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Review Article

Gut microbiome dysbiosis in traumatic brain injury: Implications for neurological recovery and microbiome-targeted interventions

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Abstract

Traumatic brain injury (TBI) is a major cause of mortality and long-term neurological disability worldwide. In addition to primary brain damage, TBI induces complex secondary pathophysiological responses involving neuroinflammation, systemic immune dysregulation, gastrointestinal dysfunction, and alterations in the microbiota–gut–brain axis. Increasing attention has therefore been directed toward the role of gut microbiome dysbiosis in the progression of secondary brain injury and its potential as a therapeutic target. This narrative review aimed to synthesize current evidence regarding the relationship between TBI and disruption of the microbiota–gut–brain axis, with particular emphasis on the mechanisms underlying gut microbiome dysbiosis and its contribution to secondary brain injury. The review discusses neuroinflammatory responses, alterations in intestinal barrier integrity, enteric and autonomic nervous system involvement, vagal signaling, and microbiota-derived pathways implicated in brain–gut communication after TBI. In addition, the therapeutic rationale, available evidence, translational considerations, and current limitations of microbiome-targeted approaches, particularly probiotics and fecal microbiota transplantation, are critically discussed. This review provides an updated framework for understanding the microbiota–gut–brain axis in TBI and identifies areas requiring further mechanistic and clinical investigation.

Keywords: Traumatic brain injury, gut microbiome, microbiota–gut–brain axis, probiotics, fecal microbiota transplantation

Introduction

Traumatic brain injury (TBI) is a common neurosurgical cause of death and disability worldwide and comprises a critical global health problem that produces lifelong impairment and death; a proportion of patients die early during hospitalization [1]. TBI is a complex condition with a substantial impact on multiple organ systems, including the gastrointestinal (GI) tract, liver, kidneys, and lungs [2]. The transition from primary to secondary brain injury involves a heterogeneous cascade of pathophysiological processes—excitotoxicity, electrolyte imbalance, oxidative stress, systemic inflammation, autophagy, apoptosis, and cerebral edema—that are increasingly linked to disruption of the microbiota–gut–brain axis after TBI [3]. The concept of a brain–gut axis emerged in the 1980s from studies of gastrointestinal endocrine hormone signaling within neurons and brain cells [4]. The microbiota–gut–brain axis is a major bidirectional signaling route between the CNS and the GI tract that integrates afferent and

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efferent signaling, as well as the regulation of the autonomic nervous system, the enteric nervous system, and immune activation [5,6].

Consistent with this system, previous studies have reported a strong link between TBI and gastrointestinal dysfunction [7,8]. Prolonged microglial activation after a single moderate-to-severe TBI or repeated mild TBI drives inflammation that leads to neuropathological and neurobehavioral changes [9]. TBI also triggers a stress response that significantly affects the well-documented autonomic regulation of gastrointestinal function [10,11]. Changes in the gut microbiome are common after TBI and in neurodegenerative disorders, prompting mechanistic studies of the role of specific microbiota and their metabolites in secondary brain injury and as prospective therapeutic targets [12].

Whereas earlier reviews have primarily addressed the mechanistic basis of this relationship, they included studies published only up to 2024 or early 2025. Additionally, previous reviews regarding FMT have largely focused on its therapeutic application in gastrointestinal disorders, with limited focus on secondary brain injury. The present review integrates the most recent preclinical and clinical evidence and focuses on the translational readiness of two microbiome-targeted interventions—probiotics and FMT—for limiting secondary brain injury. Accordingly, we provide an updated synthesis of the relationship between TBI and gut microbiome dysbiosis and its implications for future microbiome-targeted therapy.

Traumatic brain injury and disruption of the microbiota-gut-brain axis

The Global Burden of Disease study reported 20.83 million new TBI cases worldwide in 2021, of which 56.63% were moderate or severe; East Asia had the highest regional burden, with 4.3 million cases, 69% of which were moderate or severe. TBI is clinically defined as an external physical force applied to the head that results in varying degrees of intracranial damage [13]. The principal mechanisms of injury are falls, road-traffic collisions, and violence [14]. In 2021, road-traffic collisions accounted for 1.19 million injury-related deaths and were the leading cause of mortality among children and young adults aged 5–29 years worldwide [15].

TBI is classified as mild, moderate, or severe using the Glasgow Coma Scale (GCS), which grades eye, verbal, and motor responses (severe 3–8; moderate 9–12; mild 13–15) [16]. Across studies incorporating all severities, mild TBI accounts for more than 80% of cases in most series [17]. Even mild TBI can cause persistent disability with long-lasting effects on health and quality of life, and recurrent mild TBI increases the risk of delayed neurodegenerative disease [18]. Severe TBI is a major risk factor for seizures and epilepsy; the ensuing processes—necrosis, axonal injury, apoptosis, demyelination, microgliosis, inflammation, microhemorrhage, and oxidative stress, followed by neurodegeneration, regeneration, revascularization, and remodeling—may drive the circuit changes underlying post-traumatic epilepsy [19]. Many of these processes are associated with TBI-induced disruption of the microbiota–gut–brain axis. Following TBI, blood–brain barrier disruption, neuroinflammation, oxidative stress, and immune dysregulation trigger systemic inflammatory responses that in turn increase intestinal permeability and promote gut dysbiosis [20].

