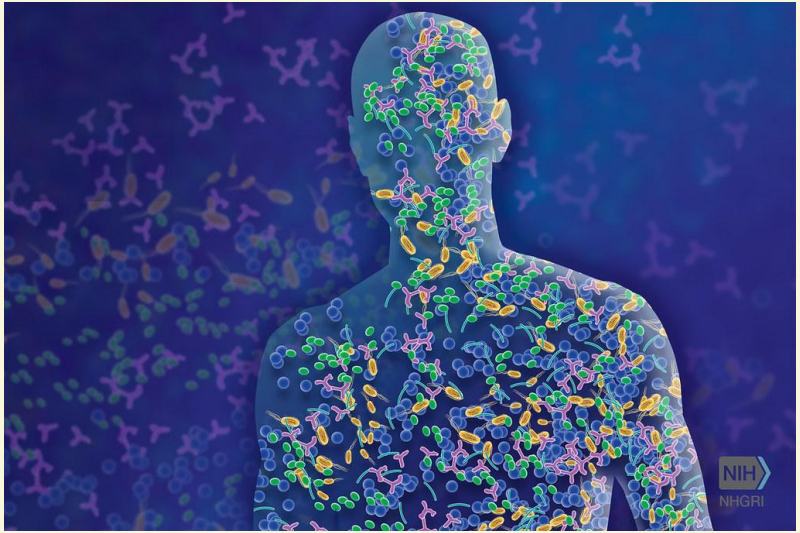
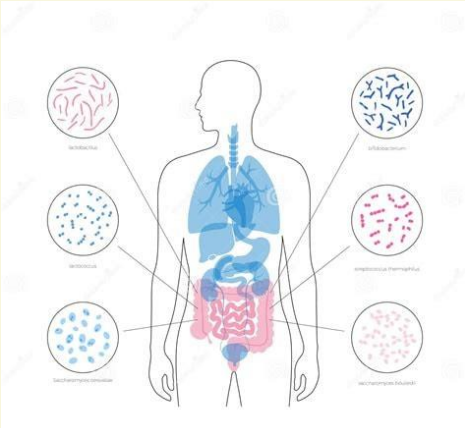
The Human Microbiome

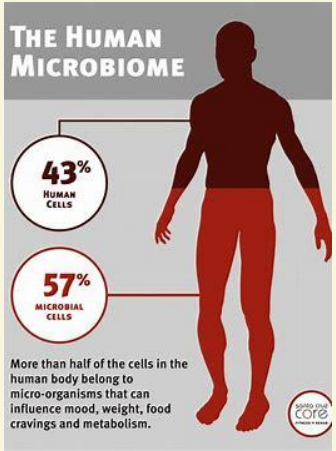
Created by Sahaj Satani, Blogging Director of Spacetime Archives



Introduction To The Human Microbiome

The human microbiome is the collection of microorganisms that reside in the human body. This includes bacteria, archaea, viruses, eukaryotes, and fungi that inhabit various body sites such as the skin, gastrointestinal tract, oral cavity, urogenital tract, and respiratory tract. The ratio of microorganisms to cells is about 1:3. While there are pathogenic microorganisms, the majority of the community assists in supporting the immune system, breakdown of food, and prevents colonization of the gut from harmful bacteria.





Importance

Assistance in Digestion: The Microbiota helps break down complex carbohydrates like starch and fibers with digestive enzymes like cellulase and amylase.

Production Of Vitamins: Certain bacteria and microbes can synthesize vitamins and amino acids. This includes the essential Vitamins B and K.

Regulating the Immune System: Microbiomes closely interacts with the immune system and distinguishes between harmful pathogens and harmless antigens, thus promoting immune tolerance.

Protections Against Harmful Pathogens: The microbiome acts as a barrier against colonization by harmful pathogens. Beneficial microbes compete with pathogens for space and nutrients.

