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Respiratory

The gut-lung link: a vital connection

How a healthy gut microbiome fights respiratory disease

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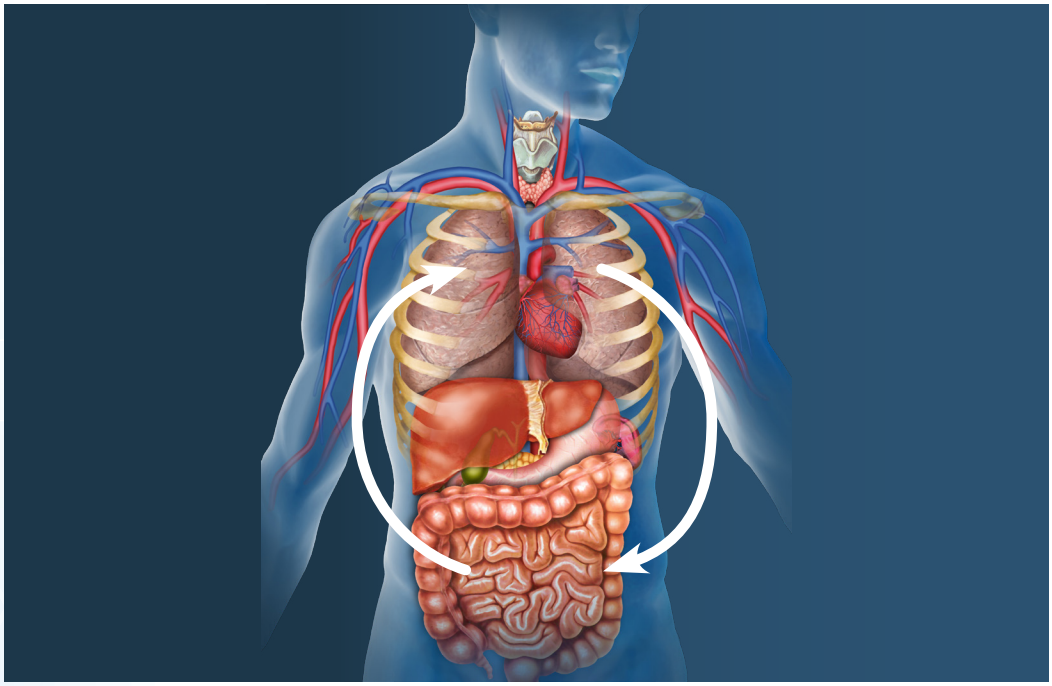
Learning objectives

You will learn:

- A healthy gut microbiome is key to human immune response. Ensuring stable gut microbiota from early infancy decreases the risk of autoimmune disorders later in life
- At every life stage, there are opportunities to modulate the gut biome. Early interventions may have lifelong impacts
- The gut microbiota communicates with other organs. One important connection is the gut-lung axis (GLA), implicated in respiratory diseases
- The use of probiotics in early life could help support lifelong immune health, including improved respiratory health via the GLA.

Introduction

Growing evidence from human microbiome studies suggests that the gut microbiome, which houses approximately 70% of the immune system, is intrinsic to a healthy immune response. In addition, research increasingly suggests that the gut microbiome maintains gut homeostasis and general health by communicating with cells in other organs - and even microbial communities associated with organs.[1] This report considers one such inter-organ microbiome 'dialogue', the gut-lung axis (GLA), i.e. the gastrointestinal and pulmonary microbiomes and their complex interactions, and outlines some of the recent evidence to support the concept. The focus here is on implications for the immune system, as well as on the promise of interventions to modulate these processes, particularly in early life, to support lifelong health.



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The gastrointestinal tract: a rich ecosystem with near and far reach

The human gastrointestinal tract (GIT) is rich in nutrients and mucous, making it ideal for microbial growth: indeed, it plays host to an intricate ecosystem of bacteria, fungi and viruses. A homeostatic (balanced) microbial population plays an important role in nutrition, as well as, crucially, the development of a healthy immune response: it is estimated that the GIT is the site of approximately 70% of the human immune system. Mucosal surfaces in the gut are a first line of defence against pathogens and protect against over-stimulation of the immune system that may be caused by commensal microorganisms.[1]

Gut dysbiosis (an imbalanced or impaired microbiome) is associated with various medical conditions, not only gastrointestinal problems such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), but also autoimmune disease, allergies and obesity.[2]