Dysbiosis refers to a change in the composition of the gut microbiome with reduced diversity of commensal organisms [21]. The human body hosts trillions of microbes that form a complex ecosystem known as the human microbiome, and the GI tract harbors the highest microbial density of any anatomical site, estimated at more than 100 trillion organisms [22]. The composition and stability of the gut microbiome are strongly affected by multiple factors, including disruption of the microbiota–gut–brain axis after TBI [23]. Several preclinical studies have consistently demonstrated that TBI induces gut microbiome dysbiosis characterized by reduced microbial diversity and altered bacterial composition (**Table 1**). In a longitudinal rat model, mild TBI was associated with changes in 13 genus-level bacterial taxa, indirectly reflecting TBI-induced dysbiosis [24], and a further preclinical study demonstrated gut dysbiosis as early as 2 hours after moderate TBI in rats [25].

Table 1. Preclinical studies on the effect of traumatic brain injury on the gut microbiome

Study (year)	Animal model	TBI model	Gut microbiota assessment	Sampling time	Key findings	Reference
Bansal *et al.* (2010)	Mice	Traumatic brain injury (impact model)	Distal-ileum sampling for GFAP and TNF-α; FITC-dextran permeability assay	Acute phase post-injury	Increased intestinal permeability; altered intestinal GFAP and pro-inflammatory cytokine expression.	[26]
Ma *et al.* (2017)	Mice (C57BL/6J; male; adult)	Controlled cortical impact (CCI)	Enteric infection with *Citrobacter rodentium* at 28 d post-TBI	Acute (24 h) to chronic (PID 12 after infection)	Chronic morphopathological changes in colon; TBI altered colonic homeostasis; subsequent infection worsened brain lesion and neuroinflammation.	[9]
Nicholson *et al.* (2019)	Adult male C57BL/6 mice	Controlled cortical impact (CCI) to induce moderate traumatic brain injury	16S rRNA gene sequencing (V4 region) of fecal samples	Pre-TBI and at 2 hours, 1 day, 3 days, and 7 days post-injury	Significant alterations in the gut microbiome were detected as early as 2 hours post-TBI and persisted through 7 days. The study suggests that microbiome changes could serve as a novel biomarker for staging TBI severity and predicting functional outcomes.	[25]
Matharu *et al.* (2019)	Rats	Repeated mild TBI	Jejunal microbiome sampling; 16S rRNA sequencing	Longitudinal repeated-injury timeline	Altered microbial diversity in the jejunum; significant increase in *Helicobacter*.	[71]
Celorrio *et al.* (2021)	Mice (C57BL/6J; male; 6–8 weeks)	Controlled cortical impact (CCI)	Broad-spectrum antibiotics (VNAM) in drinking water to induce dysbiosis	3 d to 3 months post-injury	Antibiotics severely reduced richness and diversity; depletion of *Lactobacillus*, *Clostridium*, and *Bacteroides*; expansion of *Atopobium* and *Ruminococcus* in injured mice.	[28]
Taraskina *et al.* (2022)	Rats (Wistar; male; 3–4 months)	Focal brain injury (cortical impact)	Fecal pellet collection; 16S rRNA sequencing (V3–V4)	Days 0, 3, and 7 post-TBI	Substantial decrease in alpha-diversity (p=0.03); changes in abundance of 26 genera, with the most marked reduction in *Agathobacter*.	[23]
Wang *et al.* (2023)	Adult male Sprague-Dawley rats, weighing 250–300 g	Mild traumatic brain injury (mTBI) induced using a modified Feeney weight-drop contusion model	16S rRNA sequencing of the V3-V4 hypervariable regions from oral cavity and fecal samples	12 distinct time points: sham (0 h), and 0 h, 2 h, 6 h, 12 h, 24 h, 2 d, 3 d, 5 d, 7 d, 10 d, and 14 d post-injury	Temporal analysis highlighted the 2-hour post-injury period as a critical window for detecting microbiota changes and estimating injury timing. Oral microbial diversity significantly decreased at 6 hours, whereas fecal microbial diversity declined at 2 days after injury. These findings suggest that microbiota succession may serve as a promising objective approach for mTBI identification and post-injury time estimation in forensic applications.	[30]
Stamper *et al.* (2025)	Rats (male and female; adult)	Lateral fluid-percussion injury (LFPI)	Longitudinal fecal sampling; 16S rRNA sequencing	Pre-injury to day 30 post-injury	Limited effect on overall diversity; significant changes in 13 genera (11 sex-specific); increase in SCFA-producing bacteria (e.g., Blautia, Faecalibaculum).	[24]
Rewell *et al.* (2025)	Mice (C57BL/6J; male and female; adult)	Experimental TBI (CCI)	Post-injury LPS immune challenge; shallow shotgun sequencing	5 d post-TBI (24 h post-LPS/vehicle)	TBI+LPS reduced alpha-diversity; increased Curtobacterium and Proteus; concurrent decrease in Prevotella.	[31]
Zhang *et al.* (2026)	Rats (Sprague-Dawley; male; 280–320 g)	Weight-drop model (mTBI)	Time-series fecal and brain-tissue collection; 16S rRNA sequencing (V3–V4)	16 h, 1 d, 3 d, 5 d, 7 d, 14 d, 2 months	Multi-level dysbiosis; decline in Lactobacillus; enrichment of Staphylococcus (1 d), Aeromonadaceae (3 d), and Streptococcus (5 d).	[32]

16S rRNA: 16S ribosomal RNA; FITC-dextran: fluorescein isothiocyanate-dextran permeability assay; GFAP: glial fibrillary acidic protein; LPS: lipopolysaccharide; PID: post-injury days; SCFA: short-chain fatty acids; TBI: traumatic brain injury; TNF-α: tumor necrosis factor-alpha.

