

Disruption of the microbiota-gut-brain-axis in severe traumatic brain injury: implications for novel therapeutic strategies-a narrative review

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ABSTRACT

Severe traumatic brain injury (TBI) frequently disturbs the normal balance of intestinal microorganisms, resulting in gut dysbiosis that can exacerbate neuroinflammation and worsen patient outcomes. The microbiota-gut-brain axis (MGBA) represents the integrated signalling pathways connecting the brain and gastrointestinal tract. Following severe TBI, this communication network becomes impaired, contributing to the cascade of secondary injury. As a result, the MGBA has emerged as a promising therapeutic focus.

This narrative review examines the workings of the MGBA and highlights evolving therapeutic approaches-including probiotics, prebiotics, postbiotics, prokinetics, and fecal microbiota transplantation (FMT)-that aim to re-establish microbial and neuroimmune balance in patients with severe TBI.

Keywords: Traumatic brain injury, microbiota-gut-brain axis, gut dysbiosis, probiotics, fecal microbiota transplantation

INTRODUCTION

Traumatic brain injury (TBI) results from mechanical trauma to the skull or brain and may lead to disturbances in consciousness and short- or long-term neurological deficits.¹ It remains a significant global health problem, particularly among young adults, where it contributes substantially to disability and death.² The incidence is higher in males, with road traffic crashes constituting the most common aetiology globally.³⁻⁷

Based on severity using the Glasgow Coma Scale (GCS),⁸ TBI is classified as mild (GCS 14-15), moderate (GCS 9-13) and severe (GCS 3-8).⁹ While mild and moderate TBI generally have favourable outcomes, severe TBI remains a major cause of disability and death despite advances in neurosurgical and critical care.¹⁰

Although the injury occurs within the cranial vault, its physiological influence extends systemically due to the brain's regulatory role over multiple organ systems.¹¹ The central nervous system (CNS) maintains a bidirectional relationship with the gastrointestinal tract (GIT) through the activities of the gut microflora.¹²

The GIT hosts a vast array of microorganisms that support digestion, immunity, and neural function.¹³⁻¹⁵ This microbial ecosystem communicates with the CNS through neural, endocrine, and immunological pathways collectively termed the microbiota-gut-brain axis (MGBA).¹² Under normal conditions, this system maintains intestinal stability and contributes to metabolic and neuromodulatory processes.¹⁶ Conversely, the gut microbiota produce some neuroactive compounds- including bacterial metabolites and neurotransmitters-that influence the activity of the enteric nervous system (ENS), and modulate vagal output signaling.¹⁶ Severe TBI, however, disrupts these interactions, promoting dysbiosis and systemic inflammation, which in turn may aggravate secondary brain injury.^{11,17} Consequently, the MGBA has become a potential therapeutic target in TBI management. Growing evidence suggests that modulating gut microbial composition through targeted interventions- such as probiotics, prebiotics, postbiotics, prokinetic drugs, and FMT- may help mitigate complications and improve recovery. This narrative review evaluates the MGBA and explores therapeutic strategies that may be incorporated into the management of severe TBI.^{18,19}



METHODOLOGY

A comprehensive literature search was performed using ClinicalTrials.gov, the European Union Clinical Trials Register, PubMed, and Google Scholar. The search focused on studies examining the relationship between severe TBI and the gut microbiome and included both animal and human research from 1990 up to 2025. Keywords included combinations of “traumatic brain injury,” “brain injury,” “head injury,” “gut,” “gastrointestinal,” “intestinal,” “gut-brain axis,” “microbiome,” “microbiota,” “probiotics,” “prebiotics,” “postbiotics,” “prokinetics,” “fecal microbiota transplantation,” “human” and “animal.” Boolean operators deployed were AND, OR and NOT while search strings included “microbiota” OR “microbiome” AND “gastrointestinal” OR “gut” OR “intestinal” AND “traumatic brain injury,” OR “brain injury” OR “head injury” AND “gut-brain axis” AND “human” OR “animal” AND “probiotics,” OR “prebiotics,” OR “postbiotics,” OR “prokinetics,” OR “fecal microbiota transplantation.” Priority was given to randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Where these were unavailable, relevant narrative reviews and preclinical studies were included to provide mechanistic insights. The selection of literature for this review is summarized in **Table 1**, which categorizes the included evidence by study design and thematic focus.

