

# FECAL MICROBIOTA TRANSPLANTATION IN ASTHMA

## Abstract

Asthma is a chronic lung disease that affects people of all ages and is expected to affect 400 million people by 2025, with over 250,000 deaths recorded each year and enormous health-care costs. Chronic inflammation causes airway hyperresponsiveness, which results in recurring episodes of wheezing, dyspnea, chest tightness, and/or coughing that increase in frequency and intensity over time. Although the pathophysiology of asthma is unknown, it has been linked to a variety of genetic, environmental, viral, and dietary factors. Asthma has been linked to microbial triggers in the gut as a major environmental component.

Human body inhabits large number of different types of bacteria and they have close contact with human cells in the gut and they have numerous effects on host intestine because of this, human gut microbiome considered important and active. Human health is dependent on various microbial species in the gastrointestinal and respiratory tract. Antibiotics, antiulcer medications, and other medications severely degrade gut and lung microbiota. Dysbiosis and decreased microbial diversity result in the dysregulation of bidirectional interaction across the gut-lung axis, resulting in hypersensitivity and hyperreactivity to respiratory and food allergens. Overall, gut and lung dysbiosis appear to be important causes of the increased emergence of asthma.

Fecal microbiota transplantation (FMT) is a simple therapy that manipulates the human gastrointestinal (GI) microbiota by transferring a healthy donor microbiota into an existing but disturbed microbial

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ecosystem. Fecal microbiota transplantation (FMT) has successfully alleviated symptoms of several diseases and restored gut microbiota balance. This review aims to provide several insights into the development of FMT therapy for asthma.

**Keywords:** FMT, Asthma, Microbiota transplantation

## I. INTRODUCTION

Asthma is a chronic lung disease that affects people of all ages and is expected to affect 400 million people by 2025, with over 250,000 deaths recorded each year and enormous health-care costs [1]. Chronic inflammation causes airway hyperresponsiveness, which results in recurring episodes of wheezing, dyspnea, chest tightness, and/or coughing that increase in frequency and intensity over time [2]. Although the pathophysiology of asthma is unknown, it has been linked to a variety of genetic, environmental, viral, and dietary factors. Asthma was once thought to be a single disease, but as it has become more complex, more precise therapy, such as microbiome analysis, is becoming available for diagnosis and treatment [3].

The gut microbiota is made up of a large and diverse community of bacteria that live in the gut. It has around 1014 species, divided into major phyla and 3000 to 5000 species weighing between one and two kilogrammes [4]. Bacteria in the gut provide the host with a number of benefits, including vitamin production, ion absorption, pathogen protection, histological improvement, improved immune functions, and food fermentation [5].

In healthy adults the most common genera are “*Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Tenericutes*, *Faecalibacterium*, and *Bifidobacterium*”. The “*Streptococcaceae*, *Pasteurellaceae*, *Veillonellaceae*, *Prevotellaceae*” and “*Neisseriaceae*” families, as well as *Gemella* genus, colonise in the oral cavity; the *Lactobacillaceae* family dominates the stomach; and “*Lactobacillaceae*”, “*Enterobacteriaceae*” and *Streptococcaceae* dominate the small intestine. In the large intestine bacteria densely colonized belongs to the families named “*Enterococcaceae*, *Enterobacteriaceae*, *Bacteroidaceae*, *Bifidobacteriaceae*, *Lachnospiraceae*, *Rikenelleace*”[6].

Asthma has been linked to microbial triggers in the gut as a major environmental component [7]. Human body inhabits large number of different types of bacteria and they have close contact with human cells in the gut and they have numerous effect on host intestine because of this, human gut microbiome considered important and active. Human health is dependent on various microbial species in the gastrointestinal and respiratory tract. The mature gut microbiota, which includes microorganisms such as “bacteria”, fungi, “archaea”, and viruses, is stable, adaptable, resistant, and diverse, and can regularly be regained to its pre-perturbation state [8].

