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The microbiota-gut-brain axis in myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review of an emerging field

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Abstract

The intricate relationship between gut microbiota and the brain has emerged as a pivotal area of research, particularly in understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). This complex condition is characterized by debilitating fatigue, cognitive dysfunction, and a wide array of systemic manifestations, posing significant challenges for diagnosis and treatment. Recent studies highlight the microbiota-gut-brain axis as a crucial pathway in ME/CFS pathophysiology, suggesting that alterations in gut microbial composition may impact immune responses, neurochemical signaling, and neuronal health. This narrative review systematically explores English-language scholarly articles from January 1995 to January 2025, utilizing databases such as PubMed, Scopus, and Web of Science. The findings underscore the potential for targeted therapeutic interventions aimed at correcting gut dysbiosis. As research progresses, a deeper understanding of the microbiota-gut-brain connection could lead to innovative approaches for managing ME/CFS, ultimately enhancing the quality of life for affected individuals.

Key Words: microbiota-gut-brain axis, myalgic encephalomyelitis, chronic fatigue syndrome.

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The intricate relationship between gut microbiota and the brain has emerged as a pivotal area of research in recent years, particularly in understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).[1] This complex condition is characterized by debilitating fatigue, cognitive dysfunction, and a wide array of systemic manifestations, all of which present significant challenges not only for accurate diagnosis but also for the development of effective treatment strategies.[2] Recent studies have illuminated the importance of the microbiota-gut-brain axis as a crucial pathway in the pathophysiology of ME/CFS, raising important questions about the causal mechanisms that may be at play.[1-8] These studies suggest that alterations in gut microbial composition could significantly impact immune responses, neurochemical signaling, and neuronal health, thereby contributing to the diverse and often debilitating symptomatology associated with ME/CFS.[1-8] However, it is essential to critically evaluate whether these

associations consistently translate into causal relationships or if they merely reflect correlated phenomena without direct influence.[8] This intricate interplay between microbiota and neurological function transcends traditional views of gut health, emphasizing the potential for targeted therapeutic interventions aimed at correcting gut dysbiosis.[3] As the field continues to evolve, a thorough and critical overview of existing research will not only facilitate a deeper understanding of the complexities surrounding ME/CFS but also encourage the exploration of innovative approaches to both management and treatment.[5-7] This reflective analysis marks a significant and necessary step toward addressing this multifaceted disorder, as we must remain open to questioning and potentially reshaping existing paradigms in the relentless quest for effective solutions.[3] Ultimately, advancing our understanding of the gut-brain connection may lead to more effective interventions that can alleviate the burdens faced by those suffering from ME/CFS, paving the way for enhanced quality of life and well-being for affected individuals.[3-8]

Materials and Methods

In this narrative review, the methodology for gathering data involved a systematic exploration of English-language scholarly articles published from January 1995 to January 2025. This approach was chosen to comprehensively cover research related to the microbiome and ME/CFS. Key databases such as PubMed, Scopus, and Web of Science were searched using specific terms including "microbiota-gut-brain axis," "ME/CFS," "microbiome dysbiosis," "gut health," "pathophysiology," and "therapeutic approach." The objective was to collate both qualitative and quantitative insights concerning the composition of gut microbiota, the evaluation of inflammatory markers, and the effectiveness of microbiome-targeted therapeutic interventions. Where possible, additional information from clinical trials and observational studies was incorporated to enhance the review and support the comprehensive narrative being constructed. The review adopted a narrative format, aiming to integrate current research findings while emphasizing crucial mechanistic understandings and clinical ramifications.

Results

Definition, prevalence, and diagnosis of ME/CFS

ME/CFS is a profound multisystem disorder marked by significant physical impairment, potentially confining individuals to complete bed rest with extensive care needs.[1] The condition manifests as severe fatigue that does not improve with rest, cognitive dysfunctions, and symptoms akin to influenza including muscle aches, pain, headaches, sore throats, and sensitive lymph nodes.[2] A notable worsening of these symptoms occurs after minimal physical, orthostatic, or mental exertion, a phenomenon known as Post-Exertional Malaise (PEM). PEM typically manifests with a delay, approximately 24 hours post-exertion, and results in a drastic decrease in energy and activity levels by at least 50%. Recovery from such episodes extends beyond 24 hours and may last several weeks. The progression of ME/CFS is variable, with symptom severity shifting dramatically within days. Patients frequently report sensitivities and allergic reactions to various stimuli including extreme temperatures, light, noise, certain smells or chemicals, and even engaging in simple conversations.[1] Gastrointestinal issues like constipation, diarrhea, and abdominal pain are common, and there is a notable overlap with irritable bowel syndrome, affecting between 38% and 92% of patients.[9] Research involving 48 participants revealed that over 70% experience gastrointestinal complaints, and more than 35% use medication for these issues.[10,11] A substantial portion of patients, at least 25%, are confined to their homes or beds, indicative of the moderate to severe spectrum of ME/CFS.[12] Epidemiological data suggests nearly half of those affected are unable to maintain employment, with a previous study indicating an unemployment rate of 87% among patients.[11,12] During their most severe episodes, 48% of individuals are completely unproductive, with those severely impacted often limiting communication and spending extended periods in dark, quiet rooms, unable to partake in regular showers or engage in activities like listening to music or watching television.[11] Although ME/CFS can be as incapacitating as diseases like multiple sclerosis or systemic lupus erythematous, it is classified by the ICD-11 as a disease of the nervous system under the code 8E49, postviral fatigue syndrome.[1,13] Nonetheless, ongoing debates regarding its pathogenesis and etiology raise questions about the accuracy of this classification.[14]