Table 1. Summary of evidence and study characteristics

| Evidence category | Included (n) | Primary thematic focus |
|-------------------------------------|--------------|--|
| Meta-analyses & systematic reviews | 12 | Clinical efficacy of prokinetics ^{7,79} & probiotics ⁵⁷ |
| Randomized controlled trials | 8 | Direct human outcomes in TBI cohorts ^{61,64,76,78} |
| Preclinical (animal) studies | 15 | MGBA mechanisms, FMT pathways ⁸⁹ , & dysbiosis ^{33,34} |
| Observational & prospective studies | 10 | Infection rates & feeding tolerance ^{6,58,62} |
| Narrative reviews & consensus | 25 | Theoretical frameworks ^{47,48} & postbiotic definitions ⁸⁵ |
| Foundational pathophysiology | 15 | TBI classification ^{8,9} & HPA axis disruption ³⁵ |

TBI: Traumatic brain injury, MGBA: Microbiota-gut-brain axis, FMT: Fecal microbiota transplantation, HPA: Hypothalamic-pituitary-adrenal axis

Exclusion Criteria

During the literature screening process, records were excluded based on the following pre-defined criteria: (1) studies focused exclusively on mild TBI without relevance to the severe injury cascade; (2) microbiome studies related to chronic metabolic or skin conditions with no CNS implications; and (3) sources published prior to 1990 (except for critical historical definitions) or those lacking full-text availability/peer-review status.

THE MICROBIOTA-GUT-BRAIN AXIS

The MGBA is a dynamic communication network linking gastrointestinal (GI) microorganisms with the CNS.²⁰ It serves as a conduit between the brain and the bowel, facilitating continuous physiological interaction. Signalling occurs through immune mediators, autonomic pathways-including the vagus nerve-and the ENS,^{20,21} as depicted in **Figure 22** below.

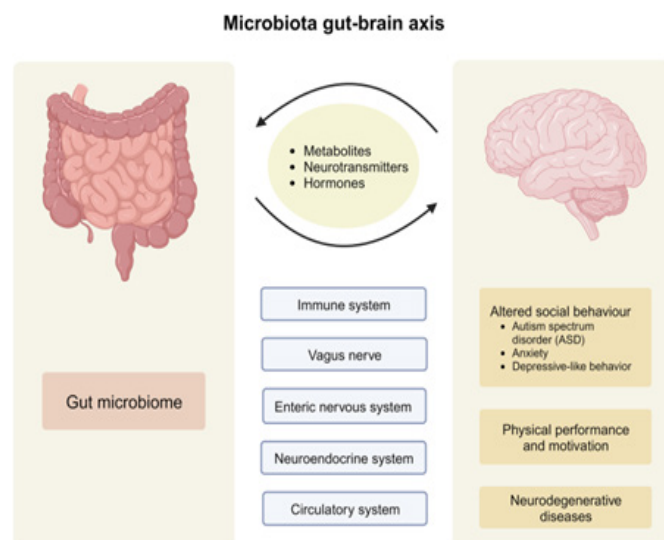


Figure. The microbiota-gut-brain axis-the bidirectional communication between the brain and the bowel. Adapted from Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases¹²

Autonomic fibers connect the GIT to the CNS via the vagus nerve and spinal afferent fibers associated with the gut's extrinsic innervation.²⁰ Through these routes, the brain regulates intestinal activities such as motility and secretion, while gut microbes generate metabolites and neurotransmitter-like substances capable of influencing neural function.^{21,23}

Conversely, the gut microbiota can influence CNS functions through a number of mechanisms. Gut microbes produce neurotransmitters and organic compounds such as serotonin, gamma-aminobutyric acid (GABA), and short-chain fatty acids (SCFAs) which can control brain activity.^{24,25} SCFAs, for example, can cross the blood-brain barrier and modulate neuroimmune responses.^{24,26}