## II. MICROBIAL DYSBIOSIS AND ASTHMA

Microbial dysbiosis in lungs and stomach can be produced by a range of lifestyle and environmental factors in people who have asthma. Dysbiosis, or microbial imbalance, has been related to the emergence of a number of ailments, including allergies and asthma [9].

Antibiotic therapy and alterations in the microbiome, particularly in infancy are important fields of research, meanwhile the microbiome has been linked to people's health in a variety of disorders, including asthma [10].

The changes in the gut “microbiome” among young adults, old asthmatic, nonasthmatic people are being explored and revealed that, in asthmatics compared to nonasthmatics genes involved in the “pentose phosphate pathway”, lipopolysaccharide

“biosynthesis”, flagellar assembly and “bacterial chemotaxis” as well as “nitric oxide” production remained upregulated, which could be linked to increased “inflammation” and bacterial colonisation in young adult patients of asthma. Furthermore, non-asthmatics of both ages showed higher levels of genes linked to inflammation reduction and the degradation of air pollutants [11]. Another study found that asthma patients had lower levels of prostaglandin E2 (PGE2) and higher levels of chemicals linked to respiratory tract inflammation for example metabolites of “arachidonic acid”, “lysine residues” and mucopolysaccharides [12]. Children who developed asthma at school age exhibited decreased “gut microbiome” diversity up to one month of age when compared to “non-asthmatic” children [13]. One more study showing intestinal microbiome of asthmatic infants in their first three months of life and comparative number of the species “*Lachnospira*”, “*Veillonella*” and “*Faecalibacterium*” was much lower in these children [14]. The stool samples of asthmatic children aged between 4 to 7 yrs were compared to healthy children in a recent study based on metabolomics, with a emphasis on gut metabolites such as “amino acids” and “butyrate” and found that asthmatic children containing lesser amount of gut metabolites [38].

According to taxonomic categorization, the phylum “*Firmicutes*” (67.8%), “*Actinobacteria*” (20.7%), and “*Bacteroidetes*” (8.4%) existing 97 % of all sequences analysed among gut bacteria. When compared to healthy controls and children with asthma had significantly reduced abundances of the genera *Faecalibacterium* and *Roseburia* whereas significantly increase in the *Enterococcus* and *Clostridium*. In asthmatic children, microbial dysbiosis in the phylum *Firmicutes* was shown to be substantially lower, which could be connected to an increased asthma risk. It is necessary to discover a relationship between the microbiome of the lungs and the microbiome of the gut. An early life period for microbiome development, bacterial diversity, abundance and bacterial effects on the immune system are all important determinants for the establishment of the microbiome in all habitats [15].

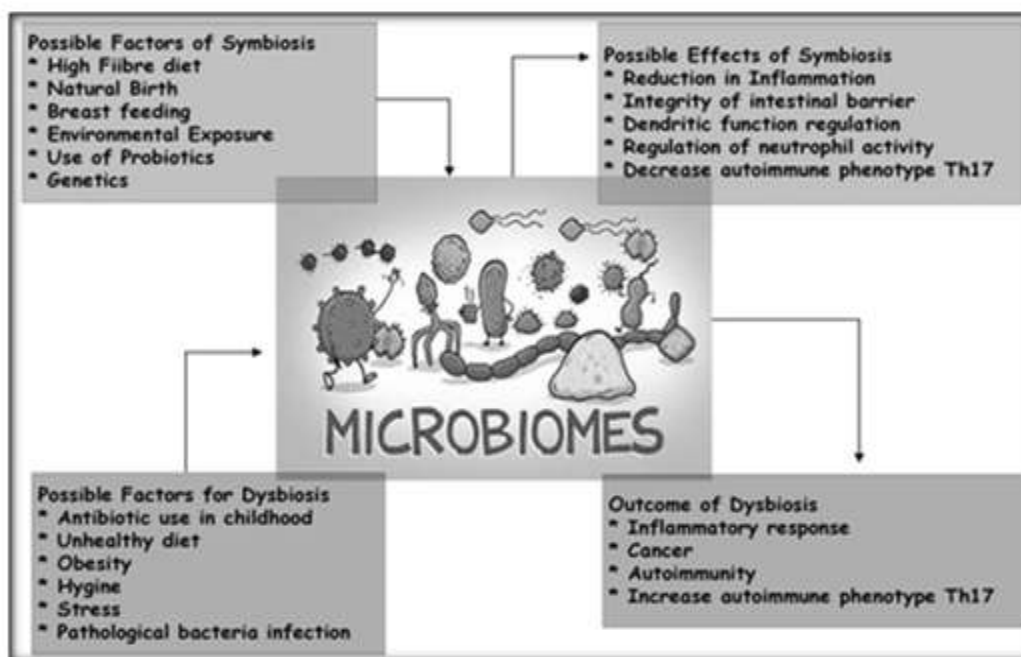
Despite the fact that research on the gut microbiota is still in its early stages, data suggests that it could be a potential target for allergic asthma prevention and therapy. As a result, faecal microbiota transplantation (FMT) may be an alternative for treating asthma.

