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Review

Role of the intestinal microbiota in sepsis-associated encephalopathy

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Abstract

Sepsis-associated encephalopathy (SAE) is a secondary cerebral dysfunction of the central nervous system (CNS) caused by sepsis and is associated with high mortality rate and poor prognosis. It significantly affects the quality of life of survivors. The pathological mechanisms associated with SAE include dysfunction of the blood–brain barrier (BBB), activation of glial cells, ischemic injury, leukocyte transmigration, and disturbances in neurotransmitters. The mechanisms of SAE interact with and contribute to its development. Numerous studies have demonstrated that the intestinal microbiota affects not only the health of the gut but also that of other organs. Throughout the progression of SAE, alterations in the gut microbiome composition lead to the production of toxic substances that damage the intestinal barrier and enter the bloodstream. This damage negatively affects BBB permeability and initiates a cascade of neuroinflammatory responses that result in neuronal injury. Conversely, specific microbiome-derived derivatives play exhibit a neuroprotective role in regulating brain function. Therefore, gut–brain crosstalk may be a crucial factor in brain dysfunction. This paper reviews the relationship between the intestinal microbiota and SAE, aiming to explore the role of the intestinal microbiota in SAE and potential therapeutic targets.

Keywords: Sepsis-associated encephalopathy; microbiota dysbiosis; bacterial translocation; microbiota theraputic

Highlights

- The pathophysiological mechanisms of SAE and the function of intestinal microbiota are concluded.
- The relationship between various central diseases, including SAE, and intestinal microbiota changes are summarized.
- SAE has the potential to alter the composition of intestinal microbiota, and gut microbiota may serve as an upstream mediator affecting SAE.
- The use of intestinal microbiota-based SAE treatment shows promises as a viable treatment option.

Background

Sepsis is an abnormal or dysregulated host response to pathogens that can cause life-threatening organ dysfunction [1]. It is a significant global health concern, which affects millions of individuals annually with mortality rates ranging from one-third to one-sixth [2]. Sepsis-associated encephalopathy (SAE) is the most prevalent complication of sepsis in the CNS and is characterized by neuroinflammatory responses and severe blood–brain barrier (BBB) dysfunction with clinical manifestations of confusion, delirium, and even coma [3]. SAE not only negatively affects the prognosis of patients but also increases mortality, and surviving SAE patients will also have long-term sequelae due to brain dysfunction, resulting in a decline in the quality of life of survivors [4].

Intestinal homeostasis is essential for the overall health. The intestinal microbiota and its derivatives play crucial roles in maintaining intestinal barrier function and intestinal homeostasis [5]. Disruption of the gut microbiota impairs barrier function, which leads to bacterial translocation and subsequently causes diseases via various crosstalk mechanisms [5, 6]. Bidirectional communication exists between the brain and the intestines, and their interaction may influence SAE development [7]. Patients with SAE exhibit significant disturbances in their gut microbiota composition, which are not only associated with increased BBB permeability and neuroinflammation but also may contribute to differential susceptibility to SAE [8, 9]. Therapeutic approaches targeting the gut flora aim to utilize these microorganisms and their derivatives to enhance intestinal barrier function and restore stability within gut flora communities while reducing the BBB dysfunction and neuroinflammation associated with SAE development [10, 11].

Therefore, summarizing the role of intestinal microbes in the development of SAE is necessary to provide research

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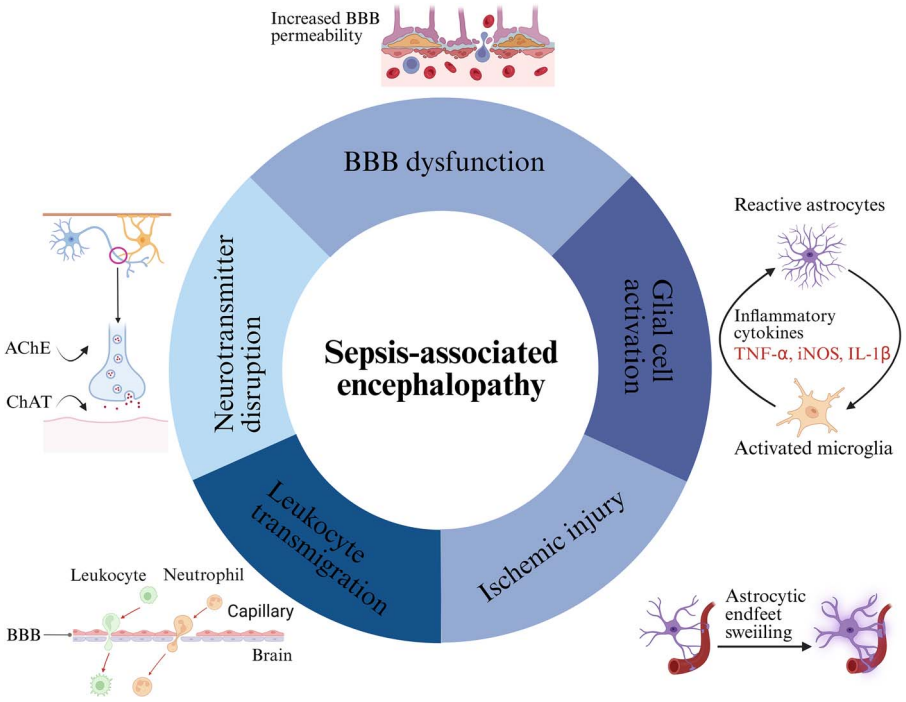


Figure 1. Pathological changes in SAE include BBB dysfunction, glial cell activation, ischemic injury, leukocyte transmigration, and neurotransmitter disturbances. Created with BioRender (https://biorender.com/)

directions for future prevention and treatment strategies for SAE. In this review, we discuss how the intestinal microbiota interacts with SAE according to the pathogenesis of SAE and the characteristics of the intestinal microbiota.

Review

Pathogenesis of SAE

The current understanding of the pathogenic mechanisms underlying SAE encompasses BBB dysfunction, activation of glial cells, ischemic injury, immune cell transmigration, and neurotransmitter disruption (Figure 1).

BBB dysfunction

The BBB is a physiological barrier that consists of brain capillary endothelial cells (ECs), basement membrane (BM), pericytes, and neuroglia, which maintain the relative stability of the intracerebral environment [12]. ECs are tightly connected by tight junctions (TJs) which consist mainly of transmembrane proteins (such as claudin, occludin, and junctional adhesion molecules) and intracellular support proteins such as zona occludens (ZO). TJs regulate selective passage of solute molecules through the interstitial space between cells [13, 14]. ECs are surrounded by a continuous BM, beyond which astrocytic endfeet envelop brain capillaries. This structure of multiple layers forms a protective barrier, which is essential for normal CNS function [15].