The GIT does not operate in isolation: research increasingly suggests that the microbiomes associated with other organs engage in complex physiological communication with the gut microbiome to maintain health and homeostasis or be negatively influenced by any dysbiosis.[2]

The GLA represents one such inter-organ 'dialogue': the development and severity of respiratory conditions such as asthma and allergic rhinitis could depend in part on complex interactions with gut microbiota. Similarly, a dermatological condition such as atopic dermatitis could be influenced by interactions within the gut-skin axis.[3]

The GIT does not operate in isolation: research increasingly suggests that the microbiomes associated with other organs engage in complex physiological communication with the gut

Protecting the microbiome at every life stage

Development of the gut microbiome is a complex, dynamic, lifelong process. Microbial composition fluctuates with age, diet, antibiotic use, health and stress, with possibilities for modulation at each stage. There is growing evidence that the development of stable gut microbiota early in life, supported by diet and modalities such as the use of probiotics, may decrease the risk of subsequent health problems such as autoimmune disorders, and be important for lifelong health.[2].

There are windows of opportunity for far-reaching intervention in gut health at every stage of development: at birth, infancy, childhood and adulthood – beginning even *in utero*.[1]

Microbial protection before birth

Little is known about the first group of bacteria that colonises the infant microbiome. Recent research suggests, however, that the intestinal tract of a foetus is not sterile, as previously believed, but already contains some bacteria transferred from the mother *in utero*. Evidence for this includes the presence of bacteria in the placenta and amniotic fluid, and in umbilical cord blood and foetal membranes of healthy newborns.[1]

As additional evidence, *Streptococcus mitis* and *Lactobacillus plantarum* have been found in foetal meconium, and staphylococci, enterococci, *Escherichia coli, Klebsiella pneumoniae* and *Serratia marcescens* in the first stool of neonates.[1]

These revelatory findings may change understanding of the role bacteria play in early life, the selection of strains with probiotic properties and treatment of bacterial disease.[1]

At birth and beyond, several early-life exposures have been linked to both changes in the intestinal microbiota and protection against or predisposition toward respiratory and other diseases.[1]

The microbiome and delivery

The mode of delivery affects which microbes colonise the neonatal gut, and these subsequently have a major impact on microbiome composition into adulthood. During vaginal delivery, the infant acquires beneficial microbes from the vaginal tract. Lactobacilli, for example, the largest bacterial component in the vagina, appear to play a major role in the development of the gut microbiome.[1,4]

Caesarean-born infants, by comparison, are exposed to fewer microbes. A 2019 study of gut bacteria in over 600 children in the United Kingdom[5] found that vaginally delivered infants had high levels of beneficial bacteria from four days postpartum; Caesarean-born infants, however, showed lower gut microbe diversity, fewer beneficial bacteria and more potential pathogens. This less robust microbial profile could potentially contribute to Caesarean-born children's predisposition toward asthma and increased risk of hospitalisation due to respiratory syncytial virus infection in infancy. Children born by Caesarean section are also at higher risk for food allergies, IBD, diabetes and obesity, compared with vaginally delivered children.[5,6]

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How early antibiotic use affects the microbiome

Use of antibiotics may cause microbiome dysbiosis at any age, but treatment with these drugs in early life may lead to more profound long-term effects. Antibiotic exposure during early infancy, especially when recurrent, impacts significantly on microbiota diversity early on, and strongly correlates with the development of an asthmatic phenotype later in life.[7]

A direct link between gut microbiota changes as a result of early-life antibiotic exposure and the immune response toward aeroallergens has been confirmed in rodent studies. Furthermore, rodent studies revealed loss of protection against respiratory viruses in the absence of a microbiota or after prolonged antibiotic regimens. Other studies suggest that antibiotic use in a child's first two years may also possibly raise risk for eczema, obesity and IBD in later life.[7,8]

The growing gut: microbiome shifts towards adulthood

The first major changes in the gut microbiota take place as early as three days after birth and are affected by the mother's handling of the infant. Further shifts in microbial populations occur during the first two years, and according to some studies may only reach homeostasis after age five. As the child grows, the GIT undergoes several physiological changes, including the amount of mucous produced, the rate at which mucin is glycosylated, bile secretion rate, and fluctuations in production of antimicrobial peptides and hormone levels.[1]

The adult gut maintains a fairly consistent core microbial population. However, over time, the makeup of this microbiome may shift, depending on diet, medication, hormone levels and stress. Diet in particular is key: a high-fat, sugar-rich, typically Western diet encourages the growth of Bacteroidetes, whereas a high-fibre diet allows Firmicutes to thrive.[1]