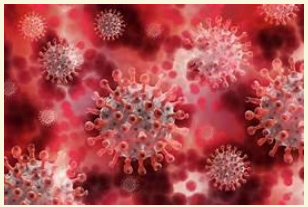
Composition Of Microbiomes

Bacteria

- Living, unicellular, prokaryotic organisms.
- Diverse population of bacteria are found in the Gastrointestinal tract.
- Aids in digestion and nutrient absorption.
- Roughly 40 trillion bacterial cells in body and only 30 trillion cells.

Viruses

- Nonliving microscoping agents made up of an outer protein called capsid.
- Bacteriophages are viruses that infect bacteria.
- Influences bacterial population dynamic and contribute to microbial diversity.
- Human viruses infect human cells and can be found throughout the body.



Fungi

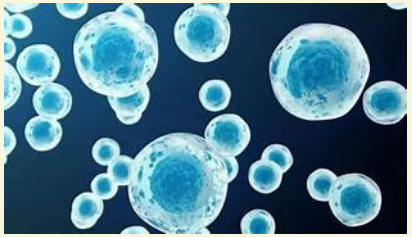
- Living, multicellular worms.
- Can influence skin health and disease.
- Present in oral cavity and contribute to microbial communities.
- Can co-exist with bacteria and regulate homeostasis.

Protozoa

- Protozoa feed on bacteria and other microorganisms.
- Plays a pivotal role in nutrient recycling within the gut ecosystem.
- Have a symbiotic relationship with human host.
- Outcompetes pathogenic microorganisms.

Archaea

- Primarily found in the gut and contribute to methane production.
- Produces methane gas as byproduct of digestion.
- Can adapt in extreme environments.



Role In Digestion and Nutrition

Digestive Enzymes

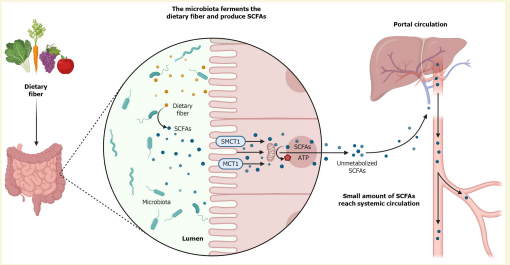
- Microbes in the gut produce enzymes such as cellulase and amylase to break down complex carbohydrates.
- Gut bacteria ferment dietary fibers into simpler compounds and produces a beneficial byproduct called SCFAs.
- Certain gut microbes can break down proteins into amino acids and nitrogenous compounds in aid for digestion.

Vitamin Production

- Bacteria in the colon produce vitamin K2, which plays an important role in blood clotting and bone health.
- Gut bacteria synthesize Vitamin B7 that is vital for fatty acid production.

Short-Chain Fatty Acids (SCFAs)

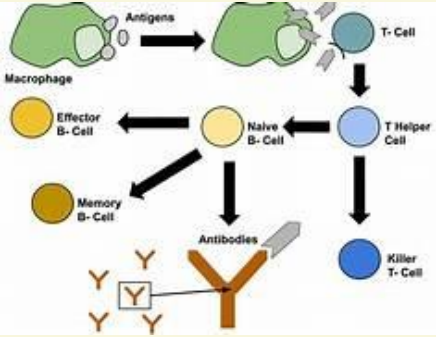
- SCFAs can cross the blood-brain barrier and influence brain function.
- Can influence glucose and lipid metabolism.



Immune System Interactions

Immune Modulation

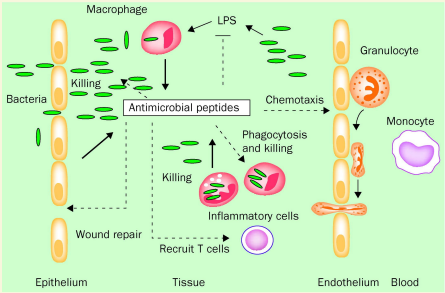
- Gut bacteria stimulate production of regulatory T cells which maintains immune tolerance and prevents autoimmune responses.
- Certain microbes in the gut produce SCFAs which have anti-inflammatory components.
- Exposure to diverse microbial communities can contribute to the immune system's functionality.