The worldwide incidence of ME/CFS varies significantly depending on the definition of the disease used and is also influenced by the absence of objective diagnostic tests.[9] A recent meta-analysis has shown that the prevalence can be as high as 0.89% according to the most commonly used case definition, CDC-1994, and 1.14% when based on clinical interviews.[16] ME/CFS is more commonly diagnosed in females than males, with a ratio ranging from 1.5 to 2.[15] Typically manifesting in mid-life, ME/CFS has two primary patterns of onset: a sudden onset that patients clearly recall and a gradual onset marked by progressive deterioration.[16] The severity and symptoms of ME/CFS can fluctuate over time. The progression of the disease varies among individuals; however, a significant majority reports no improvement over time, with only about 4% experiencing a complete recovery.[11]

Despite the existence of multiple consensus criteria documented in scholarly articles, such as the Canadian Consensus Criteria, Fukuda, Oxford, and International Criteria, there is currently no commercially available blood test or diagnostic tool for ME/CFS.[9] The absence of a universally accepted set of consensus criteria could potentially lead to diagnostic inaccuracies in up to 80% of ME/CFS cases.[1,9] This represents a significant challenge not only for affected individuals who encounter inexperienced healthcare providers but also poses broader societal and public health challenges.[1] However, recent scientific publications have suggested the potential development of diagnostic tools for ME/CFS in the foreseeable future. Innovations such as nano-electronic blood-based assays, CD8+ T cell analysis,

fecal metagenomic profiling, and metabolite analysis have shown promise in reliably distinguishing ME/CFS patients from healthy controls in certain studies.[17-20]

Overview of the microbiota-gut-brain axis

Since the mid-19th century, it has been recognized that there is a bidirectional communication between the gut and the brain. More recently, this interaction has been conceptualized as the "gut-brain axis." The interplay between the gut microbiota and various physiological and pathological mechanisms is crucial.[21] For instance, one study highlighted the role of the gut microbiome in shaping the development of the hypothalamus-pituitary-adrenal axis and influencing stress responses in germ-free animals.[22] Similarly, another study found that fecal microbiota transplantation in germ-free mice from their own strain preserved typical behaviors, whereas transplantation from a different strain altered their behavior to match the donor strain.[23] While the precise physiological pathways involved remain under discussion, the significance of gut-brain communication in patients with ME/CFS is supported by multiple studies.[24-27] However, the specific pathophysiological mechanisms through which the gut-brain axis affects neuropsychiatric symptoms are still not fully understood.[5] The potential pathways for this communication may involve changes in the immune system, such as alterations in regulatory T-cells, NK-cells, or CD8+ T-cells, as well as variations in cytokine production including increased TGF-ß and immunoglobulins.[28-33] These findings are subject to debate since chronic inflammation might also stem from other underlying conditions.[1,34] In ME/CFS, altered levels of tryptophan, influenced by the microbiome, have been associated with the condition.[35] Additionally, the gut microbiome has been shown to directly affect neural stimulation of the vagal nerve, which also innervates the colon, suggesting a possible bidirectional influence.[36]

Despite uncertainties about direct mechanisms, several indirect indicators underscore the importance of the gut-brain axis in neuropsychiatric symptoms generally and in ME/CFS specifically.[1-8] A study reported alleviation of ME/CFS symptoms following rectal bacterial infusion, with a significant proportion of participants also suffering from Irritable Bowel Syndrome (IBS), indicating that while the treatment targeted IBS, it also pointed to significant gut-brain communication in ME/CFS.[37] Moreover, modulation of the intestinal microbiome through antibiotics or probiotics has shown improvements in various neuropsychiatric symptoms, further supporting the relevance of the gut-brain axis.[24-27] Nevertheless, a recent pilot study has reported faecal microbiota transplantation as safe but ineffective on fatigue severity and health-related quality of life in patients with ME/CFS.[38] This contradiction highlights the importance of further research in this regard and clarifying the potential role of the microbiota-gut-brain axis in the pathophysiology of ME/CFS.

Metagenomic analysis has also identified distinct clusters of fecal bacteria that are characteristic of ME/CFS, which vary between patients with and without concurrent IBS.[19] Specifically, in those suffering from IBS, there was a notable increase in unclassified *Alistipes* and a reduction in *Faecalibacterium*. Conversely, in ME/CFS patients without IBS, there was a rise in unclassified *Bacteroides* and a decrease in *Bacteroides vulgatus*. Furthermore, the study highlighted variations in metabolic pathways including the synthesis of unsaturated fatty acids, degradation of atrazine, production of vitamin B6, and breakdown of pyrimidine ribonucleosides.[39] Considering that the gut microbiome includes both bacterial and viral components, and acknowledging that ME/CFS is often reported as a post-viral condition such as following SARS-CoV-2 infection, another research effort examined viral taxa in feces, blood, and saliva. However, this investigation found no significant differences in viral populations between ME/CFS patients and healthy controls.[40]

The role of gut dysbiosis in CFS/ME

Alterations in the intestinal microbiota and dysbiosis have been observed in numerous studies on ME/CFS, though a distinct microbial pattern has yet to be consistently identified.[10,19,41-44] Reviews of microbiome research in ME/CFS patients indicate variable outcomes, making it difficult to definitively link changes in gut bacteria to the pathophysiology of the disease.[6] Newberry and colleagues, through a systematic review, noted eight concordant and seven discordant findings across different studies, yet still supported the presence of dysbiosis.[45] In a particular study, researchers were able to accurately identify 83% of subjects as either ME/CFS patients or healthy controls by assessing dysbiosis in the gut microbiome and noting elevated inflammatory markers in the blood due to microbial translocation. However, this study had a small sample size (N=48) and requires further verification. Analysis of 16S rRNA stool samples indicated a decrease in bacterial diversity and richness, reduced carriage of anti-inflammatory species, and an increase in pro-inflammatory bacterial species such as *Enterobacteriaceae*.[10] Typically, greater microbial diversity is linked to a healthier host. The cardiorespiratory fitness, measured by peak oxygen consumption (VO2 peak), accounts for approximately 20% of the variation in gut diversity, suggesting that the reduced microbial diversity in ME/CFS patients might correlate with altered physical fitness levels. ME/CFS patients are known to exhibit significantly lower VO2 peaks.[46,47] While Armstrong and colleagues reported significant reductions in intestinal anaerobic bacteria, other studies have found increases in these microorganisms in ME/CFS patients.[42,43] Elevated levels of *Enterococcus spp.*, *Streptococcus spp.*, and increased *Enterobacteriaceae* have been documented, alongside lower levels of beneficial *Bifidobacteria* and decreased anti-inflammatory *Firmicutes*.[10,25,33,41,43,48] Metagenomic analyses by Nagy-Szakal and colleagues identified specific bacterial taxa such as the *Firmicutes phylum*, and *genera Faecalibacterium*, *Roseburia*, and *Clostridium* as linked to ME/CFS. Notably, increases in *Alistipes* and decreases in butyrate-producing *Faecalibacterium* were highlighted as potential diagnostic biomarkers. Their observations of higher *Clostridium* abundance contrast with findings from Giloteaux and others. Replications also confirmed lower *Faecalibacterium* levels.[10,19] A case study comparing ME/CFS-discordant monozygotic twins revealed reduced