The microbiome further matures with ageing: for example, the *Bifidobacterium*-dominated microbiota of infants transforms into the characteristically adult Bacteroidetes- and Firmicutes-dominated microbiome. Composition further shifts as the body transitions into adulthood and then old age.[1]

The GLA

The gut and lungs, while anatomically distinct, are part of a shared mucosal immune system, the GLA. The microbiotas of these organs are dynamically connected, influencing immune responses both locally and at remote sites in the body. The GLA involves human host-microbe as well as microbe-microbe interactions, with important implications for maintaining homeostasis. In other words, the lung and gut microbiota appear to 'cross-talk', effecting modification of immune responses, and the development and severity of respiratory diseases (Figure 1).[3,9]

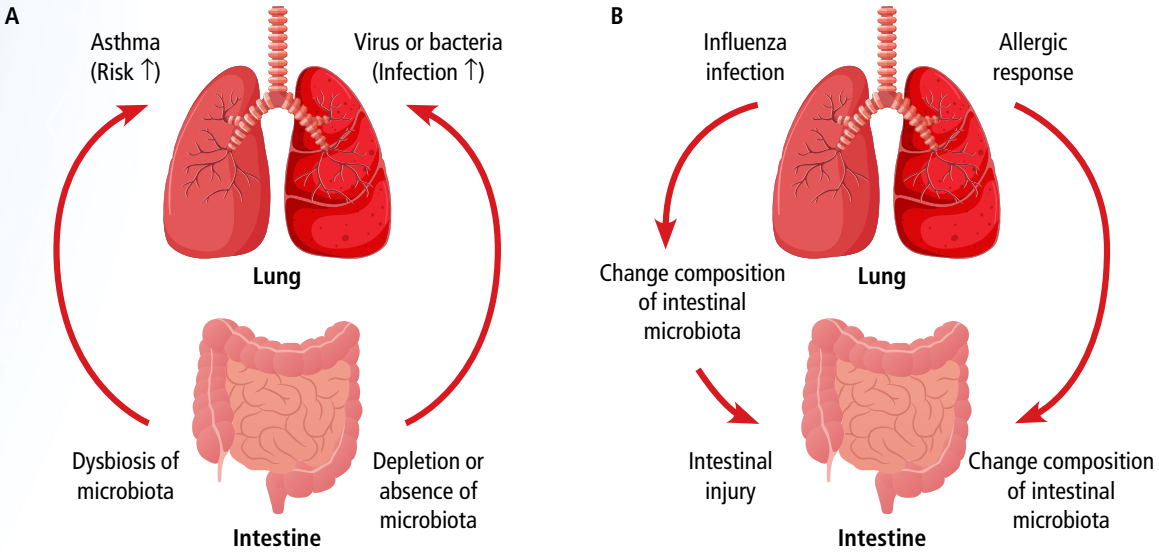

Figure 1: Dialogue in the GLA

A: Gut microbiome dysbiosis is linked to pathogenesis and progression of asthma; gut microbiota depletion leads to impaired immune responses following respiratory infection. B: Respiratory infection changes gut microbiota composition and causes intestinal immune injury; the allergic response in the lungs affects composition of the gut microbiota.[9]

This newfound understanding has created several possible therapeutic strategies for the treatment or prevention of acute and chronic respiratory diseases

As knowledge of the GLA and microbial influences on immunity continues to grow, so progress has been made in better understanding the role of the microbiota in respiratory diseases, both chronic conditions such as asthma and acute respiratory infections. Current research has identified specific taxa, their components and metabolites that can influence host immunity. This newfound understanding has created several possible therapeutic strategies for the treatment or prevention of acute and chronic respiratory diseases.[10]

The GLA's role in chronic respiratory diseases

Multiple studies have considered the influence of gut and lung microbiota on chronic respiratory diseases, including asthma, cystic fibrosis (CF) and chronic obstructive pulmonary disease.[2] These are strongly linked to a dysbiotic airway microbiota, usually the result of a loss in bacterial diversity due to proliferation of harmful bacteria. However, shifts in composition of the gut microbiota and the manifestation of intestinal disease have also been observed, particularly in the cases of asthma and CF, indicating communication along the GLA. Respiratory viral infections are often accompanied by intestinal symptoms as well.[2,3]

In asthma, the GLA, mainly via the gut microbiota, is likely to play a major role. Early-life disturbances in bacterial and fungal gut colonisation, such as those resulting from antibiotic use, have been shown to induce the development of childhood asthma (Table 1).[3,11]