### III. FACTORS AFFECTING THE COMPOSITION OF GUT MICROBIOTA

The composition and amount of the “gut microbiota” is largely influenced by several environmental factors. It is revealed that environment plays a significant role in development of inflammatory disorders; for example, asthma prevalence varies greatly between western and developing countries. The importance of the “gut microbiota” in regulating “inflammatory responses”, as well as the fact that it is heavily influenced by the environment, suggests that altering the gut microbiota is one of the key ways to disease development.

- 1. Diet:** Because bacteria have diverse preferences for energy sources, diet has a direct impact on gut microbial composition. Beneficial microorganisms feed on complex plant polysaccharides, which favour their growth over that of other microbes. In reality, the symbiotic association with gut bacteria permitted the transition to an herbivorous niche: digestion of complex plant polysaccharides is impossible without the “enzymatic” capabilities of “gut commensals” [16, 17]. The differences in the Westernized diet have been cited as a possible cause of the rapid rise in asthma [18].

- 2. Hygiene:** The “hygiene hypothesis” [19] is the most often accepted theory for the rise in “asthma” and atopic problems in “western countries”. It shows that increased environmental “cleanliness” has resulted in a reduction in the amount of infectious stimuli required for optimal immune system development, impacting the switch from Th2-predominant immunity (Th2 stimulates humoral immune response) to Th-1-predominant responses (Stimulates cellular immune response) after birth. However, hygiene could be linked to different levels of exposure to commensals, which could be crucial for immunological activating actions.
- 3. Antibiotic Use:** Antibiotics have transformed Western medicine, significantly reducing infectious illnesses and their accompanying morbidity. Antibiotic use, on the other hand, could be connected to an increase in allergy illnesses in Western countries [20,21].
- 4. Maternal Transfer:** Infants are born sterile, but their guts get colonised with bacteria, mostly from their mothers, in the hours and days following birth. Immunological learning is thought to be critical at this period, thus any interruption could have an impact on immune function. Colonization of a newborn is influenced by the delivery method, hospital hygiene, and breast-feeding [22,23,24]. There were differences in colonisation between those who were born vaginally and those who were born via caesarean section. In vaginally born newborns, *Bifidobacteria* and *Bacteroides* were more common, whereas *Candida difficile* colonisation was more common in caesarean-section-born infants [25]. Premature infants were also more likely to be infected with *Clostridium difficile* with higher numbers [23].
- 5. Stress:** Stress has been shown to affect the immunological, metabolic systems and it also appears to affect the gut flora. Study found that monkeys exposed to stress during pregnancy had different microbial colonisation in their offspring, with lower levels of *Bifidobacteria* and *Lactobacilli* [26]. Stress lowers *Lactobacilli* and increases *E. coli*, *Pseudomonas* growth and epithelial adhesion, according to other studies. Early life stress has been responsible to modify the “brain-gut axis” in rats, with increases in “plasma” “corticosterone” level, enhanced peripheral immunological response to lipopolysaccharide and changes in “gut microbiota” [27].
- 6. Pathogens:** Colonization resistance is the ability of commensal organisms to protect themselves from infections by competing for nutrition and space. Pathogens, on the other hand, sometimes outsmart commensals due to the fact that various pathogens have unique survival strategies. *Salmonella enterica* induces and spreads intestinal inflammation by competing with the healthy bacteria in the gut [28].