abundance of *Bifidobacterium* and *Faecalibacterium* in the affected twin, along with lower gut alpha diversity.[49] Interestingly, reductions in *Faecalibacterium* have also been observed in patients with fatigue associated with inflammatory bowel disease, cancer-related fatigue, and other autoimmune conditions such as multiple sclerosis and type 1 diabetes mellitus.[50-53] Numerous investigations have indicated a decrease in a butyrate-producing *Bacteroides* species in individuals with ME/CFS.[45] Advanced 16S rRNA sequencing of fecal samples has shown changes in the gut microbiome associated with heightened gut inflammation, specifically notable increases in *Lactonifactor* and *Alistipes*.[41] A particular study involving 48 patients and 52 controls pinpointed 26 markers, including bacterial taxa that distinctly characterized ME/CFS compared to healthy individuals.[54] The most significant differences between patients and controls were observed in the levels of *Coprobacillus*, *Eggerthella*, and *Blautia*. There were reductions in *Faecalibacterium* and rises in *Coprobacillus*, corroborating findings from earlier research.[10,19] To assess the diagnostic capabilities of these markers, researchers categorized patients based on the duration of ME/CFS into short-term and long-term groups. They noted that microbiome alterations were substantially more common in cases with shorter disease duration (≤3 years) than those with longer disease spans (>3 years). The researchers proposed that these microbial markers reflect transient shifts at the initial stages of the disease, presenting potential for their use as future biomarkers.[54] Moreover, research comparing the microbiome profiles of patients with ME/CFS to those with acute Q-fever fatigue and healthy individuals revealed similar microbial patterns between the two patient groups, both of which were distinctly different from that of healthy controls. Both ME/CFS and Q-fever patients exhibited similar proinflammatory markers, allowing for their differentiation from healthy individuals. Increased levels of *Firmicutes* and *Actinobacteria* were observed in 50 ME/CFS patients compared to 72 healthy controls; while *Bacteroidetes* levels were lower.[55] A subsequent study involving 35 patients and 70 controls also identified a unique microbial composition characterized by reduced anti-inflammatory *Firmicutes*, supporting earlier findings.[8,10,41] This research compared patients with internal (relatives) versus external controls, identifying several commonalities between patients and their relatives, but not with external controls, highlighting the importance of selecting appropriate controls that account for lifestyle and genetic factors.[8] These findings, though somewhat inconsistent, clearly indicate dysbiosis in ME/CFS as noted in prior reviews; however, the precise role of these microbial discrepancies in the pathogenesis of the disease remains to be elucidated. The referenced studies vary significantly in terms of sample size, participant recruitment criteria including disease severity at the time of sampling, and microbiota analysis techniques (predominantly culturing or 16S amplicon sequencing, with only one employing whole genome shotgun sequencing).[6,45] It is crucial to recognize that ME/CFS patients often use various medications regularly to manage their symptoms,[11,56] and it is well-established that not only antibiotics but also other medications can substantially alter the commensal microbiota.[57-59] Future studies should consider these factors. Additionally, diet can quickly affect the microbiome composition in the short term, and long-term dietary patterns have been linked to specific fecal microbiome genera; for instance, diets rich in protein/animal fats tend to favor *Bacteroides*, while carbohydrate-rich diets are associated with a higher prevalence of *Prevotella*.[60,61] Therefore, dietary intake within at least 48-24 hours before stool sample collection should be taken into account. Furthermore, larger studies with well-defined clinical inclusion criteria are necessary to address the various subgroups within the ME/CFS patient population and to explore both viral and eukaryotic components of the gut microbiome.[6,44,45,62]

Mechanisms linking gut microbiota to CFS/ME symptoms

Under normal composition of the gut, bacterial translocation through the gut barrier should not be possible.[63] However, numerous studies have found that patients with ME/CFS exhibit greater intestinal permeability, lending support to the theory that bacteria may translocate into the systemic circulation.[64-67] This is used to account for the anomalously high concentrations of IgA and IgM antibodies against lipopolysaccharide observed in the peripheral blood of these patients, with 67% and 40% of ME/CFS patients showing elevated levels of IgA and IgM, respectively, in contrast to none in the control group. Moreover, it has been noted that IgA levels correlate with the severity of the disease.[33] Additionally, increased bacterial components in the plasma of ME/CFS patients suggest heightened gut permeability. Giloteaux and colleagues propose that elevated endotoxin levels might compromise the epithelial barrier, allowing entry into the bloodstream, triggering an immune response and leading to systemic inflammation. The presence of higher levels of lipopolysaccharide in the bloodstream could be due to a greater abundance of Gram-negative bacteria in the intestine, as their outer membrane contains this bacterial endotoxin, often linked with gut dysbiosis.[10,63] Nagy-Szakal and associates also observed raised plasma ceramines levels, suggesting these might result from increased lipopolysaccharide hydrolysis. They hypothesized that elevated ceramines could induce toxic responses in various cell types including gut epithelial cells; potentially impairing the epithelial barrier and further increasing gut permeability.[68] Notably, higher ceramines levels have been identified in other chronic conditions such as IBS, diabetes, cardiomyopathy, and atherosclerosis.[68-70] An additional factor contributing to heightened intestinal permeability could be the elevated by-products resulting from the fermentation of amino acids to generate Short-Chain Fatty Acids (SCFAs).[42] Furthermore, there has been a noted decrease in the presence of bacteria that produce SCFAs, particularly those that generate butyrate, such as *Faecalibacterium*, *Roseburia* (belonging to the *Firmicutes phylum*), and certain *Bacteroides* species.[10,19,42] This observation has been consistently made across various studies involving patients with ME/CFS. SCFAs, including butyrate, are byproducts of bacterial fermentation and play crucial roles in the communication between the gut and brain.