During SAE, peripheral immune cells and proinflammatory mediators compromise the BBB, downregulating the expression of TJ proteins expression and causing BBB damage [13]. Proinflammatory cytokines stimulate mitogen-activated protein kinase (MAPK), inducing transient occludin phosphorylation. This process reduces the expression of TJ proteins, alters EC morphology, and increases the permeability of the BBB [16]. Inflammatory mediator-induced disruption of the BBB allows cytotoxic factors to infiltrate the brain, triggering microglial activation and immune responses [14]. Persistently activated microglia produce nitric oxide (NO), cytokines, and reactive oxygen species (ROS), causing neuronal death in the hippocampus and prefrontal cortex and exacerbating BBB damage via a vicious cycle [17]. Additionally, sepsis-derived tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) further increase BBB permeability [18, 19].

Glial cell activation

Neuronal glial cells in the CNS are categorized into microglia, astrocytes, and oligodendrocytes. The proliferation and activation of microglia and astrocytes are key pathological features of SAE. BBB breach allows inflammatory factors and neurotoxins to infiltrate and activate microglia, which release cytokines and ROS, further damaging the BBB and worsening brain injury. Microglial activation also increases inducible nitric oxide synthase(iNOS) activity and NO production in endothelial cells, leading to autonomic nervous system central neuron and glial apoptosis and diffuse brain injury [14, 20, 21]. Excess NO induces oxidative stress and peroxynitrite formation, exacerbating neuronal apoptosis [22, 23].

Astrocyte activation triggers TNF-α release, upregulating iNOS and causing cerebral oedema. TNF-α signal via the TNF-α receptor (TNFR1) promotes iNOS upregulation and NO production. Increased aquaporin-4 (AQP4) expression in astrocyte endfeet, also linked to the TNF-α/TNFR1 pathway, contributes to oedema [24]. Lipopolysaccharide (LPS)-induced systemic inflammation induces in astrocytes structural changes and the release of chemokines such as C-C motif ligand-11(CCL11) and CCL21, which lead to damage to hippocampal neurons and cognitive impairment [25].

Astrocyte-microglia interactions drive SAE pathology. Activated astrocytes produce CCL11, which binds to microglial receptors to upregulate nicotinamide adenine dinucleotide

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phosphate-oxidase 1(NOX1) and promote microglial migration into the CNS, inducing oxidative stress and increasing glutamate-mediated neurotoxicity [26]. The release of TNF-α from microglia increases astrocytic glutamate release, amplifying neurotoxicity. Microglia also increase astrocytic glutamate levels via stromal cell-derived factor (SDF) 1a and C-X-C chemokine receptor 4 (CXCR4) signaling, exacerbating neuronal excitotoxicity [27]. Activated microglia release interleukin-1α (IL-1α), TNF-α, and complement component 1, q subcomponent (C1q), triggering reactive astrocytes and astrocyte dysfunction, neurotoxicity, and CNS impairment [28].

Ischemic injury

Adequate cerebral blood flow (CBF) is essential for brain function. Sepsis-induced endothelial dysfunction disrupts cerebral microcirculation [29]. In septic animals, capillary density and brain oxygen tension (PbO2) decreased, as does the percentage of perfusion, which ranged from 98% to 84% in a previous study [30]. Reduced cerebral perfusion triggers a decrease in CBF, creating a state of impoverished perfusion sustained by compensatory capillary dilation and constriction [29, 31]. This state results in swollen astrocytic endfeet, which may compress the capillary membrane and disrupt vasoactive signaling, leading to microcirculatory damage [31, 32]. When compensatory mechanisms fail, ischemic brain cells experience severe metabolic disruptions. The inactivation of the Na-K pump results in the loss of ionic concentration gradients, leading to the accumulation of sodium inside the cells. This accumulation combines with osmotic gradients and draws in chloride ions and water, triggering toxic oedema in brain cells [33]. Severe hypoxia in brain tissues triggers the release of numerous free radicals and toxic amino acids, contributing to disruptions in neuronal metabolism and an influx of mixed ions, which culminates in irreversible neuronal apoptosis [34]. Prolonged ischemia damages capillary endothelial cells, further compromising the BBB.

Immune cell migration

Monocyte and macrophage infiltration into the CNS exacerbates neuroinflammation in SAE. Inflammatory monocyte accumulation is primarily regulated by C-C chemokine receptor 2 (CCR2) and is linked to long-term cognitive impairment in SAE [35]. Monocytes that highly express high levels of CCR2 and Ly6C and low levels of CX3CR1, are recruited as circulating proinflammatory cells to the site of inflammation during tissue infection to produce high levels of cytokines [36]. Their accumulation increases BBB permeability and microglial activation, thus triggering neuroinflammation and memory impairment [35]. However, the transition to reparative subtypes occurs under the action of cytokines, resulting in the transformation of inflammatory monocytes into subgroups that assume a reparative role at the lesion site [36]. Neutrophil recruitment follows monocyte influx. Persistent neutrophil accumulation is associated with oxidative injury, cerebral oedema, and tissue damage, which facilitate SAE development [37]. Inflammatory factors stimulate interactions between neutrophils and cerebrovascular endothelial cells [38]. P-selectins prompt neutrophils to migrate along the blood vessel lining [39]. Neutrophils recognize C-X-C motif chemokine receptor 2 (CXCR2) on activated endothelial cells, stimulating the expression lymphocyte function-associated antigen 1 (LFA1) and very late antigen 4 (VLA4), which bind to intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1) on the cell surface, leading to neutrophil invasion and BBB dysfunction [40–43]. Neutrophil-derived matrix metalloproteinase-9 (MMP-9) disrupts the BBB by degrading the extracellular matrix and TJs, facilitating neutrophil recruitment and causing cerebral oedema [44, 45]. Additionally, T lymphocytes can also infiltrate the brain, primarily during the chronic phase of SAE, characterized by the predominance of regulatory T cells (Tregs) and T helper (Th) 2 cells. This process is distinct from the effects of neutrophil infiltration, in which Tregs and Th2 cells may alleviate the neurological damage caused by SAE [46, 47].

