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Review

Host–Microbiome Crosstalk, Health Risks and Next-Generation Mitigation Strategies

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Abstract

Spaceflight-associated neuro-ocular syndrome (SANS), musculoskeletal atrophy, immunological dysregulation, microgravity, cosmic radiation, confinement, and nutrient-limited diets are all consequences of human spaceflight. The gut microbiota has emerged as a critical modulator of astronaut resilience, controlling SCFA production, bile acid metabolism, vitamin biosynthesis, and immunological and neuroendocrine signaling. The reduction of taxa that produce SCFA, such as *Faecalibacterium prausnitzii* and *Roseburia* spp., the growth of opportunistic infections, the decrease in microbial diversity, and the enhanced horizontal transfer of antibiotic resistance genes are all documented in spaceflight and analog investigations. These changes are linked to cardiovascular strain, bone loss, metabolic dysregulation, electrolyte imbalance, and systemic inflammation. The ISS's extreme hygiene further reduces exposure to ambient microbes, which may weaken immune function. In this study, we investigate the effects of spaceflight on the gut microbiome and astronaut health, with a focus on microbial changes associated with immunological and metabolic abnormalities. We believe that next-generation countermeasures, prebiotics, synbiotics, postbiotics, synthetic probiotics, phage therapy, and microbiome monitoring are potential options for both space missions and terrestrial healthcare.

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1. Introduction

Human spaceflight subjects astronauts to a variety of environmental hazards, such as microgravity (~10^{-6} g), galactic cosmic radiation (~0.3–0.5 mSv/day in low Earth orbit and up to 1–2 mSv/day in deep space), disturbed circadian cycles, living in cramped quarters (~120–150 m^3 per person), and diets that are low in nutrients (~2,700–3,000 kcal/day with limited fresh produce). [1–4] All of these circumstances work together to cause immunological suppression, musculoskeletal atrophy, neurovestibular recalibration, cardiovascular deconditioning, and the syndrome of spaceflight-associated neuro-ocular changes (SANS). [5–7] Since the gut microbiota controls vital physiological functions like the synthesis of short-chain fatty acids (SCFAs), the metabolism of bile acids, vitamin biosynthesis, immunological calibration, and neuroendocrine signaling, consideration has recently turned to the gut microbiota as a key factor in astronaut resilience. [8–12] Changes in this ecosystem have been regularly observed in both space missions and ground-based analogs, correlating altered microbial composition to systemic inflammation and hastened physiological deterioration. [13–16] These microbial alterations result from the combined effects of the space environment rather than being caused by a single cause. While cosmic radiation causes DNA damage in both host and microbial genomes, jeopardizing epithelium integrity, microgravity alters mucosal function and gastrointestinal motility. [17–20] In addition to space diets lacking in fiber, which restrict the formation of SCFA and destabilize gut metabolic networks, psychological stress and social

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isolation trigger neuroendocrine pathways that further reduce microbial diversity. [21–23] Key commensals like *Faecalibacterium prausnitzii*, *Roseburia faecis*, *Anaerostipes hadrus*, and *Akkermansia muciniphila* are declining, according to data from NASA's GeneLab and Mars500 studies. Environmentally acquired microbes like *Bacillus subtilis*, *Pseudomonas putida*, and *Saccharomyces cerevisiae* are also declining. * [24–28] The growth of opportunistic organisms like Staphylococcus and Enterococcus is facilitated by this ecological gap, which raises questions regarding long-term microbial imbalance in space habitats. [29–31]

In addition to these compositional shifts, another aspect of danger has been identified by the International Space Station's (ISS) distinct microbial ecology. According to a 2025 Cell study that used over 800 surface samples, the ISS is essentially too clean, even if it is thoroughly sterilized to avoid bacterial contamination. [32] The absence of exposure to ambient microbes deprives astronauts of the constant microbial inputs that support metabolic diversity and immunological homeostasis on Earth. [33–36] In turn, this over-sterilization has been linked to recurring infections, allergies, and inflammatory skin diseases, indicating that immunological resilience may paradoxically be dependent on regulated microbial exposure. [37–39] Determining how the space environment alters host-microbe interactions and creating accurate mitigation strategies are therefore crucial as we look ahead to multi-year deep-space missions. Novel techniques include CRISPR-engineered probiotics, which protect microbial diversity, functional stability, and systemic health; targeted reintroduction of safe environmental taxa, and customized prebiotic and synbiotic supplements are examples of emerging strategies. [40–43]