Butyrate serves as the primary energy source for colonocytes and is thought to be a vital component in managing the neuroimmunoendocrine system. These fatty acids contribute to gut health by exerting anti-inflammatory properties and improving the function of the intestinal epithelial barrier.[71] A study utilizing high-throughput sequencing demonstrated that well-conditioned individuals exhibit not only elevated fecal butyrate concentrations but also a correlation with enhanced physical fitness levels, notably higher VO2 max values, and increased diversity in gut microbiota. Particularly, the presence of butyrate-producing microorganisms was linked to superior fitness levels and a corresponding decrease in lipopolysaccharide biosynthesis in these fit subjects. Typically, elevated blood lipopolysaccharide triggers a significant inflammatory response; however, reduced lipopolysaccharide levels due to regular physical activity might contribute to diminished inflammation in physically active individuals.[25,43] When relating these findings from a healthy cohort to the clinical manifestations of ME/CFS, it becomes plausible that the observed scarcity of butyrate-producing bacteria in ME/CFS patients could stem from a decrease in SCFAs, potentially leading to PEM which then perpetuates a cycle of inactivity. This inactivity may further exacerbate the increase of lipopolysaccharide levels in ME/CFS patients. Conversely, it is conceivable that the chronic inactivity seen in ME/CFS could be a direct consequence of the illness itself, which over time might result in decreased SCFAs production. Another perspective might consider the depletion of SCFAs as an indirect outcome of the disease, where SCFAs-producing bacteria are suppressed by an overgrowth of D-lactate producing bacteria, which have been noted at elevated levels in ME/CFS patients and have been subject to prior investigations.[46] Contrary to the butyrate deficiency theory, a particular study identified a notable rise in fecal concentrations of butyrate, isovalerate, and valerate in ME/CFS specimens. This increase in fecal SCFAs levels was associated with heightened bacterial fermentation. The researchers proposed that these metabolic changes could be due to an increased gut pH or from the gut dysbiosis.[42] Additionally, it's worth noting that SCFAs can sometimes exert neurotoxic effects.[72] Another theory for the elevated fecal SCFAs levels could involve a malabsorption issue. It is important to recognize that fecal SCFAs excretion does not fully represent the actual SCFAs concentration and production within the gut; thus, analysis should also include serum levels.[73,74] To date, no studies have measured butyrate levels in serum. Interpreting these findings requires caution due to the potential for multiple direct and indirect causes. For instance, ME/CFS patients often undergo medication treatments and are limited in their physical activities, which could indirectly influence their gut microbiota composition. To establish causality, longitudinal studies spanning extended periods, ideally starting before the disease onset, are crucial. These studies should consider factors like medication use and physical activity levels as they might confound the results.[11,75] As another possible mechanism, some researchers have suggested that an increase in D-lactic acid might stem from enhanced intestinal colonization by Gram-positive bacteria, such as *Enterococci* and *Streptococci*, which may lead to reduced intestinal pH, increased gut permeability, systemic inflammation, immune activation, and oxidative stress.[25,43] Despite this theory, investigations targeting the bacterial overgrowth with antibiotics and probiotics have not demonstrated improvements in fatigue symptoms, casting doubt on the role of D-lactate. Furthermore, discrepancies between cerebrospinal fluid lactate levels and fecal lactate levels highlight an incomplete understanding of intestinal lactate metabolism's impact on ME/CFS patients.[25,42,76] Additionally, recent research on the etiology of ME/CFS suggests an abnormal metabolism of tryptophan, which is converted into kynurenine via the enzyme Indoleamine-2,3-Dioxygenase (IDO).[77-83] This enzyme, expressed in antigen-presenting cells, is pivotal as it metabolizes about 95% of tryptophan, with the remaining 5% converted into serotonin and melatonin. The kynurenine pathway, regulated by IDO, plays critical roles in the immune system by acting as an immunoregulator and immunosuppressor. IDO is enhanced by proinflammatory cytokines, such as IFN-γ, as well as IFN-α, TNF-α, and lipopolysaccharide during infections and inflammations. Although high IDO levels seem to relate to disease severity by activating regulatory T-cells and suppressing effector T-cell function through tryptophan degradation to kynurenine, the implications for meaningfully treating or diagnosing diseases such as ME/CFS are still under investigation.[84-87] Robert Phair's team has put forth a "metabolic trap hypothesis" suggesting that ME/CFS patients experience insufficient kynurenine production due to gene mutations in IDO isoforms, especially IDO-2.[78] This results in elevated tryptophan levels and impaired functions of the CNS, gastrointestinal, immune systems, and energy metabolism. In their study with ME/CFS patients, they found numerous gene mutations in IDO-2, and these correlated with the severity of ME/CFS symptoms. The lack of IDO-2 enzyme activity hinders tryptophan's conversion to kynurenine, aligning with typical pathological states of ME/CFS. Elevated tryptophan and reduced kynurenine were confirmed in these patients. Disruption in serotonin and melatonin pathways due to this blockage is linked to ME/CFS symptomatology. Additionally, insufficient Nicotinamide Adenine Dinucleotide (NAD+) synthesis from this metabolic disruption might explain the condition's hypometabolic phenotype. Elevated tryptophan levels fail to protect intestinal integrity against lipopolysaccharide-induced damage, unlike lower kynurenine levels.[78,88] The "metabolic trap hypothesis" suggests potential immunological and metabolic mechanisms involved in ME/CFS, emphasising the role of serotonin and tryptophan metabolism, with impacts on patients' microbiomes. Serotonin acts as a neurotransmitter in the central nervous system and a hormone in gut-brain communication, while tryptophan undergoes metabolism via serotonin, kynurenine, melatonin pathways, and through gut microbiota into indole derivatives. The function of the enzyme IDO is crucial here; decreased IDO activity can disrupt tryptophan fermentation and influence the gut microbiome. This disruption can lead to an impaired intestinal mucosal barrier, increase endotoxin translocation, and cause chronic inflammation—all factors associated with ME/CFS. Changes in these biochemical pathways