DYSFUNCTION OF THE MICROBIOTA-GUT-BRAIN-AXIS

Disruption of gut microbial composition can influence neurological processes in several ways. The MGBA plays an important role in mediating this relationship.^{27,28} Disruption of this axis due to dysbiosis has been associated with various neurological disorders and poorer outcomes in patients with severe TBI.²⁷

One major pathway involves the production and regulation of neurotransmitters. The gut microbiota produces neurotransmitters like serotonin and GABA which are essential for brain function.^{23,29} Altered microbial diversity may impair the production of neuroactive substances, promoting mood disturbances and cognitive dysfunction. Furthermore, dysbiosis can compromise the integrity of the gut barrier, resulting in increased gut permeability.³⁰⁻³² Increased intestinal permeability allows inflammatory molecules and bacterial metabolites to enter systemic circulation, potentially crossing the blood-brain barrier and provoking neuroinflammation.^{31,32}

The MGBA disruption and dysfunction following severe TBI involves several interconnected factors which include:

- **Catecholamine surge:** TBI causes sympathetic nervous system hyperactivity, leading to a “sympathetic storm” and a surge in circulating catecholamines (epinephrine and norepinephrine).³³ This surge redirects blood flow away from the GI tract, causing enteric ischemia and contributing to gut dysmotility.³³ The presence of high norepinephrine levels in the gut also directly favors the overgrowth of opportunistic pathogens like *Escherichia coli*, driving dysbiosis.³⁴
- **Cortisol/HPA axis:** The brain injury activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels.³⁵ High cortisol compromises the integrity of the intestinal epithelial barrier by reducing tight junction proteins, creating a “leaky gut”.³⁶ This increased permeability allows bacteria and their inflammatory components, such as lipopolysaccharides (LPS), to translocate from the gut lumen into the systemic circulation.³⁷
- **Enteric ischemia & ileus/feeding interruptions:** The sympathetic hyperactivity leads to reduced blood flow (ischemia) in the gut.³⁸ This, combined with damage to the ENS, results in decreased intestinal motility (ileus or gastroparesis).³⁸ Impaired motility and feeding interruptions exacerbate gut dysbiosis by creating an environment that favors pathogenic overgrowth and reduces the production of beneficial, anti-inflammatory SCFAs by commensal bacteria.³¹
- **Opioid/Sedation effects:** Opioids, commonly used for pain management and sedation in severe TBI patients, significantly disrupt the gut microbiome and physiology.³⁹ They further slow GI motility, contributing to constipation and ileus.³⁹ Opioids can decrease beneficial bacteria (e.g., *Lactobacillus*, *Ruminococcaceae*) and increase pathogenic microbes (e.g., *Enterococcus*, *Staphylococcus*), while also promoting bacterial virulence.⁴⁰ This enhances gut barrier disruption and systemic inflammation.
- **Antimicrobial exposure:** The common use of broad-spectrum antibiotics to treat or prevent infections in severe TBI patients, while necessary, further compounds gut dysbiosis by depleting diverse microbial populations, including beneficial commensals.⁴¹ This “extinction of the microbiota” can worsen outcomes, including increased neuronal loss and altered immune responses, by removing the protective effects of a healthy microbiome.²²
- **Nosocomial infection pressures:** The combination of compromised gut barrier function, systemic immunosuppression (initially induced by HPA axis activation), dysbiosis, and the presence of more virulent pathogenic bacteria creates a conducive milieu for nosocomial infections, such as pneumonia and sepsis.⁴² The translocation of gut bacteria into the bloodstream is a major pathway for these infections, which significantly increase morbidity and mortality in TBI patients.⁴³

These mechanisms underscore the importance of maintaining microbial balance and suggest that modulating gut flora may have therapeutic value in severe TBI.^{44,45} Therapeutic strategies including probiotics, prebiotics, prokinetics, and fecal microbiota transplantation (FMT) aim to restore microbial balance, reduce inflammation, and potentially improve clinical outcomes in patients with severe TBI.^{32,45,46}