This dysbiosis further increases neuroinflammation through several connected pathways, including microbiota-derived metabolites, inflammatory cytokines, and vagal signaling [33,34]. TBI can disrupt autonomic regulation of gastrointestinal function, impair intestinal epithelial integrity, and increase intestinal permeability, consequently enabling translocation of microbial-derived inflammatory mediators—particularly lipopolysaccharide (LPS)—into the systemic circulation [28]. This promotes systemic immune activation and further stimulates microglia, bringing about an exaggerated and persistent neuroinflammatory response after TBI [35]. Experimental studies indicate that the interaction between TBI and LPS reaches beyond the brain to the gut–immune axis: TBI–LPS mice showed reduced fecal microbial diversity and altered composition, including changes in *Proteus*, *Curtobacterium*, and *Prevotella* [31], and these alterations were associated with sub-acute neurobehavioral and immune-related outcomes [32,36]. Furthermore, LPS injection in rats with TBI induced a severe inflammatory response and exacerbated secondary brain damage [37]. Together, these outcomes support the concept that dysbiosis arising from disruption of the microbiota–gut–brain axis after TBI may contribute to secondary brain injury.

Mechanisms of gut microbiome dysbiosis after TBI

Neuroinflammatory response

After TBI, the primary mechanical injury is followed by secondary cascades involving necrotic cell death, glutamate excitotoxicity, mitochondrial dysfunction, free-radical formation, hypoxia-related metabolic changes, and neuroinflammation. Secondary brain injury is a prolonged process involving interactions among neurons, astrocytes, microglia, infiltrating leukocytes, chemokines, and cytokines, producing a sustained pro-inflammatory CNS microenvironment [38]. Microglia are essential to this response, acting as the brain's resident immune cells and responding rapidly to tissue damage. After TBI, damaged cells release damage-associated molecular patterns (DAMPs), cytokines, and chemokines that activate microglia and recruit them to the injured area [39].

M1-like microglia predominate in the early pro-inflammatory, defensive response and are activated by stimuli such as LPS and interferon-gamma. Once activated, they produce pro-inflammatory cytokines—including interleukin-1 beta (IL-1β), interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α)—and chemokines such as CCL2, CXCL9, and CXCL10 (**Figure 1**). They also generate reactive oxygen species and express markers such as CD16, CD32, CD86, major histocompatibility complex class II (MHC-II), and inducible nitric oxide synthase (iNOS). Functionally, M1-like microglia contribute to host defense, pathogen elimination, phagosome acidification, iron restriction, and oxidative-mediator release; during the early phase of TBI, this response helps clear danger-associated signals and damaged cellular components [40].

By contrast, M2-like microglia are associated with anti-inflammatory regulation, tissue repair and remodeling, and recovery. Their activation is stimulated by interleukin-4 (IL-4) and interleukin-13 (IL-13), which promote an M2a-like phenotype involved in tissue repair, growth stimulation, and production of anti-inflammatory cytokines such as interleukin-10 (IL-10). Common M2a-like markers include arginase-1 (Arg-1), CD206 (mannose receptor), chitinase-like protein Ym1, and found-in-inflammatory-zone 1 (Fizz1), also known as resistin-like molecule alpha (RELM-α). M2c-like microglia are induced by IL-10, glucocorticoids, or uptake of apoptotic cells and are mainly involved in tissue remodeling and extracellular matrix deposition after inflammation subsides; M2c-like markers include CD163, CD206, transforming growth factor-beta (TGF-β), and sphingosine kinase-1 (Sphk-1) [41].

Nonetheless, it should be acknowledged that the M1/M2 classification is an oversimplified model, as microglial activation is increasingly recognized as a dynamic spectrum of functional states in vivo. The excessive or sustained microglial activation exacerbates neuroinflammation and contributes to the progression of secondary brain injury [35-37]. Sustained activation is driven by a continuous reciprocal interaction between brain injury, gut dysbiosis, and the systemic immune response arising from disruption of the bidirectional axis [42].