Barrier Protection

- Gut bacteria excites the production of mucus and forms a protective layer over the gut lining, preventing pathogen invasion.

- Microbes have the ability to produce antimicrobial peptides as an additional layer of protection.



Microbiome and Disease

Inflammatory Bowel Disease (IBD)

Dysbiosis: Loss of beneficial microbiota and an overgrowth of harmful microorganisms. Can occur from overuse of antibiotics and serious infections.

Inflammation: Dysbiosis can lead to inappropriate immune responses, resulting in severe inflammation in GT.

Autoimmune Diseases

Type 1 Diabetes: It is an autoimmune disorder in which pancreatic beta cells are attacked by effector T cells. This causes the pancreas to not produce insulin for metabolic regulation. Children with T1D have less diverse microbiota in relation to health children.

Rheumatoid Arthritis: It is a chronic autoimmune disease in which the immune system attacks the joints causing inflammation pain, and join damage. Studies have shown that those diagnosed with RA have an altered gut microbiota composition.

Multiple Sclerosis: Chronic autoimmune condition that affects the central nervous system leading to communication issues between the problem. Dysbiosis in MS patients have linked to an imbalance of anti-inflammatory responses.

Microbiome Research Techniques

Method	Description	Insights
16s rRNA Sequencing	Identifies and counts different types of bacteria using the 16S ribosomal RNA gene.	Using taxonomic profiling to determine the variety and amounts of bacteria.
Metagenomics	Sequences the DNA of all microbes in a sample.	Reveals the genetic potential of the microbiome and what the microbes can do.
Metatranscriptomics (RNA Analysis)	Analyzes RNA to see which genes are active, showing what the microbes are doing.	Dweleves into microbial gene activity and regulation.
Metaproteomics (Protein Analysis)	Studies the proteins produced by microbes to understand their functions and roles.	Understanding microbial functions.
Metabolomics (Metabolite Analysis)	Examines molecules produced by microbes, revealing their metabolic activities and interactions with the host.	Insights into microbial metabolic activities.

Probiotics

Probiotics are live microorganisms and is often referred to as “good bacteria”. They can be consumed and help in restoring and maintaining the natural balance of the gut microbiota. Common examples of probiotics includes yogurt , kimchi, and dietary supplements. When consuming them, they add beneficial type of microbes to add to the microbial populations in the body. In addition to this, Probiotics can compete with pathogenic bacteria for resources and enhance the mucous barrier. Probiotics are recommended to take to those who have symptoms of dysbiosis or elsewhere.

Prebiotics

Prebiotics are live microorganisms that promote the growth activity of beneficial bacteria in the gut. They selectively stimulate the growth and activity of bacteria such Bifidobacteria and Lactobacilli, by providing them with nutrients they need to thrive. Essentially, they function as a food source for the gut's microorganisms and make it to the colon to ferment and metabolize. When broken down, they create short-chain fatty acids and it provides energy to colon cells, helps with mucus production, and controls inflammatory responses.

Case Studies In Microbiome Research

Fecal Microbiota Transplantation (FMT) for Clostridium Difficile Infection

Clostridium difficile Infection (CDI): A severe gut infection causing diarrhea, often hard to treat with regular antibiotics.

Antibiotic Resistance: CDI can occur after antibiotics kill good gut bacteria, allowing C. difficile to grow.

Intervention:

Fecal Microbiota Transplantation (FMT): A treatment where healthy stool from a donor is put into the patient's gut to restore good bacteria.

Procedure: The donor stool is processed and given to the patient through methods like colonoscopy or capsules.

Outcome:

High Success Rates: FMT has over a 90% success rate in curing recurrent CDI, even when antibiotics don't work.