The importance of the microbiome for astronaut health is becoming more widely acknowledged, but current spaceflight research still lacks a thorough understanding of a number of important factors. Notably, there are yet no clear mechanisms connecting microbial alterations to systemic health problems, long-term impacts of space-induced dysbiosis, or practical interventions for preserving microbial stability. Our goal in this paper is to identify these knowledge gaps and offer specific approaches to further microbiome-based health interventions in space travel.

1.1. Dynamics of the Gut Microbiome: On-Earth vs Spaceflight Situations

Under terrestrial conditions, the human gut microbiome is generally stable, diversified, and dominated by beneficial bacterial taxa such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii,* explained in **Table 1**. Through their production of SCFAs, preservation of the integrity of the epithelial barrier, and synthesis of vital vitamins, these commensal bacteria promote metabolic and immunological balance. [48–51] In contrast, spaceflight is typically linked to a decrease in microbial variety, with Shannon diversity indices dropping by 10-30% during long-duration missions. [52–54] By altering the redox potential and oxygen tension in the gut, SCFA-producing organisms such as *Roseburia* spp., *Faecalibacterium prausnitzii*, and *Anaerostipes hadrus* are markedly depleted, resulting in 20–40% decreased SCFA concentrations. [55–57] Through their inhibition of histone deacetylases (HDACs) and binding to G-protein-coupled receptors (GPR41/43) SCFAs function as signaling molecules that control tight-junction integrity, Treg differentiation, and systemic glucose and lipid metabolism. [58–61] Gut dysbiosis is linked to cardiovascular strain during missions because astronauts with reduced SCFA availability have impaired vascular function, insulin sensitivity, and immunological tolerance. [62–64] Meanwhile, opportunistic infections including Pseudomonas species, *Staphylococcus aureus*, and *Enterobacteriaceae* thrive in microgravity and can become more aggressive even in the absence of significant changes in abundance. [65–68]

Furthermore, improved conjugation and plasmid transfer in microgravity lead to a 1.5–2-fold increase in the horizontal transfer of antibiotic resistance genes. [69–72] The combined effects of these microbial changes increase the dangers to astronauts' health by upsetting metabolic processes, compromising immunological function, and intensifying systemic inflammation. [73–75] Dysbiosis brought on by spaceflight seriously upsets the balance of electrolyte homeostasis in the gut, which is also tightly controlled by microbial metabolism. *Faecalibacterium*, *Roseburia*, and *Anaerostipes* are among the species that produce SCFAs on Earth. They increase colonic water and sodium absorption by upregulating epithelial transporters (such NHE3 and ENaC) and encourage the intake of calcium and magnesium by acidifying the intestinal lumen. [76–77] Their depletion in space causes mineral solubility and salt reabsorption to decrease, which leads to bone demineralization, electrolyte imbalance, and dehydration. [78–79] The loss of *Bifidobacterium* exacerbates musculoskeletal deterioration by further impairing the intake of calcium and magnesium. [80–81] Concurrently, facultative pathogens increase paracellular sodium, potassium, chloride, and bicarbonate leakage, dissolving epithelial tight junctions and exacerbating fluid loss and gut barrier failure. [82–83]

Significantly, spaceflight also alters microbial behavior at the biofilm level: Salmonella enterica increases the expression of virulence genes; Pseudomonas aeruginosa forms denser, EPS-rich biofilms; Staphylococcus aureus upregulates adhesion and quorum-sensing genes; and even commensals like Enterococcus faecalis form thicker biofilm matrices in microgravity. [84–87] These biofilm-associated microenvironments act as reservoirs for horizontal gene transfer and modify local pH, ion gradients, and epithelial transport, which reinforce electrolyte imbalance. [88–90] Dysbiosis, SCFA depletion, electrolyte disruption, and biofilm remodeling all work together to negatively affect immune regulation, increase the risk of cardiovascular strain, dehydration, kidney stone formation, and gastrointestinal dysfunction, as well as to promote systemic inflammation during extended space missions. [91–93]

Table 1. Key differences in gut microbiome features under terrestrial and spaceflight conditions.