highlight their importance in understanding disease mechanisms and potential therapeutic targets for ME/CFS patients.[89-91] Recent studies in ME/CFS explore the potential increase in kynurenine production as opposed to the metabolic trap hypothesis suggesting decreased levels. The imbalance between tryptophan depletion and kynurenine generation, due to elevated IDO activity triggered by an immune response, is marked by the Kynurenine and Tryptophan (KYN/TRP) ratio. This ratio serves as an indicator of IDO activity and cellular immune response. High IDO levels are linked with chronic inflammation, supporting increased kynurenine production theories. Elevated KYN/TRP ratios and neuroactive metabolites like quinolinic acid, observed in multiple disorders, parallel symptoms found in ME/CFS such as heightened sensitivity and central sensitization. Additionally, viral infections like Epstein-Barr virus activating IDO to convert tryptophan to kynurenine support this hypothesis.[92-95] Altogether, these results indicate that tryptophan and its derivatives could play a significant role in influencing the gut microbiome, as well as the activation of the gut mucosal immune system and its interactions with the host, including the immune response.[90,96-98] However, recent clinical investigations indicate that altered immunity and kynurenine metabolism likely initiate fatigue in ME/CFS rather than sustaining it over time.[77] Recent evidence has also explored the potential link between antibiotic use and the development of ME/CFS. It has been noted that altered microbiota in patients with ME/CFS can be affected by antibiotics, yet no studies have specifically examined antibiotic intake as a trigger for ME/CFS. Many ME/CFS patients have a history of frequent infections, often treated with antibiotics, which might alter the microbiome and influence susceptibility to the syndrome.[11,99-102] This suggests that frequent antibiotic use could change intestinal microbiota, potentially impairing the production of anti-inflammatory metabolites or fostering conditions like D-lactic acidosis due to an increase in D-lactate-producing bacteria.[42,43,76,103,104] Women are more frequently diagnosed with ME/CFS, which may be linked to their higher antibiotic exposure compared to men.[105,106] Additionally, antibiotics might contribute to oxidative stress through the production of Reactive Oxygen Species (ROS), aligning with findings of elevated ROS levels in ME/CFS patients.[107-109] In contrast to some theories, antibiotics have been considered as a potential treatment for ME/CFS to address the overgrowth of certain bacterial species. A pilot study by Jackson and colleagues found that antibiotic treatment improved sleep, likely due to decreased levels of lactic acid-producing bacteria. They suggested that better sleep quality might result from a more balanced microbiome with reduced Gram-positive bacteria, consequently lowering proinflammatory cytokines.[24] Additionally, Wallis and colleagues observed improvements in neurological symptoms, including sleep quality, following a four-week combined antibiotic and probiotic treatment. However, this treatment did not alleviate fatigue symptoms associated with ME/CFS.[25] These findings indicate a possible microbiome-related pathway to enhance certain symptoms of the condition while highlighting the complexity of treating fatigue specifically.[24,25]

Potential therapeutic approaches targeting gut health in CFS/ME

Emerging therapeutic approaches targeting gut health in ME/CFS underscore the importance of the microbiota-gut-brain axis in managing this complex condition. Research indicates that dysbiosis in individuals with ME/CFS is associated with heightened fatigue and cognitive difficulties, prompting interest in interventions such as probiotics, prebiotics, dietary adjustments, and Fecal Microbiota Transplantation (FMT) to restore microbiome balance.[2] The normalization of gut microbiota through microbial treatments could potentially alleviate symptoms by enhancing immune function and reducing inflammation.[2] Additionally, the exploration of synbiotics highlights the need for comprehensive strategies that address both digestive health and neuropsychiatric symptoms.[4] Current evidence suggests that modifications in the gut microbiome, particularly decreases in beneficial butyrate-producing bacteria, may contribute to cognitive impairments commonly reported in ME/CFS patients.[7] As research progresses, it becomes increasingly clear that a nuanced understanding of gut health is vital for developing effective, multidisciplinary treatment modalities for ME/CFS (see Figure 1).

Probiotics and their potential benefits

The emerging role of probiotics in the management of ME/CFS holds significant promise for addressing the complex interplay between gut health and neurocognitive symptoms. Probiotics, which are live microorganisms that confer health benefits when consumed, may help restore gut microbiome balance, potentially alleviating symptoms associated with dysbiosis often observed in ME/CFS patients.[4] Two systematic reviews assessed the efficacy of probiotics in treating ME/CFS, but found limited and inconsistent data, including only two studies each due to variable outcomes and poor quality research.[56,111] A small cohort demonstrated significant increases in Bifidobacteria and Lactobacillus levels after probiotic intake compared to a placebo.[27] Groeger's rare RCT indicated decreased inflammatory markers, such as CRP and TNF-a, in ME/CFS patients following *Bifidobacterium infantis* consumption.[112] Another study by Sullivan suggested an improvement in anxiety through probiotics containing *Lactobacillus* and *Bifidobacterium*, although anxiety is not a core ME/CFS symptom, and the study had only 15 participants.[26] Additionally, a non-controlled pilot study with 13 ME/CFS patients reported enhanced well-being and reduced oxidative and inflammatory parameters after probiotic consumption.[113] Overall, while some positive outcomes were noted, the research is limited by small sample sizes and methodological inconsistencies. All in all, research on the microbiome's potential as a treatment target for ME/CFS shows promise, but no direct, long-term improvements in PEM or physical activity levels have been confirmed.[1] Corbitt and colleagues' systematic review highlights the current lack of evidence supporting probiotics for gastrointestinal symptoms in ME/CFS patients, mainly due to poor study quality and conflicting outcomes.[56] This aligns with a Nature evaluation indicating insufficient impact assessments