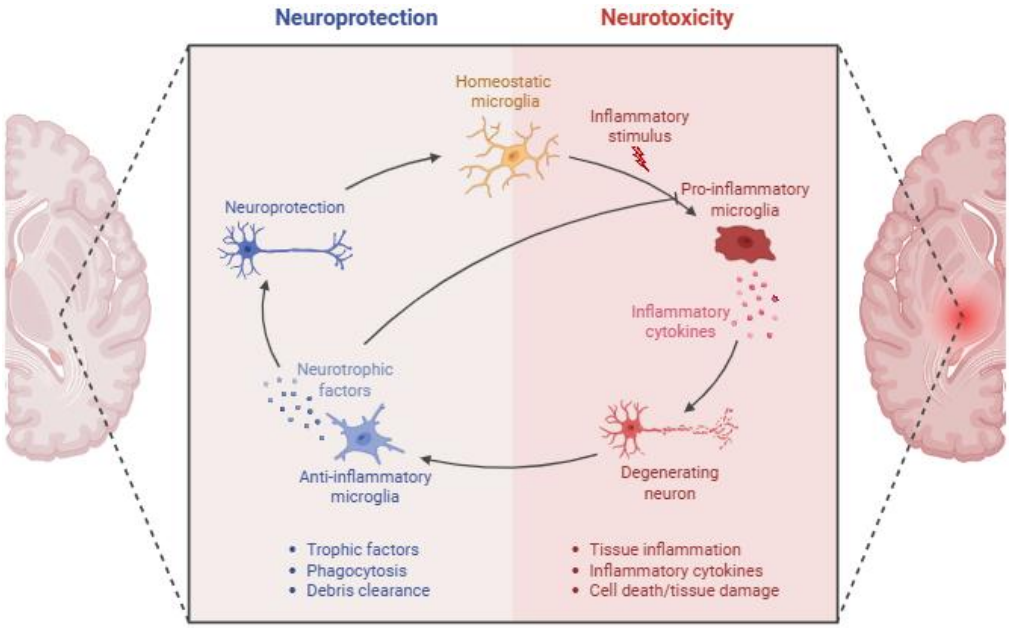

Figure 1. Roles of microglia in neuroinflammation. Homeostatic microglia initially respond to injury with protective functions, but persistent central and peripheral inflammatory signals after TBI can shift microglia toward a chronic pro-inflammatory state, leading to neuronal degeneration and secondary neurotoxicity.

Accordingly, dysbiosis and neuroinflammation after TBI should be understood as a self-reinforcing brain–gut–brain loop [43,28]. The initial brain injury triggers central inflammation and systemic stress responses; these impair gut-barrier integrity and microbiome composition; the dysbiotic gut then releases inflammatory microbial signals and reduces beneficial metabolites such as short-chain fatty acids (SCFAs), which normally help regulate immune balance and microglial function. As a result, microglia remain reactive, cytokine production increases, and secondary brain injury may be amplified [44]. Supporting this, an experimental medicine study demonstrated chronic microglial activation in brain regions associated with structural damage—particularly the cerebral white matter and thalamus—after TBI [45].

Enteric nervous system and vagus nerve

The GI tract is innervated by multiple components of the autonomic nervous system (ANS), comprising the sympathetic and parasympathetic nervous systems and the intrinsic enteric nervous system (ENS) located within the gut wall [46]. Histologically, the ENS is organized into two major plexuses: the myenteric plexus, situated between the longitudinal and circular muscle layers and controlling gastrointestinal motility, and the submucosal plexus, located in the submucosa and regulating secretion, absorption, mucosal activity, and intestinal blood flow [47]. Following TBI, central sympathetic and parasympathetic fibers relay impulses to the GI tract by synapsing with the ENS and releasing neurotransmitters such as catecholamines and acetylcholine. Sympathetic activity increases the effects of norepinephrine, causing gastrointestinal vasoconstriction and reducing mucosal blood flow. Due to TBI, sympathetic activity also stimulates mast cell activation and the release of pro-inflammatory mediators, causing mucosal injury by processes that include intestinal epithelial apoptosis and disruption of tight junctions via reduced expression of tight junction proteins such as ZO-1, claudin-5, occludin, and claudin-1. The result is increased intestinal mucosal permeability and enhanced bacterial translocation [48,49]. A preclinical study in rats demonstrated severe epithelial damage to the intestinal villi within 24 hours of injury, supporting a substantial effect of TBI on the GI tract through disruption of the microbiota–gut–brain axis [26,50].

Gut-to-brain communication is substantially mediated by afferent neural pathways—especially the vagus nerve—with most vagal fibers transmitting sensory information from the GI tract to the brain. These afferents are distributed throughout the gut, including the mucosal surface, and relay signals either via vagal projections to the brainstem or via spinal pathways

[51,52]. Indeed, approximately 90% of the fibers connecting the GI tract and the brain are vagal afferents, indicating that the brain more often acts as a receiver than a provider within the axis [50].