Table 1. The GLA in asthma[3]

Microbiota disorders associated with asthma in:	Comments
Lungs	
• Proteobacteria (*Haemophilus, Neisseria, Pseudomonas, Rickettsia, Moraxella* species) and Firmicutes (*Lactobacillus*)	• Overrepresented in asthmatic patients and/or associated with uncontrolled asthma
• Bacteroidetes, Fusobacteria	• Reduced in asthmatic patients
• *Moraxella catarrhalis, Bacteroides, Haemophilus, Streptococcus*	• Associated with worse obstruction (FEV1), higher sputum neutrophil counts
• *Malassezia*	• Overrepresented in asthmatic patients
• *Aspergillus fumigatis*	• Associated with corticosteroid treatment

Gut

Early life perturbations
- Low gut microbial diversity
- Increased bacterial abundance of *Clostridium, Streptococcus, Bacteroides fragilis*
- Decreased abundance of *Lachnospira, Veillonella, Faecalibacterium, Rothia, Bacteroides, Bifidobacterium*
- Increased fungal abundances of *Saccharomyces, Pichia kudriavzevii*
- Decreased abundance of *Candida tropicalis, Debaryomyces hansenii*
- Increased risk of childhood asthma development

In CF too, there is clear evidence of microbial communication between the gut and lungs. Children with CF exhibit distinct differences in their gut and lung microbiota compared with healthy subjects. The bacterial abundances in the gut and lungs of these patients are highly correlated, especially *Streptococcus*, which is found in a higher proportion in CF stools, gastric contents and sputa. Also, CF patients with documented intestinal inflammation exhibit a higher *Streptococcus* abundance in the gut, but a negative correlation between the degree of intestinal inflammation and the diversity of their intestinal microbiota. Furthermore, oral probiotic administration to CF patients leads to a decreased number of disease exacerbations.[2,3]

It is important to develop a combination of probiotic strains that will coexist beneficially with other intestinal microbes

Probiotics for life

While the gut microbiome is a complex environment, and much research is still needed into its interactions with the immune system, recent findings affirm that establishing a healthy gut microbiome early on is vital.

With shifts in the microbiome over time, whether due to changes in diet, medication or the development of gut disorders, impacts on the rest of the body are unavoidable. Structural changes, such as in mucous layer thickness and the number of healthy epithelial cells and receptor sites, affect microbe-host interactions, intestinal barrier integrity and the immune system. Changes in gut homeostasis may lead to inflammation caused by commensal microorganisms, which can secrete pro-inflammatory cytokines, causing damage to the epithelial barrier and other tissues.[1]

A valuable tool, along with diet, for restoring an imbalanced gut microbiome is the oral administration of probiotics – but it is important to develop a combination of probiotic strains that will coexist beneficially with other intestinal microbes, support homeostasis and not disrupt immune system function.[1]

entiro™ probiotic, developed through award-winning research at Stellenbosch University, is currently the most commonly prescribed probiotic in South Africa.[12,13]

It contains two bacterial strains, *Enterococcus mundtii ST4SA* and *Lactobacillus plantarum 423*, which colonise and adhere to the intestinal lining, competing with pathogens for adhesion sites. They also produce antimicrobial peptides against several harmful bacteria. A protective barrier forms, extending throughout the gut: *E. mundtii* adheres predominantly to the large bowel; *L. plantarum* adheres mainly to the small bowel.[14-16]

As indicated, the human microbiome is a dynamic system, changing from before birth, through childhood and adulthood, into old age. The gut microbiota may often benefit from support, for example with dietary improvements and appropriate probiotics. entiro™ probiotic is versatile in that it can be used throughout life and begun at an early stage, with formulations suitable for patients from the age of six months onwards.[17]

Key learnings

- Homeostasis of the gut microbiome is vital to a healthy immune response
- Gut dysbiosis is associated not only with gastrointestinal problems, but also autoimmune disease, allergies and obesity
- The gut microbiome communicates with those of other organs: the GLA, for example, is implicated in immune response to respiratory diseases
- The foetal gut is not sterile, but contains some bacteria transferred from the mother
- Early-life exposures, e.g. Caesarean birth and use of antibiotics, have been linked to gut microbiota changes and development of respiratory and other diseases
- At every life stage, with early childhood especially important, there are opportunities to modulate the gut biome, e.g. through diet and probiotics
- entiro™ probiotic, suitable for use from six months of age, contains two bacterial strains which form a protective barrier extending throughout the gut.

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