PROBIOTICS

Probiotics consist of viable microorganisms that, when administered in sufficient amounts, exert beneficial effects on host physiology.^{47,48} They are widely used to stabilize intestinal flora, enhance mucosal barrier integrity, and modulate immune responses thus, helping to prevent infectious complications in various clinical conditions, including severe TBI.⁴⁸ They were discovered by the Russian scientist Elie Metchnikoff about a hundred years ago.⁴⁹ The term “probiotic” was, however, first used in 1965 by Lilly and Stillwell. It was derived from a Greek word which means “for life.”^{48,50,51}

Probiotics may be composed of either gram-positive or gram-negative bacteria. Common probiotic strains include *Lactobacillus*, *Bifidobacterium*, *Streptococcus* species, and the non-pathogenic *Escherichia coli* Nissle. Formulations are available as capsules, powders, and fermented foods.⁵¹

MECHANISM OF ACTION OF PROBIOTICS

The precise mechanisms of actions of probiotics are not fully understood. However, different mechanisms have been suggested, including:

- Competing with pathogenic organisms for mucosal binding sites,
- Producing antimicrobial substances such as bacteriocins,
- Enhancing innate and adaptive immune responses
- Strengthening the intestinal epithelial barrier,
- Contributing essential metabolites that support microbial diversity.⁵²⁻⁵⁵

Through these mechanisms, probiotics mitigate gut dysbiosis not only in severe TBI but also in conditions such as Crohn’s disease and ulcerative colitis.^{14,48,54,56-58} Important properties needed for a probiotic to be effective therapeutically include ability to colonize the gut, capacity to adhere to the gut mucosa as well as resistance to gastric acid and bile.^{59,60}

POTENTIAL ROLE OF PROBIOTICS IN THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY

Studies have suggested that probiotic administration may reduce intensive care unit (ICU) stay, lower infection rates, and improve GI function in critically ill patients, including those with severe TBI.^{61,63,64} While mortality outcomes remain inconsistent, the overall trend indicates that probiotics may provide supportive benefits when added to standard care. Wan et al.,⁶¹ in a prospective study, reported that probiotic administration significantly reduced hospital stay and pulmonary infection rates in severe TBI patients compared with controls. There was however no significant difference in one-month mortality or incidence of sepsis between the two groups. Similarly, Rijkers⁵⁶ observed that probiotics significantly reduced the length of ICU stay in patients with severe trauma, while the observed reductions in ventilator-associated pneumonia and mortality in the probiotic group did not reach statistical significance. Falcao et al.⁵⁸ also noted a shorter ICU stay and lower infection rates among patients who had probiotics.

Likewise, Tzikos et al.⁶² in a study involving multiple-trauma patients with concomitant head injury, found that a probiotic mixture significantly reduced the incidence of surgical site infections. In a randomized controlled trial (RCT), involving 52 severe TBI patients,⁶³ those treated with probiotics had lower rates of nosocomial infections and shorter ICU stays compared with those who had placebo.^{63,64}

The observed inconsistencies in clinical outcomes across probiotic studies in severe TBI likely stem from significant methodological heterogeneity. While early prospective trials, such as those by Wan et al.,⁶¹ reported significant reductions in hospital stays and pulmonary infections, subsequent larger-scale observations have struggled to replicate these 'hard' clinical benefits consistently- for example, Tan et al.⁶⁴ noted no difference in 28-day mortality among probiotic treated patients compared to the placebo group. A primary confounding factor is the variability in probiotic strains-ranging from single-strain *Lactobacillus* to multi-strain cocktails-and disparate dosage concentrations-**Table 2**. Furthermore, the timing of administration is critical; some protocols initiate therapy within 24 hours of injury, while others delay until the sub-acute phase, potentially missing the peak of the sympathetic storm where gut-derived neuroinflammation is most potent. This lack of standardization makes it difficult to discern whether a failed trial is a result of an ineffective intervention or a suboptimal delivery window.