The vagus nerve (cranial nerve X) is a major component of the ANS and the principal pathway of parasympathetic regulation, serving as a key player in bidirectional sensory communication between the CNS and multiple organ systems, including the GI tract [53]. Physiologically, vagal afferents in the GI tract detect mechanical or chemical stimuli and transmit glutamatergic impulses to the nucleus tractus solitarius (NTS). The signal is then relayed to the dorsal motor nucleus of the vagus (DMV) in the brainstem, where vagal efferent neurons are located [54]. These efferents synapse onto parasympathetic postganglionic cholinergic neurons of the ENS, inducing functional responses that include increased GI tone as well as motility and stimulation of mucosal secretion [55]. Following TBI, disruption of the axis—including vagal dysfunction—is commonly characterized by reduced parasympathetic modulation, reduced vagal tone, and exaggerated sympathetic activation. Consequently, the GI tract is less efficiently regulated, leading to impaired motility, altered secretion, and, directly, gut dysbiosis [56]. An experimental study showed that TBI mice had higher levels of harmful bacteria such as *Escherichia–Shigella*, increased gut permeability, elevated LPS and TNF-α, and a severe neuroinflammatory response through activation of the Toll-like receptor 4 (TLR4) pathway; in the same study, vagus nerve stimulation augmented cognitive function and reduced neurological damage. This therapeutic approach aims to restore vagal tone and activate the cholinergic anti-inflammatory pathway, thereby attenuating neuroinflammation and preserving gut barrier integrity [57]. This evidence suggests that understanding the microbiota–gut–brain axis could guide future treatment strategies for TBI.

Promising targeted approach

Probiotics

The neuroinflammatory response is a dynamic process important for pathogen clearance and tissue repair after TBI, mediated by pro-inflammatory cytokines such as IL-1β, interleukin-6 (IL-6), and TNF-α [58]. A number of strategies target these mechanisms and modulate the gut microbiome, including probiotic supplementation. Probiotics are beneficial microbial supplements that maintain gut eubiosis and reduce pathogenic populations [29], restoring intestinal-barrier function by strengthening tight junctions, increasing mucus synthesis, regulating immune responses, producing beneficial metabolites, and suppressing pathogen adhesion and colonization [59]. A randomized, double-blind, placebo-controlled trial found that a seven-strain probiotic produced considerable improvements in inflammatory and immune parameters in patients with severe TBI, with substantial reductions in TNF-α, IL-1β, and Th17 cells and a significant improvement in GCS score [60]. Similarly, Tan *et al.*, in a prospective randomized single-blind study, reported favorable immunological changes in severe TBI: compared with controls, the probiotic group had significantly higher serum IL-12p70 on day 15 (p=0.042) and higher IL-12p70 and interferon-gamma (IFN-γ) on day 21 (p=0.023 and p=0.017, respectively), with significantly lower IL-4 and IL-10 on day 21 (p=0.017 and p=0.027, respectively), showing a shift from Th2 dominance toward Th1 activity; the probiotic group also had a shorter intensive care unit (ICU) stay [61]. Although probiotic supplementation has shown beneficial effects in severe TBI, the reported immunological mechanisms are not fully consistent across clinical trials. These differences may be related to probiotic strain, timing of administration, and pre-existing immune status. Therefore, the effects of probiotics should be considered in the context of dynamic immune change following TBI.

Serum C-reactive protein (CRP), a marker of systemic inflammation, decreased after probiotic supplementation [62], a finding echoed by Brenner *et al.* in a pilot randomized controlled trial [63]. Patients receiving probiotics also showed better nutritional status, lower inflammation, stronger immune responses, improved coagulation markers, better Acute Physiology and Chronic Health Evaluation II (APACHE-II) and GCS scores, faster bowel recovery, and fewer intestinal complications, supporting a protective effect on the gut with improved nutrient bioavailability, microbiome regulation, reduced inflammation, and enhanced

immunity [64-66]. A study reported that probiotics shifted the microbiome composition toward beneficial taxa (several members of the family Lactobacillaceae, including the genera Limosilactobacillus and Lactiplantibacillus) and reduced brain lesion volume and microglial activation, suggesting mitigation of TBI-induced neuroinflammation [67]. A randomized clinical trial also found that 14 days of seven-strain probiotic supplementation benefited dietary intake in patients with TBI [68]. Collectively, the available clinical and preclinical studies indicate that probiotic interventions may influence inflammatory, nutritional, neurological, and microbiome-related outcomes after TBI (**Table 2**).

Mechanistically, probiotics help maintain homeostasis by regulating microbiome balance, strengthening the intestinal barrier, modulating immunity, and promoting nutrient uptake and absorption [69], and may thereby enhance dietary intake by improving tolerance and immune function. Overall, probiotics appear to be a beneficial adjunctive treatment for severe TBI, plausibly diminishing the risk of secondary brain injury through modulation of the microbiota–gut–brain axis, improved immune regulation, and reduced inflammatory and oxidative-stress pathways that contribute to poor post-traumatic outcomes [68-70]. Although probiotics are generally safe, caution is advised when using them in critically ill ICU patients. Rare cases of probiotic-associated bloodstream infections (e.g., sepsis due to *Lactobacillus* or *Saccharomyces boulardii*) have been reported, particularly in patients with central venous catheters. Therefore, probiotic therapy should be used selectively in high-risk patients with appropriate monitoring for infection [71,72]. The available preclinical and clinical evidence regarding the effects of probiotics in TBI is summarized in **Table 2**.