Neurotransmitter disruption

Neurotransmitter dysregulation contributes significantly to SAE. Inflammation alters neurotransmitter levels, which affect brain function. Sepsis alters norepinephrine and gamma-aminobutyric acid (GABA) receptor activity via inflammatory mediators, disrupting synaptic plasticity and causing brain cognitive deficits in the brain [48, 49]. Cholinergic dysfunction mediates brain injury in SAE. Caecal ligation puncture (CLP) model mice exhibit increased microglial activation and proinflammatory gene expression in the cortex and hippocampus, along with reduced expression of choline acetyltransferase (ChAT) and M1 muscarinic acetylcholine receptor expression. Conversely, acetylcholine (Ach)-degrading acetylcholinesterase (AChE) is upregulated, indicating that neurotoxicity from cholinergic dysfunction may cause cognitive impairment [50]. Evidence suggests that persistent microglial activation in the hypothalamus of sepsis-surviving mice increases cyclooxygenase-2(COX-2), iNOS, and IL-6 phosphorylation, leading to cholinergic neurotransmission disruption [51]. However, AChE inhibitors or cholinergic pathway activators can reverse neurotoxicity and memory deficits [52, 53]. Additionally, dopamine, a neurotransmitter involved in memory regulation, is linked to SAE delirium symptoms [54]. Similarly, the administration of levodopa(L-DOPA)/benserazide hydrochloride reversed the decrease in dopamine concentration in the hippocampus, enhanced plasticity, and mitigated cognitive impairment in SAE surviving mice [55], suggesting that the D1 dopamine receptor is novel therapeutic target for SAE.

Effect of the intestinal microbiota on CNS diseases

Significance of the intestinal microbiota in maintaining intestinal homeostasis

The composition of the human intestinal microbiota is complex and includes mainly Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, Cyanobacteria, Spirochaeates, and VadinBE97 [56, 57]. These microorganisms have coevolved with the host to maintain the microecological balance of the human intestine. The intestinal microbiota is key for intestinal homeostasis, which maintains intestinal stability via metabolism, nutrition, and barrier function. First, gut microbes participate in metabolic pathways associated with dietary components, producing metabolites that supply nutrients to the intestinal epithelium. For instance, short-chain fatty acids (SCFAs) are the main energy source for colon epithelial cells [58]. The gut microbiota, along with the intestinal mucosa forms a barrier that prevents the invasion of pathogenic microorganisms

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and maintains intestinal homeostasis. For example, SCFAs stabilize hypoxia-inducing factors (HIFs) linked to energy metabolism to enhance colon epithelial barrier function, which coordinates intestinal homeostasis [59, 60]. SCFAs also promote mitochondrial oxidative metabolism and oxygen consumption,which favors the survival of obligate anaerobes that produce SCFAs [61–63]. A beneficial cycle of microbial composition is established in the host intestine, further maintaining intestinal homeostasis. However, pathogen invasion disrupts colonic epithelial cell metabolism, and an increase in oxygen levels leads to an increase in the abundance of facultative anaerobes [60, 63]. Dysfunction of the gut can lead to bacterial translocation, which may result in diseases such as sepsis [5]. In addition, disruption of intestinal homeostasis results in alterations in the diversity and abundance of intestinal microbial communities, subsequently impacting the expression of functional genes and metabolism-related substances, which is closely linked to the development of CNS diseases process.

Intestinal microbiota and CNS diseases

The gut microbiota plays a role in the development of multiple CNS diseases (Table 1), including Parkinson's disease (PD), by inducing α-synuclein misfolding, which provides a false template for other bacteria [106]. Misfolded proteins transmitted via the vagus nerve can accumulate in the brain, leading to Lewy body formation, neuronal apoptosis, and clinical manifestations such as tremors, rigidity, and behavioral deficits in patients. In PD, a significant alteration in gut microbial composition is marked by increased levels of *Helicobacter pylori*, *Proteobacteria*, *Enterococcaceae*, and *Enterobacteriaceae*, which contribute to the inhibition of L-DOPA absorption, proinflammatory responses, and the progression of walking disorders [64–68]. Conversely, anti-inflammatory microbial groups such as *Prevotellaceae*, *Blautia*, *Coprococcus*, *Roseburia*, and *Fecalibacterium* show a notable decrease in abundance [66]. Alzheimer's disease (AD) patients exhibit increases in the abundance of gut microorganisms that mediate inflammation and a decreases in the abundance of inflammation-resistant microorganisms, indicating a relationship between gut dysbiosis and systemic inflammation that could trigger or exacerbate AD [7, 69–79]. Symptoms of intestinal dysbiosis, which can affect the severity of brain damage, have also been reported in ischemic stroke (IS) patients, which can affect the severity of brain damage [57, 80–88]. Therapeutic microbiota transplantation has the potential to reverse microbiota dysbiosis after cerebral ischemia and ameliorate poststroke brain dysfunction [107]. Moreover, the use of antibiotics to eliminate specific intestinal microorganisms has been shown to reduce the incidence of brain injury after stroke [108]. Hepatic encephalopathy (HE), a complication of cirrhosis characterized by brain inflammation and cognitive impairment, is traditionally attributed to ammonia. However, gut microbes are also involved in the inflammation and cognitive decline seen in HE patients [103, 104]. Patients with higher levels of *Alcaligeneceae and Porphyromonadaceae* experience more severe cognitive impairment, whereas those with higher levels of *Enterobacteriaceae* exhibit more intense inflammation. Probiotic intervention can reduce pathogenic bacteria and urease activity, thereby limiting ammonia diffusion and decreasing systemic ammonia levels, indicating the beneficial effects of probiotics on HE [109, 110]. Moreover, the disturbance of intestinal microbiota during minimal hepatic encephalopathy (MHE) has also been reported, but probiotic modulation of the intestinal microbiota can reduce blood ammonia levels and reverse MHE to some extent [105, 111, 112]. Brain demyelination and BBB disruption are symptoms of multiple sclerosis (MS). Intestinal microbes influence prefrontal cortical myelination and regulate BBB function [89, 113]. Changes in the gut flora can impact MS progression [89–99]. A decrease in *Lactobacillus* exacerbates experimental autoimmune encephalomyelitis (EAE) severity in a preclinical model [114]. However, BBB damage can be reversed by SCFAs or SCFA-producing gut bacteria in patients [115], perhaps because ionized or nonionized SCFAs can cross the intestinal barrier and enter the CNS via brain endothelial transporters, where they are taken up by glial cells to regulate cellular physiological processes and influence CNS function [116, 117].

Overall, a healthy gut microbiota can regulate host immunity and plays a protective role in maintaining the intestinal barrier. Abnormal changes in the gut flora have adverse effects on organs of the CNS via the axis, thus causing detrimental consequences for the brain, as mentioned above [101, 118]. Similarly, prior to the onset sepsis, gut microbiota dysbiosis creates an environment conducive to pathogen proliferation, thereby initiating a robust immune response and inhibiting the growth of beneficial bacteria along with their metabolites [6, 119]. This cascade of events facilitates sepsis development and increases the vulnerability of the host to end-organ dysfunction, notably affecting the brain [120]. As sepsis progresses, the disruption of the gut microbiota intensifies, perpetuating a detrimental feedback loop [121]. Consequently, impairment of the gut microbiota represents a significant risk factor for both sepsis progression and subsequent brain impairments.

