increased Proteobacteria including Neisseria and Corynebacterium with increased Gammaproteobacteria and Campylobacter during food induced active inflammation
Arrieta et al, Science Translational Med 2015	Influence of microbiome on asthma risk	Decrease in Faecalibacterium Lachnospira, Beilongella, and Rothia in the gut microbiome of children at 3 months who were at risk for asthma
Durack et al, JACI 2016	Atopy, asthma, and inhaled corticosteroid response	Asthmatics had an increase in Haemophilus, Neisseria, Fusobacterium, Propionibacterium, Sphingomonadaceae and a decrease in Moraxellaceae and Lactobacillales
Fujimura et al, Nature Medicine 2016	Association and mechanistic evidence that the gut microbiota at 3 months influences risk of atopy and asthma	Infants at risk for asthma had a gut microbiome depleted of Bifidobacteria, Lactobacillus, Faecalibacterium, Akkermansia, Malassezia (mycobiome), and increased Rodotorula and Candida. The predicted metabolome was pro-inflammatory and decreased regulatory T cells and the ratio of

		CD4+/IFNg+:CD4+/IL-4+ cells <i>in vitro</i>
Marrs and Flohr, Pediatric Infectious Diseases Journal, 2016	Excellent review of literature on microbiome and food allergy/eczema	Increased gut microbiotic diversity at 3 months is generally protective for eczema but specific constituents of the microbiome vary between studies. Increased cutaneous Staph aureus colonization associates with eczema severity. Possible that gut diversity promotes greater oral tolerance to foods
Forsberg et al, Clinical Experimental Allergy 2016	Review on the use of pre- and pro-biotics for allergy prevention	Meta analyses conclude that probiotics may prevent eczema but not other allergic disorders
Zheng et al, PLOS One, 2016	Case control study of infants with eczema versus controls	Eczema subjects were colonized with bacteria known to be associated with atopy (Faecalibacterium prausnitzii, Ruminococcus gnavus) and decreased intestinal barrier (Akkermansia muciniphila). Anti-inflammatory bacteria (Bacteroides fragilis, Streptococcus salivarius) were reduced.
Harris et al, PLOS One 2016	Microbiome in adult and pediatric EoE compared to GERD and normal controls	Increased but not distinct bacterial load was found in EoE with predominance of Bacteroidetes, Firmicutes, Fusobacteria, and Proteobacteria
Stein et al, New England Journal of Medicine, 2016	Study of Amish versus Hutterite children in relation to endotoxin levels microbial composition of house dust	Both populations were genetically similar but Hutterite children had higher serum IgE, more asthma, more exposure to cockroach, dust mites, cats, dog, and lower levels of endotoxin. Dust from Amish homes was protective for allergen induced asthma in mice
Birzele et al, Allergy, 2017	Study of microbiotic diversity in farm exposed children in relation to nasal sample derived microbiota	Farm exposure associated with increased bacterial diversity in mattresses and was higher with exposure to straw and cows. Asthma was related to bacterial diversity but to a lower extent with mucosal samples suggesting that not just the type of bacteria but potentially bacterial products are important. Clostridium and Faecalibacterium were abundant in mattresses associated with farming
Depner et al, JACI 2017 in press	Association of nasal versus throat microbiota with asthma in rural children	Asthmatic children had decreased bacterial diversity and increased Moraxella overgrowth that was asthma related only in non-farm children. Nasal but not throat microbiome associated with asthma.
Dzidic et al, JACI 2017 in press	Gut IgA coated bacteria at 1 and 12 months in pediatric	Children with asthma and allergy had lower proportions of IgA coated

	patients with and without allergy/asthma by 7 years of age	bacteria as compared with healthy controls and the coated bacteria were different between the two groups with asthmatics having higher diversity of IgA coated Bacteroidetes and Proteobacteria than controls
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This table is representative of the literature published close to 2016. A complete comprehensive review is out of the scope of this manuscript but many excellent reviews on the microbiome and allergy are available.



GUT MICROBIOME

ATOPIC INFANTS/INFANTS DEVELOPING ATOPY:

Eczema:

Increased fecal Clostridium,
Decreased Bifidobacteria

Asthma:

Increased: Rodotorula, Candida
Decreased Faecalibacterium, Bifidobacteria,
Lactobacillus, Akkermansia, Malassezia,
Lachnospira, Beillonella, Rothia