Feature	Terrestrial Conditions	Spaceflight Conditions	References
Microbial diversity	High species richness and stable community structure	10–30% reduction in Shannon diversity index	[44–54]
Dominant beneficial taxa	*Lactobacillus*, *Bifidobacterium*, *Faecalibacterium prausnitzii* abundant	Depletion of SCFA producers (*Roseburia*, *Faecalibacterium*, *Anaerostipes*)	[45–57]
SCFA levels	Normal butyrate, acetate, propionate levels; support Treg activity, glucose & lipid metabolism	20–40% reduction in SCFA concentrations, impairing immune tolerance, insulin sensitivity, vascular function	[58–64]
Barrier function	SCFAs maintain epithelial tight junctions and barrier integrity	Pathogen expansion (*Enterobacteriaceae*, *Staphylococcus aureus*, *Pseudomonas spp.*) disrupts tight junctions	[65–68]
Pathogen behavior	Opportunistic pathogens kept under control	Enhanced virulence and stress adaptation in microgravity	[66–72]
Horizontal gene transfer (HGT)	Baseline rates of plasmid conjugation and ARG transfer	1.5–2 fold increase in HGT and antibiotic resistance gene spread	[69–72]
Electrolyte regulation	SCFAs stimulate Na^+/water absorption (via NHE3, ENaC); enhance Ca^{2+}/Mg^{2+} solubility	Reduced Na^+/water absorption; impaired Ca^{2+}/Mg^{2+} uptake → dehydration, bone loss	[76–81]
Ion leakage	Tight junctions restrict paracellular ion loss	Increased gut permeability → electrolyte leakage and fluid imbalance	[82–83]

Biofilm formation	Balanced biofilm homeostasis; commensals maintain mucosal health	Denser EPS-rich biofilms; enhanced virulence gene expression	[84–90]
Systemic outcomes	Immune tolerance, stable metabolism, bone & cardiovascular health maintained	Dysbiosis-driven systemic inflammation, insulin resistance, kidney stone risk	[91–93]

1. Physiological Adaptations to Spaceflight Conditions

The effects of spaceflight on the body become apparent quickly. Minutes after launch, fluid redistribution results in reduced leg volume, nasal congestion, and facial puffiness. [94–96] This is quickly followed by cardiovascular remodeling, which includes changes in heart shape and loss of plasma volume. [97–99] Usually going away in the first few days, space motion sickness is a symptom of neurovestibular adaptations. [100,101] Muscle atrophy, bone resorption, and cardiovascular deconditioning become more pronounced on longer missions. [102–104]

With evidence of decreased T-cell function and frequent viral reactivation, immune dysregulation is a serious concern. [105–108] Exposure to radiation causes extra stress, genotoxic harm, and changes the microbial and host communities. [109–112] These alterations together show how host physiology and microbial ecology are intertwined in space. **Table 2** summarizes these cumulative changes and shows the time order of the major physiological consequences during spaceflight.

Table 2. Temporal sequence of spaceflight physiological effects.

System/Effect	Description	Time of Onset	References
Fluid Redistribution	Facial puffiness, nasal congestion, leg volume loss	Minutes–hours	94–96
Cardiovascular Changes	Plasma volume loss, altered cardiac geometry	Hours–days	97–99
Neurovestibular Effects	Space motion sickness, vestibular recalibration	First 3–4 days	100–101
Musculoskeletal Atrophy	Muscle loss, bone resorption	Weeks–months	102–104
Immune Dysregulation	T-cell dysfunction, viral reactivation	Days–weeks	105–108
Radiation Effects	DNA damage, altered microbiome	Continuous exposure	109–112