Intestinal microbiota and SAE

Intestinal microbiota disorder in SAE

The development of SAE is intricately linked to the state of the intestinal microbiota (Table 1). Sepsis can disrupt the balance of the intestinal microbiota, affecting susceptibility to SAE in the CLP model [101, 102]. A recent study revealed that sepsis induces variations in the intestinal microbiota, resulting in individual differences in SAE susceptibility, defined as SAE-resistant (SER) and SAE-susceptible (SES) phenotypes, respectively [8]. SER and SES resulted in distinct gut microbiota compositions. SES mice had high levels of *Enterobacteriaceae*, which correlated with Treg cell dysfunction, worsened inflammation, promoted bacterial translocation, induced brain injury, and increased sepsis mortality risk [108, 122]. Furthermore, mice gavaged with the feces of SES mice had the shortest survival time and the lowest survival rate compared with mice gavaged with feces from SER or healthy mice. Moreover, mice gavaged with SES feces had higher TNF-α and IL-1β levels in the cerebral cortex than mice gavaged with SER feces [8]. These findings suggest that sepsis-induced neuroinflammation may stem from the translocation of the gut microbiota or its products, indicating a potential role for the gut microbiota as an upstream mediator in SAE. Consistent with these experimental findings, the levels of inflammatory mediators such as IL-6 and ICAM-5 and the number of neutrophils were significantly

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Table 1. Alterations and roles of intestinal microbiota in CNS diseases

Diseases	Intestinal microbiota species	Alteration	Functions	References
PD	*Helicobacter pylori*	Increase	Inhibit L-DOPA absorption	[64, 65]
	Proteobacteria	Increase	Pro-inflammation	[66]
	Enterococcaceae	Increase	Pro-inflammation	[67]
	Enterobacteriaceae	Increase	Associated with walking disorder	[68]
	Prevotellaceae	Decrease	Anti-inflammation	[66]
	Blautia	Decrease	Anti-inflammation	[66]
	Coprococcus	Decrease	Anti-inflammation	[66]
	Roseburia	Decrease	Anti-inflammation	[66]
	Fecalibacterium	Decrease	Anti-inflammation	[66]
AD	Escherichia	Increase	Induce pro-inflammatory cytokines and amyloid deposition	[69]
	Shigella	Increase	Induce pro-inflammatory cytokines and amyloid deposition	[69]
	Bacteroidetes	Increase	Promote activation of astrocytes and microglia	[70, 71]
			Promote amyloid fibrillogenesis	[72]
			Cause LPS translocation increases, exacerbating AD	[73]
	Pseudomonas	Increase	Increase of endothelial tau phosphorylation and permeability (AD pathogenesis)	[74]
	Faecalibacterium	Increase	Causes increase of Aβ deposits	[75, 76]
	Lachnospiraceae	Decrease	Cause low MMES score	[77]
	Eubacterium rectale	Decrease	Anti-inflammation	[69]
	Bacteroides fragilis	Decrease	Anti-inflammation	[69]
	Erysipelotrichaceae (Turicibacter)	Decrease	Promote activation of astrocytes and microglia	[69]
	Clostridiaceae (SMB53)	Decrease	Promote activation of astrocytes and microglia	[69]
	Bifidobacterium	Decrease	Anti-inflammation	[73]
			Enhance intestinal barrier function	[78]
			Reduce LPS content and bacterial translocation in the intestine	[79]
IS	Enterobacteriaceae	Increase	Increase inflammation cytokines and TLR4 expression, enhance IS	[80]
	Lactobacillus ruminis	Increase	Positively correlated with IL-6 and IL-8 level	[81, 82]
	peptococcaceae	Increase	Positively correlated with CCL5(inflammation cytokines)	[83]
	Ruminococcus_sp_15975	Increase	Could be biomarker of IS	[84]
	Oscillibacter	Increase	Increases intestinal permeability and triggers inflammation	[85]
	Deferribactere	Increase	Markers of intestinal metabolic disorders	[84, 86]
	Butyricicoccus	Decrease	Decreased intestinal epithelial permeability (TNF-α induced) and increased TJ protein integrity	[87]
	Prevotellaceae	Decrease	Cause aggravation of brain injury	[80, 83]
	Firmicutes	Decrease	Maintain intestinal function	[57, 84]
	Clostridium coccoides	Decrease	Induce the production of IL-10	[82, 88]
MS	*Akkermansia muciniphila*	Increase	Induced proinflammatory responses	[89]
	Acinetobacter calcoaceticus	Increase	Inhibit Treg development and promote inflammation	[89]
	Desulfovibrionaceae (Bilophila, Desulfovibrio and Christensenellaceae)	Increase	Pro-inflammation	[90]
	methanobrevibacter	Increase	Recruit inflammatory cells and stimulate dendritic cells, pro-inflammation	[72, 91]
	Akkermansia, Blautia and Dorea	Increase	Pro-inflammation	[92, 93]
	Parabacteroides distasonis	Decrease	Stimulate anti-inflammatory T cells and promote immunoregulatory responses	[89]
	Clostridiales (Ruminococcaceae and Lachnospiraceae)	Decrease	Produce butyrate(anti-inflammation)	[90, 94]
	Butyricomonas	Decrease	Protect barrier function and inhibit inflammation	[93]
	Erysipelotrichaceae	Decrease	Induce anti-inflammatory properties	[95, 96]
	Veillonellaceae	Decrease	Induce Treg	[88, 95]
	Prevotella histicola	Decrease	Suppress progression of EAE	[95]
	Clostridia clusters XIVa, IV, and *B. fragilis*	Decrease	Induce Foxp3 Treg and suppress progression of EAE	[88, 97, 98]
	Prevotella copri	Decrease	Induction of MS pathogenesis	[98]
	Faecalibacterium	Decrease	Produce butyrate, reduce inflammation	[75, 99]
SAE	Acinetobacter	Increase	Associated with SAE onset	[100]
	Alistipes	Increase	Associated with decreased brain function	[100, 101]
	Enterobacteriaceae bacteria	Increase	Enterobacteriaceae aggravate systemic inflammation and bacterial transmission	[8, 80, 102]
	Ruminococcaceae	Decrease	Produce butyrate(anti-inflammatory)	[94, 100]
	Faecalibacterium	Decrease	Associated with decreased brain function	[100, 101]
	Firmicutes	Decrease	Firmicutes enhance intestinal barrier function and suppress inflammation	[8, 78]
HE	Veillonellaceae	Increase	Pro-inflammation, induce endotoxemia and poor cognition	[103]
	Alcaligenecae	Increase	Positively correlated with cognitive dysfunction	[103, 104]
	Porphyromonadaceae	Increase	Positively correlated with cognitive dysfunction	[103, 104]
	Enterobacteraceae	Increase	Positively correlated with inflammatory	[103]
	Fusobacteriaceae	Increase	Positively correlated with inflammatory	[103]
	Enterococcus, Megasphaera, and Burkholderia	Increase	Associated with poor cognition, inflammation, endothelial activation	[104]
	Streptococcus salivarius	Increase	Associated with cognitive function and ammonia	[105]
	Ruminococcaceae	Decrease	Negatively related to inflammation	[103]
	Roseburia	Decrease	Negatively associated with inflammation and endothelial activation	[104]