Consequently, while probiotics show promise in reducing secondary infectious complications, their direct impact on long-term neurological recovery remains an area of significant uncertainty.^{63,64}

PROKINETICS

Prokinetic drugs enhance GI motility and are widely used for disorders such as gastroparesis.⁶⁵ They are useful in the treatment of motility disorders associated with medical conditions such as diabetic gastroparesis and ileus secondary to severe TBI.⁶⁶ They function by promoting coordinated contraction of intestinal smooth muscle and accelerating gastric emptying.⁶⁷ Besides this pro-motility effects, they are also anti-inflammatory and immunomodulatory.⁶⁸

Prokinetic agents act through several mechanisms: i. they facilitate gastric emptying; ii. they promote peristaltic esophageal contractions; and iii. they increase synchronized gastric contractions.^{65,69-71}

Classes of prokinetics include:

- Cholinergic agonists-such as bethanechol, neostigmine, and pyridostigmine,^{70,72-74}
- Dopamine receptor antagonists-including metoclopramide, levosulpiride, itopride and domperidone^{70,75}
- Serotonergic agents-such as cisapride, tegaserod, and prucalopride⁷⁰ and
- Macrolide-based motility enhancers-including azithromycin, clarithromycin, roxithromycin, and erythromycin.⁷⁰

Beyond improving GI motility, macrolide prokinetics also possess antimicrobial properties that may help prevent or treat infectious complications such as pneumonia, which can contribute to secondary brain injury in patients with severe TBI.^{68,70,76}

EFFECTS OF PROKINETICS ON OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY

By enhancing gut motility, prokinetics help preserve intestinal barrier integrity and reduce gut dysbiosis frequently observed in patients with severe TBI. TBI-associated dysmotility may lead to feeding intolerance and increased risk of infection. Clinical studies show mixed results: some report improved gastric emptying and reduced stasis with agents such as erythromycin, while others found no significant differences between treatment and placebo groups. Meta-analyses indicate benefits in feeding tolerance but limited evidence for reductions in mortality or length of hospital stay.

Makkar et al.⁷⁶ in a RCT, demonstrated that the macrolide prokinetic-erythromycin improved gut motility significantly compared with placebo in TBI patients. In this study, gastric aspirate volume (GAV) served as a surrogate marker of gut motility. The incidence of high GAV was 60.5% in the placebo group and 28.9% in the erythromycin group ($p=0.006$), indicating that prokinetics caused a significant reduction in gastric stasis.

Table 2. Clinical parameters and protocols of probiotic interventions in severe TBI

| Study (author, year) | Probiotic strains used | Formulation/delivery | Daily dosage | Duration | Primary clinical outcomes |
|------------------------------------|---|---|---|--------------|--|
| Tan et al. (2011) ⁶⁴ | <i>Bifidobacterium. longum</i> , <i>Lactobacillus bulgaricus</i> , <i>Streptococcus thermophilus</i> | Sachets (7 sachets 3 times daily) | 0.5 X 10 ⁸ to 0.5 X10 ⁷ CFU | 21 days | Reduced incidence of nosocomial infections and shorter ICU stay. 28-day mortality rate was unaffected. |
| Wan et al. (2019) ⁶¹ | <i>Bifidobacterium longum</i> , <i>Lactobacillus bulgaricus</i> , <i>Enterococcus faecalis</i> | Tablets (6 tabs two times daily) via gastric tube | ≥1.0 X 10 ⁷ CFU | 15 days | Lower inflammatory markers (IL-6, IL-10, TNFα & CRP); reduced pulmonary infection rates and shorter length of hospital stay. |
| Falcao et al. (2004) ⁵⁸ | <i>Lactobacillus johnsonii</i> | Fermented milk | 240mls | 5 to 14 days | Reduced incidence of infection rate, and shorter length of ICU stay. |
| Tzikos et al (2022) ⁶² | <i>Lactobacillus acidophilus</i> , <i>Lactiplantibacillus plantarum</i> , <i>Bifidobacterium animalis</i> , & <i>Saccharomyces boulardii</i> | Sachets (2 two times daily) via enteral route | (0.5×10 ⁸ to 1.75 x 10 ⁹ CFU) | 15 days | Reduced incidence of surgical site infection |

TBI: Traumatic brain injury, ICU: Intensive care unit, CFU: Colony-forming unit TNFα: Tumor necrosis factor-alpha, CRP: C-reactive protein

Similarly, Lewis et al.,⁷⁷ in a systematic review and meta-analysis, concluded that in critically ill patients evidence supports the use of prokinetic agents in mitigating poor feed tolerance compared to placebo; even though the effects of prokinetics on other outcome measures such as length of ICU stay, pneumonia and mortality were inconclusive.