Fecal microbiota transplantation (FMT)

Growing evidence links the gut microbiome and the brain through the microbiota–gut–brain axis. As noted above, this axis comprises several pathways—immune, autonomic, and microbial—that can be harnessed therapeutically by modifying their essential mechanisms. Because TBI-induced dysbiosis is a principal risk factor for secondary brain injury [73], microbiome modulation is an attractive strategy. Wang *et al.* examined fecal bacterial communities in rats with mild TBI and reported marked changes in relative abundance as early as 2 hours post-injury [30], and progressive dysbiosis has been demonstrated at 28 days post-TBI using 16S rRNA sequencing of colonic contents, occurring in parallel with prolonged microglial activation and neuroinflammation—hallmarks of secondary brain injury [74]. On this basis, microbiome-targeted therapies are increasingly considered for TBI, with probiotics and FMT proposed as the principal microbiome-based interventions.

FMT is a therapeutic intervention involving the administration of minimally processed stool from a healthy donor to the intestinal tract of a diseased recipient [75]. It is among the most effective and best-supported options for refractory *Clostridioides difficile* infection and other gut-microbiome-related diseases [76] and has been shown to improve neurological function in experimental models of multiple sclerosis and Parkinson's disease [77,78]. Conversely, in a prospective experimental stroke study, mice receiving FMT from cold-season stroke patients developed more severe brain injury, higher inflammation, and greater intestinal-barrier damage [79], underscoring that donor microbiome quality is critical, although their relevance to TBI requires further validation. The available preclinical evidence regarding the effects of FMT on TBI-induced neuroinflammation and neurological recovery is summarized in **Table 3**.

Neurological impairment is a key feature of secondary brain injury after TBI and a major contributor to disability. A study demonstrated that FMT protected against TBI-induced neuroinflammation in mice, with a reduction in the modified Neurological Severity Score (mNSS) on day 7 and lower CD11b (a marker of microglial activation), TNF-α, and pro-inflammatory cytokines [80]. In a randomized single-blind study, FMT-treated TBI piglets showed better recovery than untreated animals—smaller brain lesions, less bleeding, reduced edema and midline shift, and improved neuronal and oligodendrocyte survival and intestinal tissue structure [81].

Table 2. Summary of studies on the effect of probiotics on TBI

Study (year)	Study design	Population	TBI severity	Probiotic intervention	Treatment duration	Key findings	Limitations	Reference
Tan *et al.* (2011)	Prospective, randomized, single-blind pilot study	52 severe-TBI patients (26 probiotic, 26 control); ~77% male; 18–60 years	Severe TBI (GCS 5–8)	3-strain probiotic (*B. longum*, *L. bulgaricus*, *S. thermophilus*)	Days 1, 4, 8, 15, and 21	Balanced Th1/Th2 response (↑IFN-γ, ↓IL-4/IL-10); reduced late infection; shorter ICU stay.	Small sample; single-center; single-blinded.	[61]
Mazidi *et al.* (2017)	Systematic review and meta-analysis	20 prospective RCTs; human subjects (ages 6 months–85 years)	Various conditions, with one TBI-specific study	Various probiotic strains (e.g., *L. acidophilus*, *Bifidobacteria*)	7 days to 6 months	Significant reduction in serum CRP; no significant effect on IL-10 or TNF-α.	Medium sample sizes; variable CRP assays; high heterogeneity of outcomes.	[62]
Brenner *et al.* (2020)	Pilot randomized, longitudinal, double-blind, placebo-controlled clinical trial	31 US military Veterans (100% male in this sample) from the OEF/OIF/OND conflicts with co-occurring symptoms	Mild TBI with persistent post-concussive (PPC) symptoms and co-occurring PTSD	*Lactobacillus reuteri* DSM 17938 (100 million CFU daily) vs placebo	8 weeks ± 2 weeks	Decrease in plasma C-reactive protein (CRP) concentrations that approached statistical significance and a smaller increase in mean heart rate (BPM) during math tasks compared to the placebo group.	Small and gender-homogeneous sample size; an exploratory design focused on feasibility rather than clinical efficacy; administration of the intervention long after the initial injury.	[63]
Kumar *et al.* (2021)	Rodent experimental study	Male Sprague-Dawley rats; 250–350 g	Controlled cortical impact (CCI)	*Lactobacillus reuteri* DSM 17938 (oral gavage)	72 h and 21 d post-injury	21-day treatment shifted the M1:M2 ratio toward reparative microglial phenotype; increased anti-inflammatory marker CD200R.	Rodent model limits clinical extrapolation; lacks functional/behavioural memory testing.	[66]
Abbaszadeh *et al.* (2024)	Parallel randomized, double-blind, placebo-controlled trial	46 severe-TBI patients (23 probiotic, 23 placebo); ~65% male; 18–60 years	Severe TBI (GCS 3–8)	7-strain probiotic capsule (10^{10} CFU) via nasal tube	Day 1 and day 14	Significant reduction in TNF-α, IL-1β, and Th17 cells; increase in IL-10, TGF-β, and Tregs; improved GCS.	Short duration (14 d); strain synergy and concomitant drugs not accounted for.	[60]
Amaral *et al.* (2024)	Rodent experimental study	20 male C57BL/6 mice (6 sham, 7 TBI+Vh, 7 TBI+Pro); 6 months	Moderate fluid-percussion injury (FPI)	*L. helveticus* R0052 and *B. longum* R0175 (oral gavage)	14 d post-injury	Improved memory (Barnes maze); reversed reduction in hippocampal neuroplasticity markers (CaMKII/CREB).	16S lacked strain-level detail; male-only; extrapolation from mice limited.	[70]
Holcomb *et al.* (2025)	Rodent experimental study	C57BL/6 mice (male and female); 9–12 weeks	Controlled cortical impact (CCI)	Pan-probiotic (7 *Lactobacillus* strains) in drinking water	3 d (acute) and 35 d (chronic)	Reduced lesion volume and cell death at 3 dpi; decreased microglial activation; improved motor recovery in males.	Small 16S amplicon may cause taxonomic misidentification; pre- vs post-TBI treatment effects not separable. Rodent model limits clinical extrapolation; lacks functional/behavioural memory testing.	[67]