PD parkinson's disease, *AD* Alzheimer's disease, *Aβ* amyloid β, *MMSE* Minimum Mental State Examination, *IS* ischemic stroke, *IL-10* interleukin-10, *HE* hepatic encephalopathy, *MHE* minimal hepatic encephalopathy, *TLR4* toll like receptor 4, *CCL5* chemokines like C-C motif ligand-5, *TNF-a* tumor necrosis factor-a, *TJ* protein tight junction protein, *MS* multiple sclerosis, *EAE* experimental autoimmune encephalomyelitis

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greater in serum from SAE patients than in serum from non-SAE sepsis patients, whereas the intestinal microbial community composition was altered and diversity was decreased, suggesting adverse effects of SAE on intestinal microbiota homeostasis [100]. Notably, during the progression from sepsis to SAE, sepsis initially directly damages the intestinal epithelium through peripheral proinflammatory mediators, such as TNF-α and IL-1β, and oxidative stress rather than through primary dysregulation of the intestinal flora. This epithelial injury compromises the integrity of the intestinal barrier, facilitating the subsequent translocation of pathogenic bacteria and their products, such as LPS and outer membrane vesicles (OMVs). These translocated substances enter the systemic circulation, cross the disrupted BBB, trigger central neuroinflammation, including microglial activation and astrocyte dysfunction, and cause neuronal damage, ultimately driving the development of SAE.

Additionally, sepsis is nearly always accompanied by sepsis-associated intestinal paralysis (which is characterized by impaired intestinal motility) [123, 124]. On the one hand, intestinal paralysis alters the distribution of nutrients and the partial pressure of oxygen within the intestinal lumen, promotes excessive proliferation of pathogenic bacteria, and exacerbates the imbalance of intestinal microbiota [125–127]. On the other hand, it increases the probability that the retained microbiota and its metabolic products will permeate the impaired intestinal barrier and shift, indirectly promoting the development of SAE by disrupting the BBB and initiating inflammation in the CNS. Concurrently, CNS damage in SAE, including autonomic nerve dysfunction, can suppress intestinal peristalsis via the gut–brain axis. This suppression creates a vicious cycle of CNS injury, intestinal paralysis, and intestinal flora dysbiosis that may contribute to the progression of SAE.

Numerous neurotransmitters, signaling pathways, and anatomical features are shared between the CNS and enteric nervous system (ENS), which explains why pathophysiological processes associated with CNS disorders often manifest with concomitant gastrointestinal alterations [128]. For instance, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes similar neuronal damage to the CNS and ENS of mice [129]. Mechanistically, CNS injury downregulates the activity of intestinal cholinergic nerves, reducing Ach release and thus inhibiting intestinal smooth muscle contraction. This process is the key link through which neural damage indirectly affects intestinal function and further disrupts the gut microbiota. In turn, gut microbiota dysbiosis exacerbates neuroinflammation via toxic metabolites, reinforcing the aforementioned vicious cycle. Here, the gut microbiota serves as a critical intermediate messenger for pathological signaling.

Intestinal microbiota-induced BBB disruption

BBB disruption is a key pathogenic mechanism of SAE, and the intestinal microbiota has been shown to influence this process. Specifically, indigenous intestinal flora regulate BBB integrity mainly through beneficial metabolites, while translocated pathogenic bacteria and their structural components directly disrupt BBB function through two distinct pathways. A previous study indicated that the monoclonal antibody R4A causes hippocampal neuron damage upon reaching the CA1 region. These findings suggest that a decrease in the abundance of beneficial gut microorganisms reduces the expression of TJ proteins (occludin and claudin-5) and increases the permeability of the BBB [115]. This effect was reversed in germ free (GF) mice exposed to a normal gut microbiota. Induced intestinal microbiota dysbiosis in rhesus monkeys by antibiotics, particularly a reduction in the genera of bacteria that produce acetic acid and propionic acid, which is associated with sustained deterioration in the permeability of the BBB [130]. Another study demonstrated that TJ and clandin-5 mRNA and protein are expressed in early-life antibiotic-treated mice and revealed that interference with the gut microbiota of the mice altered the integrity of the BBB in the hippocampus [131]. These findings indicate a correlation between the increasingly impaired barrier function of the BBB and the severity of gut microbiota dysbiosis. During intestinal perforation-induced sepsis, the effects of the gut microbiota on the BBB are pronounced. Gram-positive bacterial (G+) cell wall components such as lipoteichoic acid and muramyl dipeptide activate glial cells to release NO and cytokines, disrupting of BBB integrity and function (Table 2). This process depends on NO, TNF-α, and IL-1β and results in increased BBB permeability [132]. Toll-like receptors (TLRs) on brain endothelial cells recognize pathogen-associated molecular patterns (PAMPs), inducing inflammation [145]. For instance, the activation of TLR2/TLR6 by fungal zymosan can result in reduced occludin and claudin-5 expression, potentially leading to a loss of TJ proteins and compromising the integrity of the BBB [133].

Intestinal microbiota-induced neuroinflammation

The intestinal microbiota and its metabolites are increasingly recognized as pivotal regulators of the cerebral immune response (neuroinflammation). Microglia, which are CNS-resident immune cells, participate in all neuroinflammatory processes. Activated microglia release a variety of chemokines and cytokines, regulate neurotransmitter release and undergo morphological alterations to maintain homeostasis. Crucially, the phenotype and function of microglia are modulated by gut microbiota. For instance, microglia isolated from GF mice and antibiotic-treated mice exhibit immature microglial attributes, differentiation and functional defects [146]. These cells decrease in number and show impaired immune responses, despite increased expression of colony-stimulating factor 1 receptor (CSF1R), F4/80, and CD31 [147], indicating that decreased gut microbiota diversity also restricts the maturation process of microglia. Furthermore, microbes influence microglial polarization. Research has revealed that intestinal barrier dysfunction (induced by microbiota dysbiosis) increases the level of secreted lipocalin-2 (LCN2), exacerbating cognitive decline and neuroinflammation in sepsis and neuroinflammation models [148, 149]. This protein upregulates M1 gene expression in microglia and impedes M2 signaling by inhibiting the phosphorylation of STAT6 in microglia, thereby promoting M1 polarization [148]. However, SCFA supplementation or microbiota restoration reverses microglial immaturity and dysfunction in GF mice [147, 150]. Additionally, antibiotic-induced dysbiosis also reduces the expression of microglial major histocompatibility complex (MHC), likely due to decreased CIITA transcription factor levels [151]. Nevertheless, microglia activate T cells via MHC-mediated antigen presentation [152]. Therefore, reduced gut microbiota and antigen-presenting mechanisms can impact the role of microglia in neuroinflammation. Collectively, the absence of beneficial microorganisms leads