In contrast, Nursal et al.⁷⁸ in another RCT, observed no significant advantage of prokinetics over placebo in TBI patients. Complication rates and feeding intolerance were comparable in both groups ($p=0.543$ and $p=0.930$, respectively).

In another systematic review and meta-analysis, Peng et al.⁷⁹ concluded that prokinetic therapy may improve tolerance to gastric feeding in critically ill adults.

Critical analysis of prokinetic therapy in severe TBI reveals a disconnect between physiological markers and clinical endpoints. Studies such as those by Makkar et al.⁷⁶ demonstrate that macrolide prokinetics significantly improve gut motility, using GAV as a successful surrogate marker for reduced stasis. However, these improvements in gastric emptying do not consistently translate to improved patient outcomes, such as 28-day mortality or improved GCS scores.^{78,79} This discrepancy suggests that while prokinetics are effective at mitigating feed intolerance, the sheer complexity and severity of the primary and secondary brain injury cascade may overshadow the incremental benefits of improved gut motility. Furthermore, the reliance on meta-analyses in this field is hampered by 'low' evidence quality regarding hospital stay duration, as most trials are not sufficiently powered to detect subtle neurological improvements. Future research must move beyond motility markers to investigate whether prokinetic-led gut stabilization actually reduces the systemic translocation of inflammatory mediators.

PREBIOTICS

Prebiotics are non-digestible substrates fermented by gut bacteria, resulting in growth of beneficial microbial species and production of SCFAs.⁸⁰ According to the International Scientific Association of Probiotics and Prebiotics (ISAPP), prebiotics are fermented ingredients that cause changes in the composition and/or activity of the gut microflora thereby promoting the host's health.⁸⁰ Examples include fructans, pectin, galacto-oligosaccharides, and flavanol-rich fibres.^{80,81}

EFFECTS OF PREBIOTICS ON GUT MICROBIOTA

Prebiotics are energy sources for beneficial gut microbials, thereby modulating both their activity and composition.⁸² They also influence the gut milieu by altering the physicochemical profile of the gut. Prebiotic fermentation produces acidic metabolites, mainly SCFAs, which lower luminal pH.⁸² Significant alteration in the gut microflora can occur with a drop in gut pH by one unit. This change may reduce acid-sensitive species like *Bacteroides* while promoting Firmicutes to produce butyrate -the so called butyrogenic effect.⁸⁰

SCFAs are small molecules and are able to traverse enterocytes into the bloodstream and can also traverse

the blood-brain barrier.^{82,83} Therefore, prebiotics not only influence gut function but also have effects on distant organs, like the brain.

PREBIOTICS AND THE CENTRAL NERVOUS SYSTEM

The effects of prebiotics on the CNS are not fully understood yet.

A search through major clinical trial registries and academic literature databases including ClinicalTrials.gov, European Union clinical trials register, Pubmed and Google Scholar showed that no RCTs have yet investigated the role of prebiotics specifically in severe TBI. Although no clinical trials have directly assessed prebiotics in severe TBI, their known effects on immune modulation, microbial composition, and SCFA production suggest potential relevance.⁸⁴ However, some review articles have suggested that prebiotics, either alone or as synbiotic formulations (prebiotics combined with probiotics) may offer enhanced therapeutic benefit.^{46,84}

Currently, the absence of RCTs specifically evaluating prebiotics in severe TBI constitutes a significant barrier to evidence-based clinical practice. While animal models suggest that prebiotics may modulate the gut dysbiosis associated with neurotrauma,⁸⁴ the lack of human data prevents the establishment of standardized enteral protocols. This gap forces clinicians to rely on 'clinical extrapolation' from general ICU populations, which may not account for the unique TBI-driven catecholamine surge that acutely alters intestinal motility. Without RCTs to define the optimal 'dose-response' relationship for prebiotic-induced fermentation, there remains a risk that early administration in the hyper-acute phase could exacerbate GI intolerance or bloating in patients already suffering from gastroparesis. Future research must prioritize trials that combine prebiotics with specific probiotic strains (synbiotics) to determine if synergistic effects can more effectively mitigate the systemic inflammatory response in the first 72 hours post-injury

POSTBIOTICS

Postbiotics consist of microbial-derived compounds produced during fermentation.⁸⁵ These include SCFAs, cell fragments, extracellular polysaccharides, and proteins.⁸⁵ They may exert anti-inflammatory and immunomodulatory effects without requiring live bacteria.