and approved therapy recommendations for probiotics, particularly as biased industry-driven studies yield inconsistent results.[114] Recent suggestions propose using biopsies instead of stool samples to better understand gut health, considering individual variability and gut microbiota resilience. In other neuroimmunological diseases like multiple sclerosis, probiotics seem to modulate immune responses by increasing anti-inflammatory mediators. Additionally, SCFA supplementation emerges as a novel area of interest; depleted SCFA-producing bacteria in patients may lead to inflammatory states relevant in such diseases. Clinical studies with multiple sclerosis patients show propionic acid supplementation boosts Treg cells and interleukin-10 levels, potentially relevant findings for ME/CFS treatment strategies as well.[115-123]

Prebiotics and their potential benefits

Prebiotics are indigestible carbohydrates that nourish gut microbiota, primarily including fructo-oligosaccharides and galacto-oligosaccharides. They are broken down by bacteria into SCFAs, which benefit both gastrointestinal and systemic health.[1] By selectively enhancing beneficial bacteria and altering gut microbiota composition and function, prebiotics show promise as supportive treatments for disorders like IBS, Crohn's disease, autism, obesity, and colorectal cancer.[3-7] Research demonstrates that various oligosaccharides can correct microbiota imbalances by fostering *Lactobacilli* growth, decreasing *Proteobacteria*, and reducing the *Firmicutes/Bacteroidetes* ratio in obese rodents.[3] These studies also show improvements in gut barrier integrity and reduced systemic inflammation. Rodents consuming prebiotics such as bovine milk oligosaccharides and oligofructose-enriched inulin experienced lowered plasma lipopolysaccharides, serum pro-inflammatory cytokines, intestinal inflammation, and enhanced tight-junction integrity.[1-8] Collectively, these findings suggest that prebiotics could help manage conditions like ME/CFS involving dysbiosis and chronic inflammation.

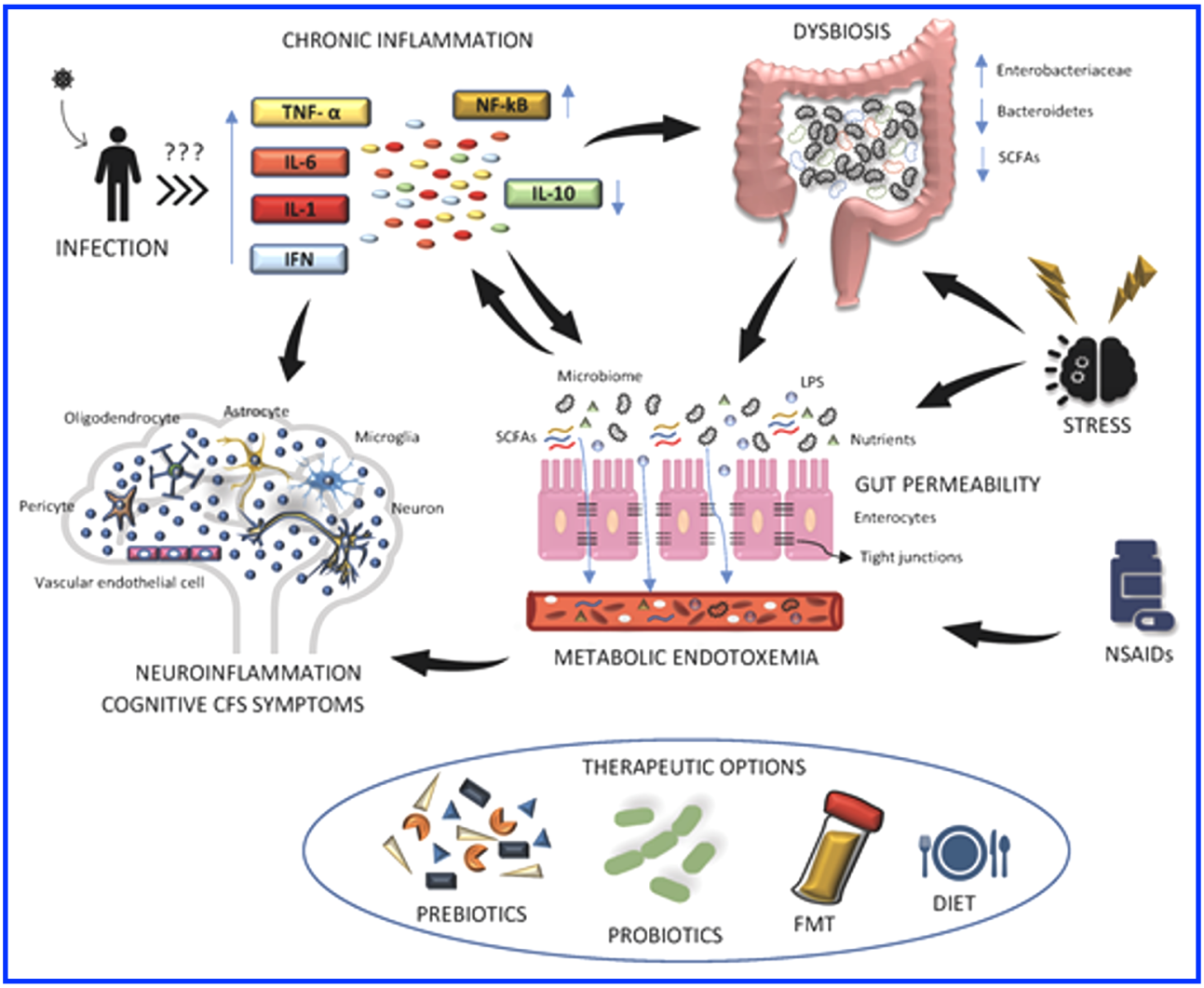

Figure 1. *Mechanisms linking chronic inflammation, dysbiosis, and therapeutic options for cognitive symptoms in ME/CFS (Adapted from Varesi* et al. *2021[3]).*

However, more clinical studies are required to confirm these potential benefits.

