

# ALLERGY AND THE MICROBIOME

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## ABSTRACT

Over the past few decades, the rise in the prevalence of allergic conditions has been notable. The literature suggests an association between the human microbiota and the development of allergic conditions such as asthma and atopic dermatitis. Patients with atopy exhibit alterations in the relative levels of 'beneficial' and potentially harmful bacteria compared to healthy controls. One proposed mechanism is that changes in gut microbiome composition and function, which are altered by various environmental exposures, influence the healthy development of the immune system and thereby affect immune tolerance. Specific species of commensal bacteria and their functions as well as biologically active metabolites may play either a protective or a pathogenic role in the development of allergy or asthma. This article aims to summarise briefly the human gut, skin and respiratory microbiome and the link to allergic conditions as well as to consider the African data.

## INTRODUCTION: THE HISTORY OF MICROBIOTA AND THE HUMAN HOST

Trillions of commensal microbes reside on the human skin, mucous membranes and the gastrointestinal and respiratory tracts. Although human beings have co-evolved with these microbes, this complex relationship is not yet fully understood. Human beings and their resident commensal microbes, also known as the 'normal flora', have a symbiotic relationship. Microbes obtain nutrients and residence from the host while human beings also benefit significantly. For instance, the normal gastrointestinal flora assist the host with the digestion of food, the production of vitamins, the training and development of the immune system and with colonisation resistance.

Many environmental factors can influence the composition and function of human microbiota. Improved technology such as high-throughput DNA sequencing and bioinformatics analysis tools has allowed researchers to gain greater insight into the composition and function of previously non-culturable microorganisms.<sup>1</sup> This technology has made it possible to assess the effect that environmental factors can have on the microbiota as well as the ability to assess the changes in the human microbiota in certain disease states.

Most microbiome research has been carried out on the gut microbiota. The gut microbiota can be affected by many internal and external factors, including diet, genetics, birth mode, hormones, medication, pollutants and age.<sup>2</sup> These factors can cause a functional and taxonomic imbalance of gut flora, known as 'dysbiosis'. There is increasing evidence that the

human microbiota in the human gastrointestinal tract as well as in the skin and the respiratory tracts, for example, contribute to health and disease. Many disease states, including atopy/asthma and allergy, have been associated with dysbiosis. The potential contribution of the microbiota to the increase in the rates of asthma, AD and food allergy has come under the spotlight. The human gut microbiome plays an important role in the development of the immune system and immune tolerance. Immune tolerance is a healthy response to an allergen whereas an allergic state is an excessive response. Asthma and other atopic conditions are classically associated with the hyper-activation of the T helper 2 (Th2) arm of adaptive immunity.

The role played by early-life exposure to microorganisms in the susceptibility to allergic conditions has been known and documented for years. Strachan observed an inverse relationship between hay fever and family size due to unhygienic contact with older siblings and proposed that the frequency of exposure to beneficial microbes may be protective.<sup>3</sup> The 'hygiene hypothesis' that was proposed soon after states that the rise in allergic conditions may be a consequence of the reduction in microbial exposure in early life. Other exposures that are associated with enhanced microbial exposure in early life, such as living on a farm,<sup>4</sup> a lack of early antibiotic exposure, vaginal delivery, and exposure to pets during pregnancy seem to be associated with lower rates of allergy.<sup>5,6,7</sup> There may be a critical period in early life when disruptions in microbial colonisation may affect immunological development and maturation and therefore affect allergic sensitisation, with