Similar to prebiotics, a search through major clinical trial registries and academic literature databases also showed that there are currently no RCTs investigating the role of postbiotics in the management of severe TBI. Nevertheless, some review articles have suggested that postbiotics may have therapeutic potentials in this context.^{46,86} Thus, current evidence in TBI is theoretical, based on extrapolation from other inflammatory and metabolic conditions.

The observation that no RCTs currently exist for postbiotic therapy in TBI patients highlights a critical 'translational gap' in neuro-gastroenterology. Postbiotics, such as SCFAs like butyrate, represent a potentially safer alternative to live

probiotics in immunocompromised patients in the ICU settings; however, their clinical utility remains speculative without human efficacy data. The implications of this vacuum are twofold: first, the therapeutic window for modulating the blood-brain barrier (BBB) via microbial metabolites remains undefined; and second, the potential for postbiotics to serve as 'adjunct neuroprotectants' cannot be realized. Until rigorous trials are conducted to monitor the 'butyrogenic effect' in real-time-using fecal or serum metabolite markers-the transition from bench-to-bedside for postbiotic interventions will remain stalled, leaving a significant portion of the MGBA therapeutically unaddressed.

FECAL MICROBIOTA TRANSPLANTATION

FMT involves the administration of processed stool from a healthy donor to restore microbial diversity in a recipient's gut. It represents a novel method for modulating the MGBA.⁸⁷ Even though the exact mechanisms and therapeutic effects of FMT in TBI remain unclear, evidence suggests that FMT can improve gut and blood-brain barrier integrity and lessen microglial activation, thus offering potential routes for clinical intervention.⁸⁶ While widely used for recurrent *Clostridioides difficile* infection, its role in neurological conditions is still experimental, and its safety, efficacy, and long-term outcomes are all still being debated.⁸⁸

Preclinical studies in TBI models demonstrate reduced microglial activation, improved white-matter integrity, and decreased ventricular enlargement. In an experimental animal study, Davis et al.⁸⁹ demonstrated that FMT led to a marked reduction in ventriculomegaly and maintenance of white matter circuitry up till 59 days post-TBI. These findings suggest that restitution of gut microflora via FMT may attenuate microglial activation and reduce neuropathological changes following TBI, representing a potential novel therapeutic strategy in its management. However, safety considerations and lack of clinical trials limit current application in TBI patients.

BARRIERS TO CLINICAL TRANSLATION OF MGBA-TARGETED THERAPIES

Despite the therapeutic potential of modulating the MGBA, several critical barriers hinder its integration into standard clinical protocols for severe TBI:

- **Individualized microbiome vs. standardized protocols:** A significant challenge is the one-size-fits-all approach to treatment. While current TBI management is highly standardized, the human gut microbiome is intensely

individualized, influenced by genetics, diet, and pre-existing health status.^{13,31} The absence of baseline pre-injury microbiome data makes it difficult for clinicians to determine the specific degree of dysbiosis in an individual patient or to identify a precise target for microbial restoration.⁴⁵

- **Safety concerns in the critically ill:** In the context of severe TBI, the compromise of the intestinal epithelial barrier-often referred to as "leaky gut"-presents a significant safety risk.^{36,37} There is a theoretical but serious concern regarding the translocation of live probiotic microorganisms from the gut lumen into the systemic circulation, which could potentially lead to iatrogenic sepsis in already immunocompromised, critically ill patients.^{42,63}
- **Logistical and regulatory hurdles of FMT:** While preclinical models show that FMT can reduce neuroinflammation and lesion size, translating this to the ICU remains challenging.⁸⁹ Barriers include the lack of standardized donor screening protocols, the risk of transferring multi-drug-resistant organisms, and the significant aesthetic and logistical challenges of processing and administering stool in a sterile critical care environment.^{87,88}
- **Confounding effects of standard care:** The mandatory use of broad-spectrum antibiotics to prevent nosocomial infections and opioids for sedation in TBI patients creates a "moving target" for microbial restoration.^{40,41} These essential treatments often act as major disruptors of the microbiota, potentially neutralizing the beneficial effects of concurrently administered probiotics or prebiotics.^{39,41} This creates a clinical paradox where the treatments required to save a patient's life simultaneously undermine the therapies intended to restore their microbial balance.