**Figure 1:** Factors affecting Gut Microbiota

#### IV. FAECAL MICROBIOTA TRANSPLANTATION

“Faecal microbiota transplantation” (FMT) is the transport of faecal material comprising colonic “microbiota” from a healthy individual (donor) to colon of patient (recipient) with a dysbiosis-related disease condition or a changes in their "normal" gut microbiota. FMT has been practiced to cure disease by returning diversity of gut microbiota that is typical of a "healthy" individual. In various experimental research and clinical applications in the treatment of various diseases, FMT has already demonstrated a relatively excellent therapeutic effect.

FMT has been widely marketed as a treatment for *Clostridium difficile* (CDI) infections due to its efficacy in treating recurrent *Clostridium difficile* infections, particularly in Western countries [29]. In several case studies, retrospective case designs and a single “randomized controlled study”, FMT has been proven to be helpful in patients with severe or recurrent CDI, with a average cure rate of 87-90 percent for the over 500 cases reported to date [30, 31]. Irritable bowel syndrome, obesity, autoimmune diseases, diabetes, anorexia nervosa, “inflammatory bowel disease”, “cancer”, metabolic syndrome, neuropsychiatric disorders, multiple sclerosis and cardiovascular illnesses are among the diseases associated with gut microbiota alteration [32].

Probiotics and/or prebiotics oral administration as supplementary therapy in asthma has been supported by solid evidence. Numerous “clinical trials” of probiotics in human individuals with asthma have been conducted as significant experimental research [33].

In the restoration of altered gut microflora, “faecal microbiota transplantation” may be more effective than “probiotics” and overcomes probiotics' inherent quantitative gap.

Furthermore faecal flora injection causes a long-term change in the gut microbiota of the recipient, whereas probiotics colonise the gut lumen only temporarily [34, 35].

FMT can be utilized to treat both GIT and non-GIT disorders in which the intestinal microbiota has been disturbed. According to the previous research data, FMT therapy has been used in the treatment of “Parkinson's disease”, myoclonus dystonia, “chronic fatigue syndrome”, metabolic syndrome, “multiple sclerosis”, fibromyalgia, insulin resistance, obesity and “childhood regressive autism”[36].

**Table 1: Disorders Developed by Changed Gut “Microbiota”**

<b>GIT disorders</b>	<b>Non GIT disorders</b>
Recurrent <i>Clostridium difficile</i> infection	“Arthritis”
“Inflammatory bowel disease” (IBD)	Asthma
“Cholelithiasis”	“Atopy”
“Idiopathic constipation”	Autism
“Colorectal Cancer”	“Autoimmune disorder”
“Irritable bowel syndrome”	Chronic fatigue syndrome
“Hepatic encephalopathy”	Diabetes mellitus and insulin resistance
	Fibromyalgia
	Hay fever
	Metabolic syndrome
	Multiple sclerosis
	Obesity
	Parkinson’s disease

## V. FMT PROCEDURES

**1. Donor Selection:** FMT has the potential to transfer infectious pathogens, hence thorough screening tests are recommended to limit this risk [37]. Once a donor has been chosen, microbes must be screened in blood and faeces. Donors are selected from the family member, close partners, unrelated volunteers or friends. Intimate partners benefit from the fact that they share “environmental” risk factors which may reduce the chance of transmission of infection.

First-degree relatives of the maternal line may benefit from sharing the most bacteria in their intestine with the receiver. As a result, adaptive immunological components in the intestine's “mucosal immune system” (such as “antigen-specific antibodies”) may be more accepting of “microbiota” from such donors [38].