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Table 2. The key mechanism of intestinal microbiota components and their metabolites in SAE

Gut microbiota/metabolites	Target/pathway	Pathological phenotype of SAE	References
Lipoteichoic acid (LTA) and muramyl dipeptide (MDP)(G+)	NO; TNF-α and IL-1β	Glia cells activation ↑; BBB integrity ↓	[132]
Zymosan (fungi)	TLR2; TLR6	Occludin and claudin-5 protein expression ↓; BBB disruption ↑; TJ proteins ↓	[133]
LPS(G-)	TLR4, NF-κB, MMP, NLRP3 and IL-1β	TJ proteins ↓, BBB permeability ↑, neutrophil influx ↑; astrocyte activation ↑	[134–136]
Acetate, propionate, and butyrate (SCFAs)	CD11b; GPR43; c-Jun N-terminal kinase (JNK) and NF-κB p65 phosphorylation	TJ protein↑, BBB integrity ↑; activity of microglia and neuroinflammatory injury ↓; behavioral dysfunction ↓	[130, 137]
Metabolite of tryptophan	AhR IL-22, TNF-α, IL-1β and IL-6	Neuronal oxidative stress ↓; neuroinflammation ↓; macrophage phagocytosis ↑	[8, 138, 139]
γ-aminobutyric acid (GABA) (*Lactobacillus*)	GABA receptors	Microglia overactivation ↓; oxidative stress ↓; BDNF expression ↑ ;AChE inhibitor	[52, 53, 140–143]
Probiotic	TNF-α, IL-1β and IL-6; Iba-1; β1-p38 MAPK	Microglia overactivation ↓; neuron injury ↓; cognitive disorder ↓; BDNF expression ↑ ;gut barrier function ↑; bacterial translocation ↓	[10, 144]

BBB blood-brain barrier, *TJ* tight junction. *NO* nitric oxide, *IL* interleukin, *LPS* lipopolysaccharide, *TLR* toll like receptor, *NF-κB* nuclear factor kappa, *BMMP* matrix metalloproteinase, *NLRP3* NLR family pyrin domain containing 3, *GPR43* G-protein-coupled receptor 43, *BDNF* brain-derived neurotrophic factor, *AChE* acetylcholinesterase, *Iba-1* ionized calcium binding adaptor molecule

to microglial developmental arrest and impaired immune responses to pathogens. This immune dysregulation can further stimulate microglial overactivation, resulting in a sustained inflammatory state in the brain [153]. In addition to microglia, the gut microbiota also regulates astrocyte function. For example, astrocytes expressing lysosomal-associated membrane protein 1 (LAMP1) and TNF-related apoptosis-inducing ligand (TRAIL) limit neuroinflammation by inducing T-cell death. Their function is maintained through interferon-γ (IFN-γ) regulation mediated by the gut microbiome [154]. Furthermore, the aromatic hydrocarbon receptor (AhR) in astrocytes plays a crucial role in limiting CNS inflammation. AhR activity is regulated by small molecules, some of which are derived from dietary sources and commensal microbiota. Metabolites generated from dietary tryptophan via gut microbiota-mediated metabolism can activate AhR signaling in astrocytes and suppress CNS inflammation [155].

Mechanistically, SAE progression increases intestinal barrier and BBB permeability, amplifying the effects bacteria on neuroinflammation. Bacterial OMVs (50–250 nm in diameter) derived from gram-negative bacteria(G-) contain LPS in their outer leaflet as well as comprise bioactive proteins, lipids, and nucleic acids [156, 157]. SAE patients show increased intestinal G- abundance [8]. And ischemic injury caused the proliferation of *Enterobacteriaceae* (G-) results in a higher concentration of LPS in the outer membrane of OMVs [108]. On the one hand, LPS, a toxic component of the bacterial cell wall, can directly target the intestinal mucosal epithelium to disrupt, TJs between epithelial cells and increase intestinal mucosa permeability [158], thereby potentially inducing SAE. On the other hand, LPS in the outer membrane of OMVs activates nuclear factor kappa B (NF-κB) translocation to the nucleus through binding to TLR4. This activation promotes the upregulation of inflammatory mediators that induce the expression of ICAM and cytokines, thereby activating endothelial cell and neutrophil recruitment and excessive accumulation in the damaged region of the brain [134, 135]. Moreover, LPS stimulates microglial activation and upregulates of TLR4 expression, thereby activating the NLR family pyrin domain containing 3 (NLRP3) inflammasome to produce IL-1β, a key mediator of SAE development [136, 159]. OMVs from *Escherichia coli* (*E. coli*) in the plasma of patients with severe sepsis trigger a systemic inflammatory response by inducing the proinflammatory cytokines TNF-α and IL-6, which further induce distant organ dysfunction [160]. In summary, OMVs secreted by the intestinal microbiota may play a role in the pathogenesis of SAE by increasing intestinal permeability, facilitating the entry of LPS into the circulation, producing cytotoxic and proinflammatory mediators, and impairing brain endothelial function (Figure 2).

Intestinal microbiota-based therapeutics for SAE

Currently, a definitive treatment for SAE is lacking because of its complex pathogenesis and the interplay of multiple factors. However, interventions targeting indigenous intestinal microbiota modulation have emerged as potential treatments that may improve this condition (Figure 3).

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is an effective method to directly supplement the healthy indigenous intestinal flora, thereby reversing the dysbiosis of intestinal microbiota and multiple organ dysfunction syndrome (MODS) in sepsis patients [161, 162]. Studies have demonstrated disruption and structural changes in the intestinal microbiota of SAE model mice compared with controls [8, 100, 163]. Moreover, increased expression of inflammatory markers including Iba-1, TNF, IL-6, IL-18 and IL-1β was detected in the brain cortex of SAE mice. Furthermore, the surface expression of acetylcholine receptors (AChRs) on microglia within the brain cortex was markedly reduced, indicating a severe imbalance

