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Citation for published version:
Trujillo, J, Lunjani, N, Ryan, D & O'Mahony, L 2021, 'Microbiome-immune interactions and relationship to asthma severity', *Journal of Allergy and Clinical Immunology*. https://doi.org/10.1016/j.jaci.2021.12.774

Digital Object Identifier (DOI):
10.1016/j.jaci.2021.12.774

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Journal of Allergy and Clinical Immunology

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OPEN ACCESS

Download date: 27. Dec. 2022

Microbiome-immune interactions and relationship to asthma severity

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Keywords:

Microbiome, microbiota, severe asthma, inflammation

Conflicts of Interest Statement:

LOM has participated in speaker's bureau for Nestle, Nutricia, Reckitt and Abbott. LOM is a consultant to PrecisionBiotics and has received research funding from GSK and Chiesi. JT, NL, DR have no conflicts of interest to disclose.

Microbial-derived factors are integral components of the molecular circuitry that regulate immune and metabolic functions required for host fitness and survival. Recent advances in culture-based methods and sequencing technologies have revealed previously unappreciated complex communities of bacteria, fungi and viruses that inhabit the respiratory tract, whose composition and activity correlates with acute and chronic inflammatory responses. In this article, we will summarise our knowledge to date on the role of the microbiota in severe asthma, acknowledging that data specific to severe asthma is currently limited.

Disrupted communication between the microbiota and the host due to altered microbiota composition and/or metabolism is thought to negatively influence immune homeostatic networks as the balance between immune tolerance and inflammation within tissues is regulated in part by the crosstalk between immune cells and the microbiota. In addition to the microbial cell structures that activate host pattern recognition receptors (PRRs), many microbial-derived metabolites, including short-chain fatty acids (SCFAs), biogenic amines and polyamines, aryl hydrocarbon receptor ligands, modified bile acids and a wide range of G protein-coupled receptor (GPCR) ligands, have all been shown to exert immunomodulatory effects. Importantly, recent microbiota surveys in humans consistently show reduced species diversity and richness in industrialised populations. At the same time, a shift away from diets rich in plant-based dietary fibres has occurred and this is thought to be important for both microbial diversity and immunological tolerance.[1] Thus, changes in microbiota diversity and changes in dietary habits that occurred simultaneously may interact in unanticipated ways resulting in additive detrimental effects on the host immune system.

Following birth, infants acquire microbes from their mother, other family members, animals, and their environmental exposures. The complexity of the infant microbiome develops and matures during the first years of life and is supported by the introduction of

diverse complementary and solid foods. Several studies have demonstrated that delayed maturation of the infant microbiome is associated with an increased risk of asthma later in life. Lower abundance of gut microbes including *Bifidobacterium*, *Akkermansia, Lachnospira*, *Veillonella*, *Faecalibacterium* and *Rothia* were associated with the development of asthma later in life. In addition, changes in the infant fecal metabolome also correlated with asthma risk, where 12, 13 DiHOME (which decreases Treg abundance and increases Th2 cytokines) was associated with increased risk, while SCFA levels (which increase Treg abundance and decrease Th2 cytokines) were associated with reduced risk of later life asthma.[2,3] Microbiota composition in children is also correlated with changes in asthma control and asthma severity. One study suggested that fifteen bacterial genera and seven fungal genera showed a significant difference in overall abundance between severe asthma and non-asthma bronchoalveolar lavage samples (BALs), while another study found that *Moraxella* was the most commonly associated genus in the nasal airways of children with severe persistent asthma (average age of 11 years old in both studies).[4,5]

Microbial dysbiosis of the airways and the gut is increasingly being associated with the incidence and severity of asthma in adults (Figure 1).[6,7] Within the airways, the phylum *Proteobacteria* is often associated with worse asthma control, whereas *Actinobacteria* can correlate with improvement, or no change in asthma control. *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae, Neisseria Haemophilus*, *Campylobacter* and *Leptotrichia* species are also often found in the airways of severe asthmatics or in corticosteroid-resistant patients. The mechanisms responsible for changes in the airway microbiota are not well understood and in addition to medications it is possible that the type of inflammatory response (i.e. eosinophil versus neutrophil), changes in host secretions (e.g. lipids) and cellular metabolism might influence microbial colonisation and growth within the airways. Interestingly, neutrophilic exacerbations of asthma and chronic obstructive pulmonary

disease (COPD) correlated with the presence of *Proteobacteria* in the sputum, whereas increased eosinophils in asthma patients, regardless of their BMI, was associated with an increased relative abundance of the genera *Rothia, Dorea, Lautropia and Haemophilus* within BALs.[8] The gut microbiota is also altered in asthma patients with severe disease. A significant reduction in the family *Verrucomicrobiaceae* was observed in the gut microbiota of severe asthmatics, compared to patients with mild/moderate asthma, which was primarily due to reduced levels of *Akkermansia muciniphila*.[8] In experimental models, *A. muciniphila* protected mice from respiratory inflammatory responses to acute and chronic house dust mite extract exposure, associated with higher numbers of lung Tregs and reduced accumulation of the IL-5-dependent Siglec F^{high} eosinophils within lung tissue.[8] This mechanism was MyD88 independent, but did require viable bacterial cells, suggesting that heat sensitive factors or metabolites secreted *in vivo* were required for the *A. muciniphila* protective effects. In contrast to *A. muciniphila*, increased levels histamine secreting microbes, in particular *Morganella morganii*, were observed in the gut microbiota of severe asthma patients.[9]

Recently there has been significant attention focussed on defining asthma disease endotypes based on a range of host factors. However, a more detailed and accurate endotyping of patients with asthma may be assisted by including an analysis of the composition and metabolic activity of an individual's respiratory and gut microbiota (Figure 2). In particular, the potential for analysis of the microbiota to assist in the early prediction and differentiation of severe from non-severe asthma, perhaps even in early life, open exciting new areas of research and clinical applications in the management of severe asthma. However, future studies must carefully include demographic, clinical, exposure and lifestyle factors as possible confounders in their analysis to correctly interpret their findings. Specific microbes, and their metabolites, are being examined for their preventive and therapeutic effects, but given the explosion in knowledge regarding disease endotypes, it is possible that

specific microbes will need to be carefully selected to mechanistically fit with specific disease endotypes and it is likely that one intervention will not work for everyone with severe asthma. In addition, the efficacy of existing therapeutics may be significantly influenced by the microbiota. Therefore, microbiota profiling should be included in future clinical studies examining novel asthma medications. Responsiveness to glucocorticosteroids may be microbiota dependant, while the optimal choice of biologic may be heavily influenced by microbial factors. In other fields, such as cancer immunotherapy using checkpoint inhibitors, the importance of the microbiota in therapy success is well established.[10]

In conclusion, it still remains unclear whether and, if so, to what extent patterns of microbial dysbiosis actually drives rather than merely reflects associated patterns of immune reactivity within the lung. However, interactions between the host and microbiota are almost certainly bidirectional, with species- and strain-specific behaviors shaped by the genetic background and microenvironment in which they exist. Microbial factors are evolutionarily hardwired into the molecular circuitry governing immune cell decision making processes and we expect that research focussed on the mechanisms that contribute to this intimate and sophisticated inter-kingdom dialogue will yield important diagnostic and therapeutic advances for patients with severe asthma.

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Figure Legends.

Figure 1. Microbiota and metabolite changes in the gut and the lung associated with severe asthma.

Figure 2. Asthma endotyping will be improved with the inclusion of microbiome analyses.