TABLE I: DEFINITIONS

<b>Atopy:</b> A predisposition to developing certain allergic reactions such as allergic rhinitis (AR), asthma and atopic dermatitis (AD).
<b>Coloniser/commensal:</b> A microorganism that forms part of the normal microbial flora of its host and exists in a relationship in which one organism derives benefits from another organism without necessarily either hurting or helping it.
<b>Colonisation resistance:</b> When commensal organisms prevent the host or microbial community from being colonised by exogenous and potentially pathogenic microorganisms.
<b>Dysbiosis:</b> An imbalance of microbial composition and function that may be associated with disease.
<b>Diversity:</b> Microbial diversity: the number and abundance distribution of distinct microbial types. The two main components include richness (the number of microbial species) and evenness (the abundance of microbes relative to others). A healthy microbiome is generally associated with greater diversity. <i>Alpha diversity:</i> a measure of the diversity in a sample. <i>Beta-diversity:</i> a term for the comparison of the diversity of two samples to each other (dissimilarity between samples).
<b>Microbiome:</b> Collective genetic material of the microbiota in a certain community. This term is often used interchangeably with microbiota.
<b>Microbiota:</b> The human microbiota refers to the collection of microorganisms (bacterial, archaeal, fungal and parasitic) and viruses that inhabit the human body.
<b>Micro-organism:</b> A microscopic organism not visible to the naked eye.
<b>Pathogen:</b> A microorganism that causes disease.
<b>Relative abundance:</b> The number of organisms of a particular kind relative to the total number of organisms in a given community.
<b>Symbiosis:</b> The interaction between two different organisms living in close association, usually to the advantage of both organisms.
<b>Taxonomy (taxa/taxon):</b> The science of classification where organisms are grouped and systematically categorised. Taxa are a set of groups into which organisms can be classified. Taxa can be ranked, forming a hierarchy. Example: <i>Proteobacteria</i> is a major phylum of gram-negative bacteria. They include a wide variety of pathogens, such as <i>Escherichia</i> , <i>Salmonella</i> , and many other notable genera. Within each Genus there may be various species associated with illness i.e., <i>Escherichia coli</i> .

subsequent development of atopy in later life. The mechanisms involved in this process may be related to immune training and/or excessive histamine production by the resident populations of organisms in these patients. The resulting allergic effects may be local in the gut or shape patterns of immunological responses to allergen exposure at distant anatomical sites such as the mucous membranes.

## GASTROINTESTINAL MICROBIOME

Recent advances in the field of allergology/immunology and the human microbiome have improved our understanding of the

importance of the gut microbiota in the development of a healthy response to allergens (immune tolerance).

Childhood allergy has been linked to changes in the relative abundance of specific gut microbial species in early life. The specific species of intestinal commensal bacteria and their relative abundances may play a protective or pathogenic role in the development of allergy/asthma. As an example, children who developed allergic conditions were significantly less often colonised by organisms such as *Lactobacillus rhamnosus*, *Lactobacillus casei* and *Bifidobacterium adolescentis* during their first two months of life. These organisms, together with other well-known probiotic strains such as *Bifidobacterium longum*, appear to be protective.<sup>8,9</sup> Other bacteria in the human gut, such as *Escherichia coli*, *Morganella morganii* and *Lactobacillus vaginalis*, can produce histamine in large quantities. Histamine-producing bacteria appear to be more abundant in patients with asthma and severe asthma, compared to controls, and this may influence host immunological processes.<sup>10</sup>

## THE RESPIRATORY AND SKIN MICROBIOME

While it was long believed that the lungs are sterile, the presence of large numbers of bacterial genomes have been described in recent literature.<sup>11</sup> Evidence suggests that the microbiome in the lungs of healthy subjects (mostly *Bacteroidetes*) differs from that in patients with obstructive lung disease (mostly *Proteobacteria*—a major phylum containing many species associated with respiratory illnesses)