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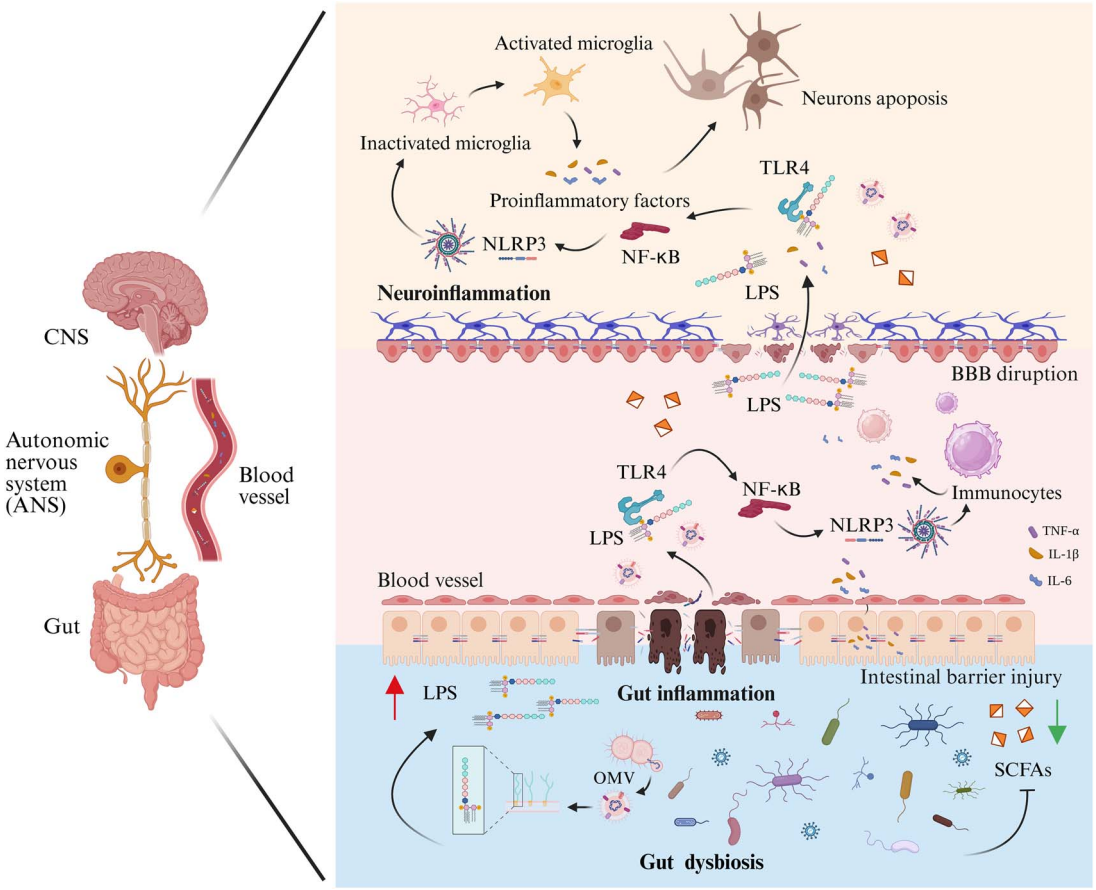


Figure 2. Microbiome–gut–brain axis in SAE. Created with BioRender (https://biorender.com/)

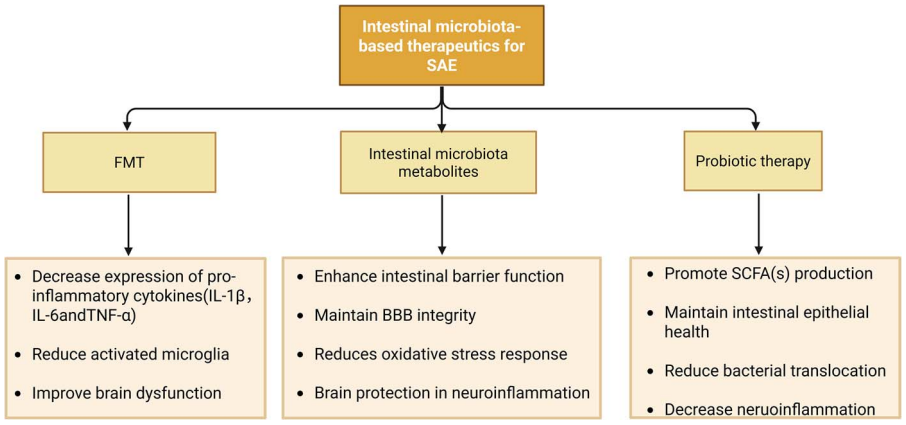


Figure 3. Intestinal microbiota therapeutic targets and functions related to SAE. Created with BioRender (https://biorender.com/)

in the inflammatory response and neuroinflammation in SAE mice. Activation of the cholinergic anti-inflammatory system typically occurs during inflammation. The nervous system triggers ACh release from vagal efferent nerve terminals via the inflammatory reflex of the vagus nerve, stimulating AChR expression on the surface of inflammatory cells to inhibit proinflammatory cytokine release and tissue damage [164]. However, FMT improved spatial memory and reduced abnormal electroencephalography (EEG) activity in SAE mice. Additionally, FMT utilizing microbiota from healthy donors attenuated SAE via vagus nerve signaling, as evidenced by decreased hippocampal expression of proinflammatory cytokines (IL-1β, IL-6, and TNF-α), reduced cortical Iba-1 expression (indicating diminished microglial activation), and reversal of these effects by vagotomy (VGX) [101]. Thus, FMT may improve SAE by regulating the vagus nerve mediated cholinergic anti-inflammatory pathway. FMT is highly important for downregulating the expression of inflammatory mediators in the CNS and represents a promising therapeutic target for SAE [165].

Intestinal microbiota metabolites

Microbial metabolites, particularly SCFAs such as acetate, propionate, and butyrate derived from dietary fiber,

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compensate for the functional deficiency of the dysbiotic gut flora by exerting direct neuroprotective effects. SCFAs lower intestinal pH, reduce the impact of pathogens on epithelial permeability, and thereby help prevent systemic infection. These properties suggest a role for SCFAs in treating neurological disorders and modulating CNS function. BBB injury and neuroinflammation caused by microglial overactivation are pivotal for SAE development, resulting in cognitive, memory, reflex, and sensory dysfunction. SAE model mice exhibit significantly reduced intestinal propionate and acetate levels, which are attributable to diminished populations of SCFA-producing bacteria [11]. Notably, pretreatment with SCFAs upregulated the expression of occludin and ZO-1 in the brain, maintaining BBB integrity. SCFAs also suppressed the expression of COX-2 and cluster differentiation 11b (CD11b), which are markers of microglial overactivation, and reduced the release of IL-1β and IL-2, demonstrating anti-inflammatory effects and ameliorating CNS cognitive impairment [137]. SCFAs may attenuate neuroinflammation and prevent SAE-induced cognitive dysfunction by binding to G-protein-coupled receptor 43 (GPR43) [11]. *In vitro* and *in vivo* studies have confirmed that SCFAs increase TJ protein expression, mitigate BBB damage, and reduce neuroinflammation and cognitive impairment in SAE mice. Additionally, SCFAs protect against SAE progression by modulating intestinal mucosal lesions, improving intestinal barrier function, and thereby reducing bacterial translocation [163]. During sepsis, oxidative stress generates excessive ROS in cellular metabolism, causing cell damage or death and promoting the release of IL-1β. However, butyrate intervention restores redox balance, while reducing ROS levels and inflammation [166]. Furthermore, the intestinal microbiota metabolizes tryptophan to indoxyl and indoxyl-3-sulfate (I3S), activating the astrocytic aromatic receptor (AhR). This activity modulates the anti-inflammatory effects of CNS type I interferons (INF-Is), thereby mitigating neuroinflammation. Indole and I3S supplementation AhR-dependently downregulate the expression of astrocytic proinflammatory markers (CCL2 and NOS2), supporting the protective role of intestinal metabolites in the brain during neuroinflammation [155]. Early research demonstrated that indole-3-propionic acid (IPA), a derivative of the intestinal microbiota, can cross the BBB, modulate astrocyte activity, and exert neuroprotective effects [138, 167]. Notably, the fecal IPA content is greater in SAE-resistant than SAE-susceptible mice [8]. IPA protected against SAE mortality and reversed CLP-induced cognitive decline. In summary, intestinal microbiota metabolites influence SAE progression by modulating neuroinflammation, immune reactions, brain barrier integrity, and energy metabolism, highlighting their therapeutic potential in SAE.