Dietary interventions and their impact on gut microbiota

Fasting and fasting mimicking diets may positively impact the immune system, enhancing chronic inflammation regulation without compromising defense against infections. They could inhibit hyperinflammation by targeting the NLRP3 inflammasome, modulating type 2 immune responses, decreasing pro-inflammatory T helper-17 cells in the gut, and exerting anti-inflammatory effects through various pathways.[124-129] These diets could also interact with circadian rhythms and mitochondrial function, which are implicated in ME/CFS pathophysiology.[130-131] As mitochondrial dysfunction is crucial in ME/CFS, interventions like caloric restriction, fasting, and ketogenic diets aim to protect mitochondria and potentially alleviate symptoms.[132,133] Ketogenic diets may bypass glycolytic blockages, providing an alternative energy substrate for cells and showing promise in managing fatigue across conditions like multiple sclerosis, Parkinson's disease, and cancer-related fatigue. However, due to potential risk of bias and adverse effects during initial weeks, these regimens should be undertaken cautiously under medical guidance. Their mechanisms are partly mediated by the gut microbiome but remain incompletely understood.[134-145] Altogether, A systematic review found no evidence supporting the benefits of elimination or modified diets for patients with ME/CFS.[146] This conclusion also applied to nutritional supplements, though they might help alleviate some specific symptoms experienced by ME/CFS patients.[146-148]

FMT as a treatment option

FMT has emerged as a compelling treatment option for addressing gut dysbiosis associated with ME/CFS. As research increasingly highlights the critical interplay between gut health and neurological function, FMT offers a means to potentially restore microbial diversity and improve clinical outcomes. Studies indicate that patients with ME/CFS frequently experience gastrointestinal symptoms, and alterations in gut microbiota composition, specifically reduced diversity and dysbiosis, are common.[5] By re-establishing a healthier gut microbiome, FMT may mitigate chronic inflammation and enhance intestinal barrier integrity, thus addressing both gastrointestinal and neurological symptoms.[7] Additionally, the overlap between ME/CFS and Long coronavirus disease 2019 suggests that FMT might also alleviate fatigue and cognitive impairments linked to these conditions.[4] However, while preliminary findings are promising, rigorous clinical trials are essential to ascertain the efficacy and safety of FMT for ME/CFS patients.[1] Emphasizing holistic approaches, the study of FMT underscores the necessity for integrative therapies in chronic diseases characterized by complex etiologies.[3]

Additional approaches mediated by the gut microbiome

Thiamine, essential for the citrate cycle and glycolysis, is partially produced by gut bacteria like Bacteroides, reduced in ME/CFS patients.[149] *Faecalibacterium*, also reduced in these patients, needs thiamine for growth.[10,19,45,150] Though microbial thiamine production is minimal, it influences the competitive microbial environment.[151] With limited therapeutic options for ME/CFS beyond dietary and pharmaceutical interventions, non-pharmaceutical treatments have been explored. Notably in China, acupuncture and moxibustion have been studied for their potential to alleviate fatigue symptoms.[152] A recent randomized controlled trial suggested improvements in fatigue with these therapies linked to changes in intestinal microbiome; however, possible bias exists due to challenges such as lack of blinding and subjective fatigue assessments.[153] Another non-pharmacological option is ginseng administration, shown to reduce fatigue in ME/CFS and other conditions through potentially gut microbiome-mediated pharmacokinetics.[154] Although indirect and not conclusive, these findings indicate a possible connection between intestinal microbiome changes and fatigue reduction in ME/CFS.[155,156]

Discussion

Challenges and limitations of current therapeutic strategies

The current therapeutic strategies for ME/CFS face numerous challenges and limitations, particularly as the field grapples with a complex interplay of biological and psychological factors. The absence of definitive biomarkers complicates diagnosis and has led to inconsistencies in treatment approaches, leaving many patients dissatisfied with conventional therapies like cognitive-behavioral therapy and graded exercise, which have mixed results in efficacy.[5] Furthermore, emerging evidence linking gut dysbiosis to symptom severity highlights potential therapeutic avenues involving probiotics and dietary interventions; however, substantial variability in study designs and outcomes restricts the ability to draw robust conclusions.[3,4] Moreover, the multifactorial nature of ME/CFS necessitates a more nuanced understanding of its pathogenesis, including interactions between genetic, environmental, and microbial factors.[2] Thus, ongoing research is critical to refine these strategies while addressing methodological limitations inherent in the current studies.[1,7]

Future directions in research

Future directions in research on the microbiota-gut-brain axis in ME/CFS hold great promise for elucidating the underlying mechanisms of this complex condition. Investigating the gut microbiomes alterations, including the notable dysbiosis observed in ME/CFS patients, may uncover potential therapeutic targets, such as probiotics and dietary interventions that could ameliorate symptoms like fatigue and cognitive dysfunction.[4] Furthermore, as emerging evidence links gut health with neuropsychiatric symptoms, exploring the effects of psychobiotic treatments may provide new avenues for intervention.[3] Additionally, addressing the methodological inconsistencies in previous studies is vital, suggesting a need for standardized diagnostic criteria and

larger, longitudinal studies that encompass diverse patient populations.[1,6] Understanding the intersection of immune function, gut microbiota, and ME/CFS pathogenesis will be crucial for developing effective personalized treatment strategies and enhancing overall patient outcomes.[2,7,8]