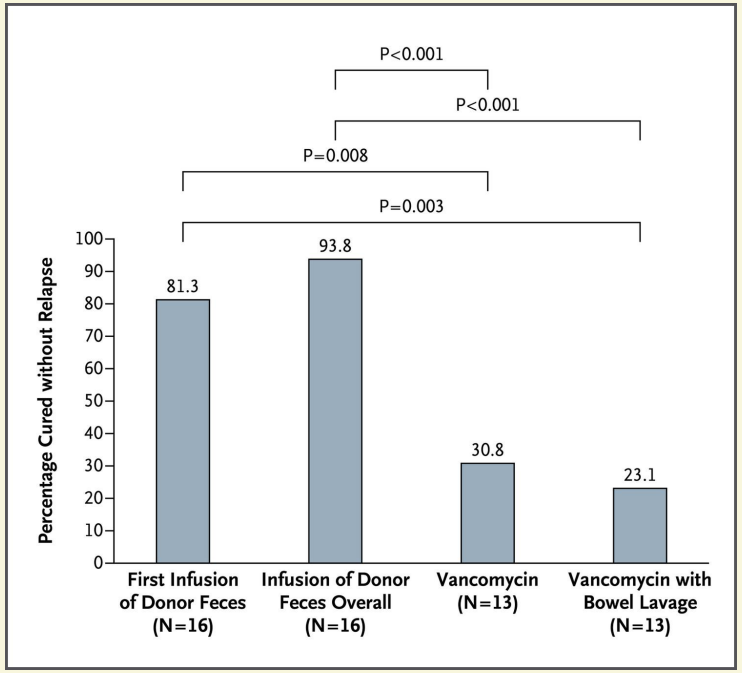
Therapeutic Potential: FMT shows that restoring healthy gut bacteria can be a powerful treatment.

Case Study 1 Charts

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Donor-Feces Infusion (N=16)	Vancomycin Only (N=13)	Vancomycin and Bowel Lavage (N=13)	P Value†
Age — yr	73±13	66±14	69±16	0.39
Body-mass index‡	22±3	22±4	24±4	0.41
Female sex — no. (%)	8 (50)	7 (54)	3 (23)	0.22
Karnofsky performance status§	50±18	50±17	56±21	0.62
Median Charlson comorbidity index (range) — score¶	3 (0–4)	1 (0–8)	1 (0–6)	0.53
Median recurrences of CDI (range) — no.	3 (1–5)	3 (1–4)	2 (1–9)	0.69
Previous failure of tapered vancomycin therapy — no. (%)	10 (62)	8 (62)	6 (46)	0.63
Reported antibiotic use before CDI — no. (%)	16 (100)	12 (92)	13 (100)	0.62
Hospital-acquired CDI infection — no. (%)	10 (62)	6 (46)	10 (77)	0.27
Admitted to a hospital at study inclusion — no. (%)	5 (31)	4 (31)	4 (31)	1.00
Days of antibiotic use for CDI since first diagnosis — no.‖	63±41	51±27	49±38	0.56
Use of proton-pump inhibitor — no. (%)	13 (81)	10 (77)	11 (85)	0.88
ICU admission in preceding month — no. (%)	1 (6)	0	1 (8)	1.00
Feeding tube present — no. (%)	3 (19)	2 (15)	2 (15)	0.96
Median stool frequency per 24 hr (range) — no.	5 (3–20)	5 (3–12)	5 (3–10)	0.72
Leukocyte count — per mm^3**				
Median	8000	8100	6500	0.39
Range	4000–15,000	4000–23,000	3000–14,000	
Albumin — g/dl**	3.7±0.7	3.8±0.7	3.9±0.8	0.66
Median creatinine (range) — mg/dl**	1.3 (0.6–10.3)	1.0 (0.5–1.8)	0.9 (0.6–5.2)	0.26
Ribotype 027 in first sample — no. (%)††	3 (23)	1 (11)	0	0.28

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. CDI denotes *Clostridium difficile* infection, and ICU intensive care unit.
† P values are for the overall comparison among the three groups.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Karnofsky performance status ranges from 0 to 100, with higher scores indicating improved functional status.
¶ Scores on the Charlson comorbidity index range from 0 to 6 for each of 17 indicators, with higher scores indicating greater severity of illness.
‖ Data were missing for one patient in the infusion group and one in the vancomycin-only group.
** Data were missing for one patient in the vancomycin-only group.
†† Data for ribotype 027 (a more virulent strain of *C. difficile*) were missing for three patients in the infusion group, four in the vancomycin-only group, and two in the group receiving vancomycin with bowel lavage.