2. Next-Generation Countermeasures for Spaceflight Through Microbiome-Based Strategies

Traditional probiotics offer only a limited level of defense against the various and complicated stressors associated with space travel. Although single-strain compositions like *Bifidobacterium animalis* or *Lactobacillus rhamnosus* GG have demonstrated some promise on Earth, they are not enough to correct the complex metabolic and microbiological imbalances seen during extended missions. [113–115]

Consequently, countermeasures that target the microbiome of the next generation are currently being researched. Prebiotics like inulin, galactooligosaccharides (GOS), and resistant starches selectively support beneficial commensals, especially those that produce butyrate. On the other hand, synbiotics, probiotic and prebiotic combinations are more effective than either one alone at reestablishing microbial balance and immune regulation. [116–119] Postbiotics, which comprise microbially produced compounds including bacteriocins, SCFAs, and extracellular vesicles, are also becoming more and more popular as treatment choices since they can have anti-inflammatory and immunomodulatory effects even in situations when live probiotic colonization is restricted. [120–122] Beyond conventional formulations, next-generation probiotics (NGPs) and multispecies probiotics are especially pertinent to spaceflight. In comparison to single strains, multispecies consortia provide a wider functional safety net by combining complementing metabolic and immunological properties. [123–124] In order to increase storage and viability for deployment in space habitats, stable, encapsulated solutions are being developed to address NGPs that routinely diminish throughout spaceflight and confinement experiments, such as *Akkermansia muciniphila, Faecalibacterium prausnitzii*, and *Roseburia* spp. [125–127]

Probiotics that have been engineered mark yet another innovation breakthrough. By using synthetic biology based on CRISPR, strains can be altered to provide therapeutic proteins or metabolites (such as butyrate, antioxidants, or antimicrobial peptides) while also allowing for the sequence-specific eradication of pathogens or genes that confer resistance to antibiotics. [128–131] the capacity to specifically lyse opportunistic bacteria like *Staphylococcus* or *Enterococcus*, which frequently proliferate in the ISS environment, is another focused strategy offered by phage therapy. [132–134] Antimicrobial peptides naturally secreted by commensals, known as bacteriocins, and synthetic phage cocktails are being researched as narrow-spectrum antibiotic substitutes with a lower chance of resistance. [135–136]

On a larger scale, fecal microbiota transplantation (FMT) has demonstrated exceptional effectiveness in reestablishing microbial diversity and function on Earth and is being contemplated as an emergency procedure for astronauts; nevertheless, practical and safety issues still exist. [137–138] Long-term missions may benefit from the safer, more regulated option provided by defined microbial consortia, which employ standardized multi-strain compositions that resemble a healthy microbiome. [139] Additionally, dietary treatments continue to be a crucial preventative tool. Fermentable fibers and polyphenols, which promote dysbiosis and lower the availability of SCFA, are frequently lacking in space diets. [140–141] It may be possible to maintain advantageous microbial metabolism while in flight by incorporating resistant starches, soluble fibers, supplements high in polyphenols, and freeze-dried or lyophilized fermented meals. [142–144]

The effectiveness of these therapies ultimately rests on prompt monitoring. Developments in lab-on-a-chip systems, biosensors, and miniaturized sequencing platforms combined with AI-guided data processing will allow for dynamic, customized countermeasure changes and real-time microbiome monitoring. [145–147] Engineered probiotics, phages, prebiotics, synbiotics, and AI-driven microbiome monitoring are some of the next-generation tactics that together offer a multifaceted strategy to maintain astronaut health. Crucially, these developments have a great deal of promise for terrestrial medicine as well, where they may be used to treat metabolic disorders, bacterial resistance, and immunological dysregulation. [148–150]