Study (year)	Study design	Population	TBI severity	Probiotic intervention	Treatment duration	Key findings	Limitations	Reference
Noshadi *et al.* (2025)	Randomized, double-blind, placebo-controlled trial	46 TBI patients (23 probiotic, 23 placebo); ~65% male; 18–60 years	Severe TBI (GCS < 8)	7-strain probiotic capsule (4 *Lactobacillus*, 2 *Bifidobacterium*, 1 *Streptococcus*)	Baseline and 14 d	Significantly increased dietary intake (energy /macronutrients); no significant effect on CAMs (ICAM-1, VCAM-1) or oxidative stress.	Fixed dose; severe-TBI ICU patients only; small sample; short duration.	[68]

BPM: beats per minute; CAMs: cell adhesion molecules; CFU: colony-forming units; CRP: C-reactive protein; GCS: Glasgow Coma Scale; ICU: intensive care unit; IFN-γ: interferon-gamma; IL-4: interleukin-4; IL-10: interleukin-10; M1: microglia pro-inflammatory; M2: microglia anti-inflammatory; RCTs: randomized controlled trials; Th1: T helper 1 cells; Th2: T helper 2 cells.

Table 3. Summary of studies on the impact of fecal microbiota transplantation (FMT) on TBI-induced neuroinflammation

Study (year)	Animal model	TBI model	FMT protocol	Assessment time points	Key findings	Limitations	Reference
Du *et al.* (2021)	Male Sprague-Dawley rats (8 weeks)	Controlled cortical impact (CCI)	FMT (fecal suspension via enema) daily for 7 days	Days 1–21 (behavior); day 8 (serum and brain)	Reduced hippocampal oxidative stress (↑SOD/CAT; ↓ROS/MDA/GSSG) and TMAO. Enhanced neurological and cognitive recovery after TBI by reduced mNSS score on days 3,7,14 and 21 post-injury and improved Morris water maze performance.	Enema method time-consuming; bacterial viability risk if given by gavage.	[82]
Hu *et al.* (2023)	Male C57BL/6J mice (2 months)	Weight-drop impact head injury (20 g from 20 cm)	FMT (0.2 mL fresh fecal solution) daily for 5 days	1 and 7 d post-FMT (14-day study)	Inhibited microglial activation (CD11b+ cells) and reduced TNF-α.	Specific gut–brain-axis mechanisms require further study.	[80]
Fagan *et al.* (2023)	Male crossbred piglets (4 weeks)	Controlled cortical impact (CCI)	FMT (healthy-donor feces) via oral gavage daily for 7 days	1 and 7 d post-TBI (MRI and tissue)	Did not significantly reduce Iba1+ microglia or GFAP+ astrocyte activation at the sub-acute stage (7 d).	Male-only cohort; long-term effects not confirmed; small sample (n=6).	[81]
Wang *et al.* (2023)	Male Sprague-Dawley rats (250–300 g)	Feeney weight-drop contusion	N/A (temporal characterization study)	12 time points (sham to 14 d post-injury)	Identified changes in bacterial taxa (Fusobacteria, Prevotellaceae) as potential markers for injury.	Links remain correlational; rat results may not fully reflect human physiology.	[30]
Davis *et al.* (2022)	Male C57BL/6 mice (14 weeks)	Controlled cortical impact (CCI)	FMT (healthy stool slurry) via oral gavage once weekly for 4 weeks	45 to 90 d post-injury	Observed an FMT–injury interaction in Iba1 staining, indicating chronic microglial activation linked to repair.	Whole-stool study limits mechanistic data on specific taxa; generalisability unknown.	[27]
Dong *et al.* (2024)	Male Sprague-Dawley rats (100 ± 5 g)	Gas explosion (10% methane mixture)	FMT (fecal bacterial suspension) via gavage daily for 21 days	Day 21 (feces); day 28 (behavior and tissue)	Improved immune environment by normalizing Treg factors (IL-10, PD-1, Foxp3) and decreasing IL-1β.	Lacks functional analysis for brain-damage characterization; microbiota may not be the sole factor.	[83]

Study (year)	Animal model	TBI model	FMT protocol	Assessment time points	Key findings	Limitations	Reference
Wang S. *et al*. (2026)	Male C57BL/6 mice (4–6 weeks)	Controlled cortical impact (CCI)	FMT (donor from control mice) daily via oral gavage	7 and 28 d post-TBI	Alleviated persistent hippocampal microglial activation and inhibited macrophage genes (Cx3cr1, Cd68) at 28 d.	Only one microglial marker (Iba1) was assessed; fungi/viruses were not considered.	[84]