Case Study 2

Probiotics for Preventing Antibiotic-Associated Diarrhea

Antibiotic-Associated Diarrhea (AAD): Diarrhea caused by antibiotics killing good gut bacteria.

Common Issue: Many people experience diarrhea after taking antibiotics.

Intervention:

Probiotics: Taking live beneficial bacteria, like Lactobacillus or Bifidobacterium, to restore good bacteria in the gut.

Method: Probiotics are taken as supplements or in foods like yogurt, kimchi, etc.

Outcome:

Reduced Diarrhea: Studies show that probiotics can significantly reduce the risk of diarrhea when taken with antibiotics.

Overall Benefit: Probiotics help maintain a healthy balance of gut bacteria during antibiotic treatment.

Case Study 2 Charts

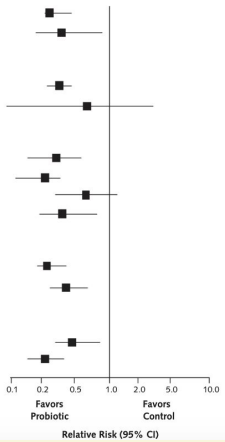
Table 2. **Probiotics to Prevent *Clostridium difficile*-Associated Diarrhea and Quality of the Evidence***

Outcome	Assumed Risk: Control Group†	Corresponding Risk: Probiotic Group (95% CI)‡	RR (95% CI)	Participants (Studies)	Quality of the Evidence§	Comments
Incidence of CDAD (complete case) Diarrhea as defined by authors + cytotoxin assay or culture Follow-up: end of antibiotic treatment to 3 mo after antibiotic therapy was discontinued	**Study Population**		0.34 (0.24–0.49)	3818 (20)	Moderate	Studies with low risk of bias (7/20) demonstrated a slightly more favorable protective effect than studies at high or unclear risk of bias (13/30). A test for subgroup differences did not find a statistically significant difference based on risk of bias ($P = 0.24$). In 13 of 20 trials, data on CDAD were missing for 5% to 45% of participants. A sensitivity analysis using plausible and worst-plausible ratios of event rates in those with missing data compared with those who were successfully followed demonstrated that the CDAD results were robust to all assumptions (worst-plausible analysis RR, 0.50 (95% CI, 0.34 to 0.76)). Effect sizes were consistent across all 20 studies ($I^2 = 0\%$; $P = 0.79$). The outcome assessed in all 20 studies was the outcome of interest for our health question. Using standard α (0.05) and β (0.20) values, for a RRR of 30%, the OIS (5676 persons) was greater than the total sample size (3818 persons), and the overall events totaled less than 150. Funnel plot inspection, the Begg and Mazumdar rank correlation test ($P = 0.79$), and the Egger regression test ($P = 0.16$) did not suggest publication bias or other small-study effects.
	59 per 1000 persons	20 per 1000 persons (14–29)				
	Moderate‖					
	50 per 1000 persons	17 per 1000 persons (12–25)				
Adverse events (complete case), as reported by patients	**Study Population**		0.82 (0.65–1.05)	3421 (17)	Moderate	Test for risk of bias in subgroup differences was not statistically significant ($P = 0.76$). Minimal heterogeneity among trials ($I^2 = 17\%$; $P = 0.28$). Outcome assessed in these 17 studies was the outcome of interest for our health question. Using standard α (0.05) and β (0.20) values, we calculated the OIS based on a relative risk increase of 30. The OIS (5686 persons) was greater than the total sample size (3421 participants). However, the number of events was relatively high (374), and the CI virtually excluded an increase in adverse events. Funnel plot inspection, the Begg and Mazumdar rank correlation test ($P = 0.68$), and the Egger regression test ($P = 0.51$) did not suggest publication bias or other small-study effects. Included studies have risk of bias regarding documentation and reporting of adverse events. Adverse events are an outcome of interest for all probiotics, yet only 17 of 20 included trials reported on adverse events, suggesting a selective reporting bias. The studies differed considerably in how adverse events were classified, and few studies stated their methods for classifying such events. Differences in classification may have overestimated the adverse events in the control groups. For example, in 3 studies, serious adverse events (all documented to be more common in the control group) were included that were not deemed to be related to the study product, whereas in other studies, symptoms (e.g., fever, abdominal cramping) classified as adverse events may have been due to conditions prevented by probiotics (e.g., *C. difficile* occurring in the control group rather than in the probiotic group).
	129 per 1000 persons	106 per 1000 persons (84–135)				
	Moderate‖					
	36 per 1000 persons	30 per 1000 persons (23–37)				