2. Emerging Insights & Future Perspectives

As astronaut missions extend in duration and risk, the accumulating evidence from 2022-2025 reveals refined understanding of how spaceflight stressors (microgravity, radiation, confinement, diet, circadian disruption) impact host-microbiome interactions not merely via loss of taxonomic diversity, but through functional disruption, barrier integrity compromise, immune modulation, and prospects for engineered and precision countermeasures. Recent studies in murine models show that during spaceflight there occur significant changes in gut microbiota species linked to bile acid and fatty acid metabolism, accompanied by host gene-expression shifts in colon and liver that indicate suppressed immunity and disrupted metabolic homeostasis, suggesting that microbiome-mediated metabolic signaling may be a key driver of insulin resistance and lipid dysregulation in spaceflight environments. [151]

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Evidence also indicates that gut permeability ("leaky gut") is elevated during actual space missions: astronaut-derived and murine transcriptomic data show downregulation of barrier function genes, raising risk of microbial translocation and systemic inflammation that could contribute to downstream tissue damage. [152] Parallel work underscores that not all microbiome changes are permanent; environmental microbiome shifts (in ISS habitat surfaces, module usage) produce microbial signatures that may reseed or reinfluence the human microbiome, but many such changes revert post-flight, and the degree of resilience varies by individual and by microbiome function. [153] Another axis of concern is that of mental health and the gut-brain axis: changes in microbial populations (e.g., loss of Lactobacillus, Bifidobacterium, and other taxa with known anti-inflammatory or gut–brain modulatory roles) appear to track with psychological stressors, disrupted circadian rhythms, and elevated systemic cytokines in astronaut and murine studies, hinting at a microbiome-mediated contribution to mood, sleep, and cognitive alterations during and after missions. [154]

In light of these insights, newer microbial engineering and precision probiotic strategies are emerging: genetically engineered probiotics, synthetic microbial consortia, and CRISPR-based modulation of gut microbes are being proposed or tested in terrestrial and preclinical models as tools to restore lost metabolic functions, enhance barrier integrity, and reduce inflammation. [155,156] Dietary interventions remain a low-risk but high-potential countermeasure: functional foods rich in fermentable fiber, prebiotics, polyphenols, and other bioactive compounds are shown to support short-chain fatty acid (SCFA) producers, stabilize gut microbial metabolic outputs, and may buffer against immune activation and metabolic disruption in analog and rodent studies. [157]

Together, these emerging findings suggest that future mission planning should explicitly incorporate multi-omics monitoring (metagenome + transcriptome + metabolome), barrier integrity assays, and psychological endpoints in astronaut health, not only to characterize risk but to validate intervention efficacy. Moreover, countermeasure design should move from taxonomic restoration alone toward functional restoration ensuring that microbes or engineered microbes can perform key metabolic, immunological, and barrier-support roles under spaceflight stressors.

By building on these recent advances, there is an opportunity to shift from *observational risk profiling* toward proactive *design of microbiome-centric therapies and habitat engineering*, with long missions (Moon, Mars) in view.

3. Conclusion

Human physiology is significantly impacted by the special set of stressors that come with spaceflight, such as microgravity, cosmic radiation, disturbed circadian cycles, confinement, and restricted meals. Because it affects immunological response, metabolic control, electrolyte balance, and neuroendocrine signaling, the gut microbiota has become a key mediator of astronaut health. On long-duration missions, microbial diversity is consistently decreased, commensals that produce SCFA (*Faecalibacterium prausnitzii, Roseburia* spp., *Anaerostipes hadrus*) are depleted, opportunistic pathogens proliferate, antibiotic resistance genes are horizontally transferred more frequently, and biofilm remodeling occurs. These factors all contribute to systemic inflammation, cardiovascular strain, musculoskeletal decline, and gastrointestinal dysfunction.

Future investigations should integrate metabolomics, longitudinal microbiome monitoring, and multi-omics techniques to gain a mechanistic understanding of host-microbe interactions in spaceflight circumstances. Personalized, next-generation microbiome-based therapies, such as phage therapy, specified microbial consortia, engineered probiotics, postbiotics, synbiotics, and prebiotics, provide promising ways to preserve microbial diversity and functional stability. Including AI-powered real-time monitoring can allow for personalized, flexible countermeasures. These approaches hold promises for treating immunological dysregulation, metabolic diseases, and antibiotic resistance on Earth in addition to promoting astronaut health during extended deep-space travel.

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