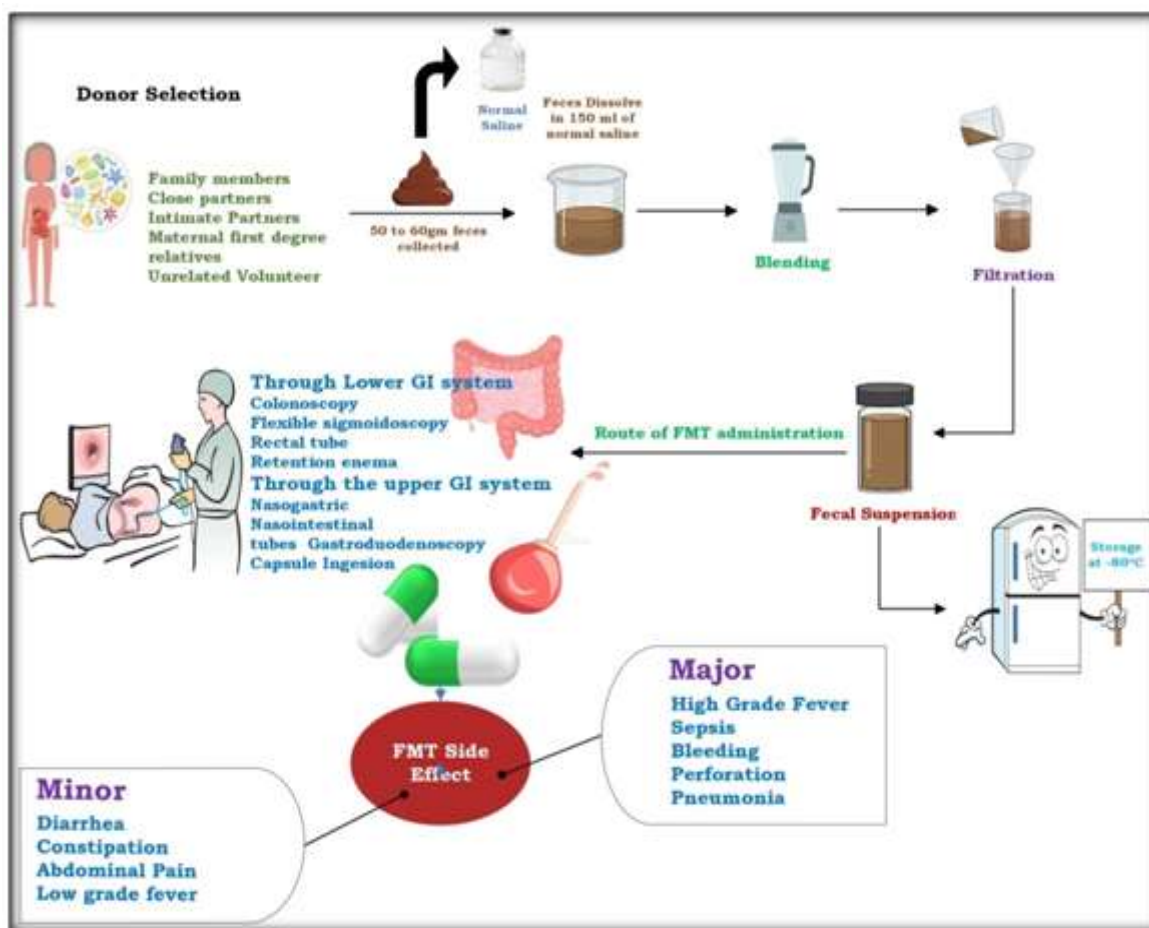
**2. Donor Screening:** The possible transfer of infectious illnesses is a major risk linked with FMT therefore; potential donors are subjected to strict screening procedures. HIV, Hepatitis A, B, and C, syphilis viruses are all tested for in blood samples from potential donors. Also donor stool must be checked for *Clostridium difficile* toxins, *Helicobacter pylori*, parasites, and other enteric pathogens including Giardia, Cryptosporidium, Isospora, and Rotavirus [38]. The potential donors with risk of infection should follow given criteria that are at high risk of microbiome associated infection (Table 2).