Need for standardized diagnostic criteria in studies

The disparate findings across studies investigating the microbiota-gut-brain axis in ME/CFS highlight the urgent need for standardized diagnostic criteria. Current research often employs varying definitions of ME/CFS, which complicates comparisons and may obscure true relationships between gut dysbiosis and symptomatology. For instance, the lack of consistency in diagnostic protocols has resulted in differential reporting of comorbid conditions and symptom severity among participants, undermining the validity of conclusions drawn from these studies.[6] Establishing uniform criteria would not only facilitate reliably replicating results but also enhance our understanding of shared pathways in related conditions such as Long coronavirus disease 2019.[4] The identification of specific microbial profiles and metabolic disturbances in ME/CFS patients necessitates rigorous methodologies to inform treatment strategies and improve outcomes, making standardized diagnostic criteria critical for future advancements in this emerging field.[1,2]

Importance of longitudinal studies to establish causality

Longitudinal studies play a crucial role in establishing causality within the emerging field of the microbiota-gut-brain axis as it relates to ME/CFS. These studies allow researchers to observe changes over time, which can help identify whether alterations in gut microbiota precede the onset of ME/CFS symptoms or result from the condition itself. This distinction is essential, as highlighted by the correlation of gut dysbiosis with increased intestinal permeability and inflammation noted in previous research.[7] Moreover, longitudinal designs facilitate the tracking of various confounding factors, such as infections and stressors, that may contribute to symptom development.[1] The discrepancies in current studies regarding microbiome composition further underscore the necessity of consistently applying longitudinal methodologies to clarify the biological mechanisms at play, thus solidifying the potential relationship between microbial health and ME/CFS symptomatology.[5] Through rigorous evaluation over extended periods, these studies can contribute significantly to refining treatment strategies that target gut health as part of a holistic approach to managing ME/CFS.[4]

Exploration of specific microbial metabolites in ME/CFS

The exploration of specific microbial metabolites in ME/CFS reveals significant insights into the potential role of gut dysbiosis in the pathogenesis of this complex condition. Dysregulated microbial profiles, characterized by decreased diversity and altered metabolic pathways, may contribute to the debilitating symptoms experienced by individuals with ME/CFS. Research indicates that patients exhibit reduced levels of beneficial SCFA, particularly butyrate, which are critical for maintaining gut barrier integrity and modulating inflammation.[7] Additionally, metabolites such as glutamic and argininosuccinic acids have been shown to be elevated in ME/CFS patients, raising concerns about their contribution to neuroinflammation and cognitive dysfunction.[2] Evidence supports the idea that gut-brain communication may be disrupted due to these microbial imbalances, emphasizing the need for targeted interventions like probiotics and dietary modifications to restore homeostasis and alleviate symptoms.[4,5] Understanding these metabolic abnormalities opens pathways for innovative treatment strategies aimed at improving patient outcomes.[8]

Investigating the interplay between genetics and gut microbiota

The investigation into the interplay between genetics and gut microbiota offers critical insights into the etiology of ME/CFS. Research indicates that genetic predispositions may influence the composition of gut microbiota, potentially affecting immune responses and symptom severity in ME/CFS patients. Alterations in microbial diversity have been consistently documented, with studies observing a decline in beneficial microbial populations like *Bifidobacteria* and *Lactobacillus*, which are linked to improved mental health outcomes.[6] Moreover, associations between gut dysbiosis and various metabolic pathways suggest that genetic factors might modulate microbial responses to environmental triggers, further complicating ME/CFS pathogenesis.[4] Understanding this dynamic relationship could pave the way for targeted interventions, leveraging specific probiotic therapies to restore microbial balance and ameliorate symptoms resulting from gut-brain axis disturbances.[2] Thus, disentangling the genetic influences on gut microbiome composition represents a promising avenue for future research.[1]

Potential for personalized treatment approaches based on microbiome profiles

The potential for personalized treatment approaches based on microbiome profiles in ME/CFS marks a significant advancement in understanding and managing this complex condition. Growing evidence indicates that dysbiosis of the gut microbiome may play a critical role in ME/CFS pathology, with specific bacterial populations influencing symptom severity and metabolism.[7] By analyzing the unique microbiome profiles of individuals, clinicians could tailor interventions such as probiotics, synbiotics, or dietary modifications to restore microbial balance and alleviate symptoms.[4] Additionally, understanding the interactions between gut microbiota and neurological function could inform more comprehensive treatment options that address both physical and cognitive challenges.[8] Despite the promising avenues for personalized therapies, further research is necessary to establish standardized protocols and clarify the mechanisms by which microbiome alterations impact the health of ME/CFS patients.[1,5] Ultimately, this personalized approach toward treatment may enhance patient outcomes and improve quality of life.

Conclusions

In conclusion, the exploration of the microbiota-gut-brain axis offers significant insights into the pathophysiology of ME/CFS, highlighting the intricate interplay between microbial communities, immune responses, and neurological function. As research uncovers distinct dysbiotic profiles among ME/CFS patients, it becomes increasingly crucial to consider how alterations in gut microbiota may contribute to the symptomatology of this complex condition. The evidence supporting the relationship between gut health and cognitive and physical fatigue underscores the need for targeted interventions, including dietary modifications and probiotic therapies, which could potentially alleviate symptoms experienced by sufferers. However, the field remains in its infancy, necessitating further rigorous studies to establish causative links and develop comprehensive treatment strategies. Ultimately, a deeper understanding of the microbiota-gut-brain axis could pave the way for innovative and effective therapeutic approaches in managing ME/CFS, transforming the landscape of care for affected individuals.

Contributions

AMAES, IIA, SU, SB, BCG, AS, KV, RP, MKa, and MKh: Conceptualization, data collection, writing-original draft preparation, and writing-review and editing. The authors have read and agreed to the published final version of the manuscript.

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