While the individual therapies discussed-probiotics, prokinetics, prebiotics, and FMT-each offer unique mechanistic advantages, they also face distinct clinical and logistical hurdles. To provide a clear overview for clinicians and researchers, **Table 3** presents a comparative analysis of these MGBA-targeted interventions, weighing the strengths of current clinical evidence against the remaining uncertainties and experimental barriers.

FUTURE RESEARCH DIRECTIONS AND HYPOTHESES

To bridge the gap between the experimental findings summarized in **Table 3** and actual clinical utility, future research should transition from broad, non-specific outcome

Table 3. Comparative analysis of clinical evidence, strengths, and translational uncertainties for MGBA-targeted interventions in severe TBI

| Intervention | Strengths of current evidence | Weaknesses and uncertainties |
|--------------|--|--|
| Probiotics | Strong clinical evidence for reducing ICU-acquired infections, such as pneumonia. ^{51,63} | High strain variability and dosage inconsistency; "optimal" strain for TBI remains unknown; potential risk of translocation in the critically ill. |
| Prokinetics | Consistently demonstrates improvement in enteral feeding tolerance and significant reduction in gastric stasis. ^{76,79} | Limited and inconsistent evidence regarding reductions in ICU/hospital length of stay or long-term neurological recovery. |
| Prebiotics | Favorable safety profile; promotes endogenous production of neuroprotective SCFAs and stabilizes gut pH. ^{40,82} | Evidence is currently theoretical in the context of TBI; lacks human RCTs to determine clinical efficacy and standardized dosing. |
| FMT | Restores the entire microbial ecosystem rather than isolated strains; addresses deep-seated dysbiosis. ⁸⁷ | Experimental status in TBI; significant safety concerns regarding the transfer of resistant pathogens; lack of standardized protocols for the acute phase. |

MGBA: Microbiota-gut-brain axis, TBI: Traumatic brain injury, ICU: Intensive care unit, RCTs: Randomized controlled trials, FMT: Fecal microbiota transplantation

measures toward a precision medicine framework. Based on the evidence synthesized in this review, we propose the following hypotheses to guide subsequent clinical investigations:

- **Metabolomic-targeted restoration:** It is hypothesized that the targeted restoration of specific short-chain fatty acid (SCFA) levels-particularly butyrate-may correlate more strongly with reduced neuroinflammation and blood-brain barrier stability than interventions aimed solely at increasing overall microbial diversity.
- **Temporal synergy in intervention:** We propose that MGBA-targeted therapies initiated during the hyperacute sympathetic storm (within the first 24-48 hours post-injury) potentially offer superior neuroprotective outcomes compared to sub-acute administration, by preemptively mitigating gut-derived systemic inflammatory cascades.
- **Synbiotic efficacy in hostile environments:** It is hypothesized that synbiotic formulations (combined prebiotics and probiotics) may demonstrate enhanced clinical efficacy over monotherapies by facilitating the survival and colonization of beneficial bacteria within the physiologically altered GIT following severe TBI.

CONCLUSION

The MGBA represents a crucial intersection between gut microbial activity and CNS function. Severe TBI disrupts this axis, promoting dysbiosis, neuroinflammation, and systemic complications. Interventions that modulate gut microbiota-such as probiotics, prebiotics, postbiotics, prokinetics, and FMT show potential to mitigate secondary injury mechanisms.

Nevertheless, robust clinical evidence remains scarce, and large, well-designed trials are required to clarify efficacy, safety, and implementation strategies before these approaches can be widely adopted in TBI management.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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