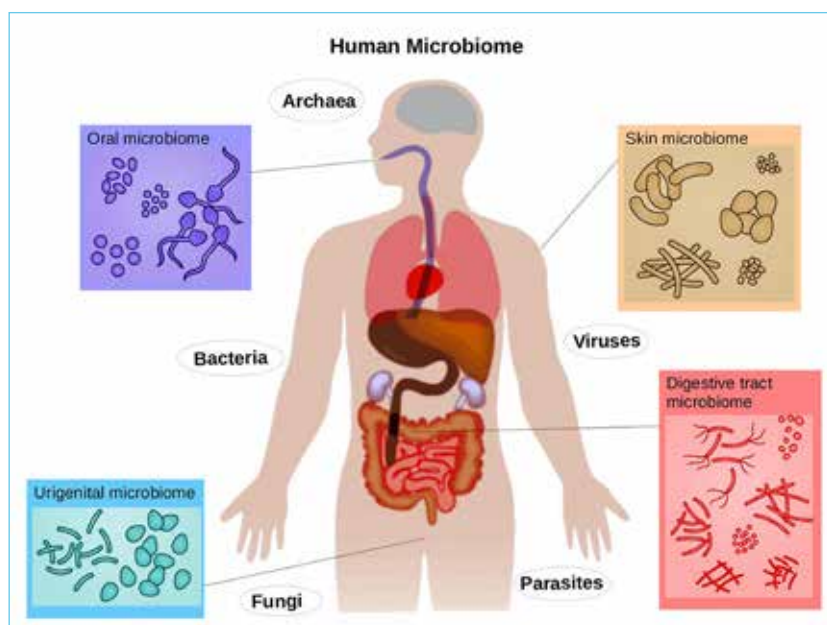


Figure 1: The human microbiome differs at different anatomical sites (© Lara Marks, WhatIsBiotechnology.org)

in their lower respiratory tracts (including *Haemophilus spp.*, *Moraxella*, *Neisseria* and *Streptococcus*).<sup>12,13,14,15</sup> The bacterial load is also higher in these patients when compared with normal subjects.<sup>16</sup> A direct effect of microbiota on the development of allergic responses and allergic-airway inflammation in asthma has been shown in mice exposed to farm dust or specific bacteria associated with farm dust (*Acinetobacter lwoffii* F78 and *Lactococcus lactis* G121). Allergic-airway responses are reduced in these mice.<sup>17,18</sup> Toll-like receptor 4 signalling and A20 activation in airway epithelial cells are thought to be the mechanism by which this occurs.<sup>17,19</sup>

Next-generation sequencing has demonstrated remarkable microbiome diversity in healthy skin at the genus level, with *Staphylococcus spp.*, and the *Corynebacterium* and *Propionibacterium* genera representing 60 per cent of the bacterial load.<sup>15,20</sup> Host factors such as age, body region and skin pigmentation affect this bacterial composition.<sup>15</sup>

In patients with atopic dermatitis (AD), the diversity appears to be lost, with an increased *S. aureus* abundance. However, the microbiome diversity improves with emollient and inflammatory therapy, suggesting that skin epithelial function maintains the normal microbiome.<sup>21,22</sup>

Importantly, commensal skin microbes (such as *Staphylococcus epidermidis* and *Staphylococcus hominis*) are associated with protection against skin pathogens such as *S. aureus*. In fact, the replacement of the dysbiotic microbiome with commensals from normal skin has been shown to correct the skin barrier and host defence against skin pathogens such as *S. aureus* (by inhibiting growth and biofilm formation).<sup>23,24</sup> The mechanism by which the skin barrier is enhanced appears to be via Toll-like receptor 2, inducing keratinocyte-derived antimicrobial peptides and increased tight junctions.<sup>25,26</sup> This suggests that microbiome transplants similar to faecal transplants performed in patients with recurrent *Clostridium difficile* infections may benefit patients with AD.

Similarly, the application of appropriate probiotics and prebiotics, topically, may be a future consideration in skin and lung conditions involving microbiome dysbioses, as has been the case in the GIT.

## MICROBIOME AND ALLERGY IN THE AFRICAN CONTEXT

Very little literature is available regarding allergy and the microbiome in Africa. Given the increasing rate of caesarean sections, the changing childhood diet (westernisation) and the more frequent use of antibiotics in Africa (greater accessibility) as well as genetics – all known to affect the gut microbiome – further exploration in the African setting is needed.<sup>27</sup>

Microbiome and allergy literature in Africa has focused mainly on AD. Globally, the incidence of AD is on the rise, but the prevalence of such atopic conditions is still lower in Africa.<sup>28</sup> This could be explained by the fact that many populations are still rural and therefore people are living more closely to their microbe-enriched environment, with daily and significant contact with animals and plants. In contrast, people of African descent living

in Western countries show a high risk for severe AD compared to African people remaining in Africa.<sup>28</sup> These differences can be reflected in and possibly explained by the differences in the microbiota of rural African versus westernised populations.