**Table 2: Criteria for Stool Donors who are at High Risk of Microbiome Associated Disease or Infection**

Criteria
Age should not less than 18 years or more than 65 years
BMI not more than 30 kg/m <sup>2</sup>
Diabetes or other metabolic diseases
Malnutrition (moderate to severe)
Antibiotics use history (in the last 6 month)
Diarrhea or Dysentery (in the last 3–6 month)
History of <i>Clostridium difficile</i> infection
Immune disorder
Travel history to a tropical countries in last 3 month
Gastrointestinal disorders -IBD, IBS, gastrointestinal malignancy

- 3. Sample Preparation:** In terms of preoperative preparation, irrespective of the mode of administration, recipients generally take a large-volume stool preparation. GIT motility inhibitors like loperamide are used in some cases to improve faecal microbiota retention [39]. Patients who receive FMT through the upper GI tract should also be given proton pump inhibitors. The optimal faecal quantity for FMT has yet to be determined, but 50 to 60 gm of 250 ml to 300 ml diluent is generally preferred. A sample of stool is suspended in either tap or bottled water or a sterile saline solution, with the latter thought to be less likely to influence the "microbiota" of the donor stool. After that, the donor stool is homogenised by stirring or using a motorised blender. Following that, the mixture is filtered through piece of cloth to remove larger particles from the stool samples [40].
- 4. Sample Administration:** Donor faeces can be administered by the lower GI system, such as colonoscopy, "sigmoidoscopy", rectal tube enema or through the upper GIT system such as nasogastric or gastroduodenoscopy. There is no conclusive proof to support the use of one modality over another. FMT by using colonoscopic is generally safe, well-tolerated and simple to perform with the benefit of consenting evaluation of the whole colon though it should be used with caution in patients with "colitis" and colonic distention because of the increased risk of perforation [38]. Retention enema and "flexible sigmoidoscopy" may be options in such cases, although a few patients may find it difficult to retain the transplanted stool, necessitating repeated small volume infusions use for 2 to 3 days course. FMT through the upper GI tract is simple and low-risk but it may inconvenient and develop the risk of vomiting and aspiration in some patients [39]. Furthermore, donor stool sample may not be spread evenly throughout the colon and increasing the possibility of small intestinal bacterial overgrowth.





**Figure 2:** The FMT Procedure and Its Consequences

## VI. POTENTIAL ADVERSE EVENTS

The FMT procedure has been used on people with serious medical comorbid illnesses on a regular basis, and it is well tolerated, safe, and has few serious side effects [40]. The most common initial side effects are “abdominal discomfort”, bloating, “latulence”, diarrhoea, constipation, “vomiting”, and a temporary fever [41]. The majorities of these side effects is self-limiting and disappear within two days of FMT. However, little is known about FMT's long-term effect on the immune system, such as the emergence of dormant infections. Asthma, “obesity”, “diabetes mellitus”, “atherosclerosis”, IBD, IBS, colon cancer, “nonalcoholic fatty liver disease”, and autism are all caused by changes in the microbial flora of the intestine [40]. A recent systematic study of FMT for recurrent infection of CDI found no significant adverse effects [42]. Following FMT without donor screening, a patient with ulcerative colitis developed cytomegalovirus infection [43]. Furthermore, even when extensive donor screening is performed, FMT has the potential to transmit occult illnesses because faeces extracts act as intermediaries between the donor and the recipient. It has been proposed that norovirus infection can be transmitted via colonoscopic FMT, but this has yet to be proven [44].

## VII. CONCLUSION

Finally, FMT appears to be a promising treatment option for asthma. Still, the existing data in this area is incomplete, and important scientific work has recently initiated. The new technologies have enabled a systematic study of the “intestinal microbiota” providing more accurate information about its composition and clinical modifications. It is important to work out how FMT alters the gut microbiota's composition or restores intestinal “bacterial flora” and how this relates to asthma. The changes in the “gut microbiome” and health status of asthma patients before and after FMT treatment should be carefully examined.

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