CAT: catalase; CD11b: cluster of differentiation 11b; CD68: cluster of differentiation 68; CX3CR1: C-X3-C motif chemokine receptor 1; FMT: fecal microbiota transplantation; Foxp3: forkhead box P3; GFAP: glial fibrillary acidic protein; GSSG: oxidized glutathione (glutathione disulfide); Iba1: ionized calcium-binding adapter molecule 1; IL-1β: interleukin-1 beta; IL-10: interleukin-10; MDA: malondialdehyde; mNSS: modified neurological severity score; PD-1: programmed cell death protein 1; ROS: reactive oxygen species; SOD: superoxide dismutase; TMAO: trimethylamine N-oxide; TNF-α: tumor necrosis factor-alpha; Treg: regulatory T cells.

FMT promotes the enrichment of *Bifidobacterium*, which enhances the production of 5-hydroxyindole from the tryptophan pathway. This microbial change suppresses hippocampal sphingolipid signaling and reduces the expression of microglial activation-related genes, including Cx3cr1 and Cd68. Consequently, FMT attenuates persistent microglial activation and chronic neuroinflammation after TBI and improves neurological recovery [84].

FMT ameliorated dysbiosis and neurological impairment in a rat TBI model, with lower mNSS scores and, in the Morris water maze, shorter escape latency and better spatial memory than controls—revealing improved cognitive performance [82]. FMT may improve neurological recovery after TBI by restoring the gut–microbiome–brain axis. It enhances beneficial microbial composition, reduces harmful metabolites such as TMAO, and preserves hippocampal MsrA function. These changes improve antioxidant defense by increasing SOD and CAT activity and reducing oxidative stress (**Table 3**).

Ultimately, FMT contributes to reduced neurological deficits and improved cognitive outcomes after TBI [82]. Additionally, a study reported that FMT preserved neurocognitive function after TBI by improving anxiety-like behavior and exploratory activity compared with untreated TBI mice [27]. A study in male rats showed that FMT ameliorated cognitive impairment by restoring microbiome balance and enhancing barrier integrity via the microbiota–gut–brain axis [83].

As summarized in **Table 3**, most evidence regarding FMT in TBI is derived from preclinical animal models and may not fully reflect the biological responses, safety profile, or therapeutic efficacy in humans. Well-designed clinical trials are required to confirm effectiveness, define optimal protocols, and evaluate risks before FMT can be recommended in routine practice.

Further work should prioritize adequately powered, multicentre randomized controlled trials of probiotics and FMT in TBI, with standardized strains, doses, and routes of administration, and with clinically meaningful endpoints—neurological recovery, cognition, ICU stay, and mortality—alongside mechanistic biomarkers. Beyond probiotics and FMT, future studies should also explore other microbiome-targeted approaches, including targeted prebiotic fiber and postbiotics such as short-chain fatty acids (SCFAs), which may serve as complementary strategies to modulate microbial composition and function. Standardization of microbiome sampling and sequencing, prospective designs spanning the acute to chronic phases, and attention to sex-specific responses would improve comparability. Integrating multi-omics approaches (metagenomics and metabolomics) may clarify the microbial metabolites—particularly SCFAs and LPS-driven TLR4 signaling—that mediate the brain–gut–brain loop and could support the generation of targeted, next-generation microbiome therapeutics and reliable biomarkers for patient stratification.

The evidence summarized in this review has several limitations. First, most mechanistic and therapeutic data derive from animal models, whose injury mechanisms (controlled cortical impact, fluid-percussion injury, weight-drop) and baseline microbiomes differ from those of humans, limiting direct extrapolation. Second, microbiome methodologies are heterogeneous—differing in sequencing regions (e.g., 16S rRNA V1–V3 versus V3–V4), sampling sites, and time points—which complicates cross-study comparisons. Third, many findings are correlational and cannot demonstrate causality. Fourth, clinical probiotic trials are generally small, single-center, and short in duration, with variable strains, doses, and outcome measures, even though robust human FMT data in TBI are essentially absent. Finally, as a narrative review, this examination did not apply a formal risk-of-bias appraisal or quantitative meta-analysis, and selection bias cannot be excluded.

Conclusion

Substantial progress has been made in understanding the bidirectional microbiota–gut–brain axis after TBI and its therapeutic implications. Disruption of this axis—encompassing the neuroinflammatory response, autonomic and enteric nervous system dysregulation, vagal dysfunction, and gut microbiome dysbiosis—provides a mechanistic link that helps explain secondary brain injury and identifies opportunities for microbiome-targeted therapy. FMT and probiotics have been proposed as microbiome-based interventions for TBI: FMT may recover microbiome balance and improve clinical outcomes but further clinical studies are needed to

confirm its beneficial effects and safety in humans; probiotics may reduce the risk of secondary brain injury by strengthening tight junctions, increasing mucus synthesis, and regulating immune responses, with positive early clinical outcomes, but large-scale trials are required to validate their safety, efficacy, and clinical relevance.

Ethics approval

Not required.

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Competing interests

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Underlying data

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Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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