CDAD = *Clostridium difficile*–associated diarrhea; OIS = optimal information size; RR = relative risk; RRR = relative risk reduction.
* The patient or population was adults and children given antibiotics; the settings were inpatients and outpatients; and the intervention was probiotics.
† Based on the mean control group risk from all included trials.
‡ Based on the assumed risk in the comparison group and the relative effect of the intervention (95% CI).
§ Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence are as follows. High quality = further research is very unlikely to change our confidence in the estimate of effect; moderate quality = further research is likely to have an important impact on our confidence in the estimate of effect and

Figure 4. **Effect of probiotics on prevention of *Clostridium difficile*–associated diarrhea among subgroups.**

Subgroup	Events/Patients, *n/n*		Relative Risk (95% CI)	*P* Value for Test of Interaction
	Probiotic Group (*n* = 1974)	Control Group (*n* = 1844)		
Age				
Adults	33/1674	90/1539	0.22 (0.23–0.49)	
Children	7/300	18/305	0.40 (0.17–0.96)	0.69
Probiotic dosage				
>10 billion CFU/d	36/1775	98/1634	0.34 (0.23–0.49)	
≤10 billion CFU/d	4/199	10/210	0.61 (0.08–4.60)	0.57
Species				
Other (mixed) species	8/335	37/339	0.30 (0.15–0.61)	
L. acidophilus + L . casei	11/431	31/350	0.21 (0.11–0.42)	0.34
L. rhamnosus	12/566	18/565	0.63 (0.30–1.33)	0.15
S. boulardii	9/642	22/590	0.39 (0.19–0.82)	0.84
Risk of bias				
Low	17/695	52/613	0.27 (0.16–0.46)	
High or unclear	23/1279	56/1231	0.42 (0.26–0.68)	0.24
Species				
Single	21/1208	40/1155	0.50 (0.29–0.84)	
Multiple	19/766	68/689	0.25 (0.15–0.41)	0.06



Summary and Implications

To conclude, the human microbiome, made up of diverse microbes, plays a crucial role in digestion, nutrition, and immune function. Imbalances are linked to chronic diseases and mental health issues. Research techniques like 16S rRNA sequencing, and treatments like probiotics and FMT, show the microbiome potential for improving health and preventing infections.Understanding the microbiome can lead to better disease prevention and treatment.

Works Cited

https://nutritionsource.hsph.harvard.edu/microbiome/#:~:text=Microbiota%20stimulate%20the%20immune%20system%2C%20break%20down%20potentially,found%20in%20bacteria%2C%20not%20in%20plants%20and%20animals.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7362776/

https://www.britannica.com/science/human-microbiome

https://microbiome.mit.edu/microbiome-news/how-your-gut-is-controlling-your-immune-system/

https://www.nature.com/articles/s41467-019-13036-1

https://my.clevelandclinic.org/health/treatments/14598-probiotics

https://health.clevelandclinic.org/what-are-prebiotics

https://www.nejm.org/doi/full/10.1056/NEJMoa1205037

https://www.researchgate.net/publication/235383789_Probiotics_for_the_prevention_of_Clostridium_difficile-associated_diarrhea_A_systematic_review_and_meta-analysis

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8645667/