Grzeskowiak et al (2012) compared the gut microbiota of six-month-old infants from rural Malawi and urban Finland. They found that the Malawian infants' gut microbiome differed significantly from that of the Finnish infants. The study showed that the Malawian infants had a significantly greater proportion of total *Bifidobacterium spp.*, higher *Bacteroides-Prevotella* group and *Clostridium histolyticum* group than the Finnish infants, but no *Bifidobacterium adolescentis*, *Clostridium perfringens*, *Staphylococcus aureus*, or Akkermanisa-like bacteria, which were detected in the Finnish infants.<sup>29</sup> More specifically, *Bifidobacterium longum* and *Bifidobacterium bifidum*, which possess immunomodulatory properties, were found to be significantly higher in the gut of Malawian infants than in those of Finnish infants. The preponderance of these bacterial species could also reflect risk of disease, because allergic infants are more often colonised by *Clostridium difficile* and *Staphylococcus aureus* and less by *Bifidobacteria*.

In 2017, Mahdavinia et al compared the stool microbiome of 38 South African children between the ages of 12 and 36 months, 29 of whom had AD (17 of these were sensitised to at least one food). No difference in alpha diversity or in the relative abundance of any taxa was found between the two groups. However, the Phylum Actinobacteria (and genera *Blautia* and *Bifidobacterium*) was found to be higher (not significantly so) in cases with food sensitisation than cases without food sensitisation, and in the controls.<sup>30</sup> A later study compared the gut microbiome of 83 rural South African children, 36 with AD and 47 controls.<sup>31</sup> In this case, the authors showed that the beta diversity differed significantly between the two groups.

A study of children from Burkino Faso showed that their gut microbiome contains a significantly higher microbial richness and biodiversity compared to European children.<sup>32</sup> The genera *Xylanibacter*, *Prevotella*, *Butyrivibrio* and *Treponema* were found exclusively in children from Burkino Faso. These organisms are able to produce high levels of short-chain fatty acids (SCFAs), which are thought to be beneficial to the host. Indeed, SCFAs have been shown to play a protective role against allergic diseases,<sup>33</sup> and the Burkino Faso cohort showed high faecal SCFA levels.

Zimmerman et al (2010) investigated the effect of iron fortification on the gut microbiome of anaemic African children. These children have an unfavourable ratio of certain *Enterobacteriaceae* to *Bifidobacteria* and *Lactobacilli*, which may be enhanced by iron fortification. This dysbiotic microbiota has been associated with increased gut inflammation and the initiation or perpetuation of allergic inflammation.<sup>34</sup>

## CONCLUSION

It is clear that a complex interaction between the host and the mucosal *microbiome* at various anatomical sites is associated

with various disease entities, including allergy. The role of microbiota manipulation through the use of probiotic/pre-biotic preparations to prevent disease or enhance health needs to be explored further. Manipulation by means of targeted environmental or behavioural modifications is another strategy by which the microbiota can be manipulated. Examples include the avoidance of elective caesarean sections, unnecessary antibiotic use and increased exposure to pets at an early age as well as dietary interventions.

A patient-targeted approach in which microbial populations are assessed and then corrected by either re-population or

manipulation may be the future of personalised preventive or therapeutic medicine. This re-population would need to be specific for the anatomical site in question – that is the skin, the respiratory tract or the gut – and occur at the crucial time points to ensure the greatest benefits. This exact personalised protocol has yet to be elucidated.

#### DECLARATION OF CONFLICT OF INTEREST

The authors have no potential conflict of interest related to this article.

This article has been peer reviewed.

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