Probiotic therapy

Beyond utilizing microbial metabolites, probiotics and prebiotics that promote the proliferation of native beneficial bacteria indirectly improve SAE by modulating the composition of the intestinal flora. They enhance the intestinal barrier, inhibit the overgrowth of pathogenic bacteria, and reduce bacterial translocation. During SAE, an imbalance in the gut microbiota occurs, which is accompanied by bacterial translocation resulting from intestinal barrier dysfunction. Translocated bacteria can then induce excessive glial cell activation and abnormal inflammatory factor expression via gut–brain axis neural pathways, culminating in neuroinflammation. Probiotics promote intestinal health through multiple mechanisms [168, 169]. For example, they increase organic acid production within the gut microbiota via cross-feeding, which benefits intestinal barrier function [170]. Polyphosphate from *Lactobacillus brevis* activates p38 MAPK to protect epithelial cells and maintain intestinal homeostasis, thereby avoiding preventing damage to the intestinal epithelium caused by toxic substances and inflammatory factors [10]. Moreover, *Lactobacillus plantarum* MB452 upregulates TJ protein expression [140]. In addition, certain *Lactobacillus* strains facilitate the recovery of ACh levels and cognitive improvement [171]. One of the key neurotransmitters it generates, GABA, is expressed on microglia, whose activation can increase the production of brain-derived neurotrophic factor (BDNF) by LPS-activated microglia and thereby reduce neuronal damage [141–143]. Furthermore, specific metabolites of *Lactobacillus* inhibit the activity of AChE, an enzyme critical to the pathogenesis of SAE, in the brain tissue of mice [52, 141]. Probiotic *E. coli* strains increase the mRNA and protein expression levels of ZO-1 in colonic epithelial cells, stabilizing TJs and preventing bacterial translocation. Similarly, the probiotic *E. coli* Nissle 1917 (EcN) increases mucin expression, which reduces pathogen binding with the intestinal epithelium and protects the intestinal barrier [172]. Unlike FMT, which aims to restore gut colonization, probiotics may alleviate SAE-related cognitive impairment by correcting dysbiosis [144, 173]. Administration of the probiotic *Clostridium butyricum* (Cb) reversed gut microbiota dysbiosis in SAE mice, thereby preventing microglial overactivation, reducing inflammation, increasing BDNF levels, and ultimately mitigating cognitive impairment [144]. Furthermore, previous research has shown that probiotics can be used to prevent and control the development of sepsis in infants [174]. In summary, probiotic therapy maintains intestinal barrier function, mitigates bacterial translocation and gut microbiota dysbiosis, and thereby prevents neuroinflammation, supporting its potential as an intervention measures for SAE.

Mounting evidence has shown that intestinal microbiota dysbiosis and its metabolites play key roles in the occurrence and development of SAE via the gut–brain axis. Structural components (such as PAMPs) and bioactive metabolites released by the gut microbiota can breach the damaged intestinal barrier, and enter the circulation to affect endothelial cells, glia, and neurons within the CNS. This interaction triggers neuroinflammation, disrupts the integrity of the BBB, alters neurotransmitter balance and ultimately causes neuronal damage and cognitive impairment, which are mediated by the activation of specific receptors and signaling pathways. To systematically outline the mechanisms of key gut microbial components and metabolites in SAE, Table 2 summarizes critical factors, detailing their targets or pathways, that induce or ameliorate pathological phenotypes in SAE. This table clearly illustrates the dual role of the gut microbiota in SAE: Different pathogenic components (such as LPS, LTA, MDP and zymosan) exacerbate neuroinflammation and BBB disruption, whereas protective components (such as SCFAs, tryptophan metabolites, GABA and probiotics) confer neuroprotection, maintain BBB integrity, and suppress excessive inflammation. Understanding these specific mechanisms is vital for developing novel strategies targeting the gut microbiota to prevent and treat SAE.

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Future research directions of SAE from the perspective of the intestinal microbiota

Sepsis can result from infections with a wide range of pathogens. For instance, bacterial sepsis caused by both G+ and G-, as well as fungal sepsis caused by *Candida* species, is frequently observed in clinical intensive care unit (ICU) settings [175]. During the development of sepsis, live gut bacteria have been detected in the brain, and changes in bacterial communities are associated with the severity of neuroinflammation [6]. However, the consistency of alterations in the gut microbiota across SAE patients with different infection sources has not yet been characterized in detail. Furthermore, compared with the healthy groups, the SAE groups tended to have inverse distributions of the Firmicutes (G+) and Proteobacteria (G-) ratios, which may indirectly exacerbate SAE pathogenesis and its adverse outcomes [8, 176]. Intestinal *Enterococcus* levels decrease in sepsis, concurrently with a surge in the relative abundance of *Enterobacteriaceae* and *Bacteroides* species, which are commonly linked to inflammatory processes [177]. Nonetheless, investigations into. The implications of the differential proportions of cocci and bacilli for SAE progression are lacking. These findings warrant further exploration.

The current standard treatment for sepsis adheres to the 2021 Surviving Sepsis Campaign Guidelines, which include the following: (i) infection control; (ii) hemodynamic management; and (iii) Organ function protection. SAE lacks a specific treatment, and management primarily relies on the basic treatment of sepsis combined with symptomatic support. Among these measures, antibiotics significantly impact intestinal flora: The early, adequate administration of broad-spectrum antibiotics can quickly control infection but may reduce indigenous flora and promote drug-resistant bacteria, whereas delayed use or inappropriate changes in medication may exacerbate the spread of infection and further disrupt the balance of the flora, which is closely related to a poor prognosis for patients with SAE [178–182]. However, gut microbiota-based approaches remain unadopted in clinical practice. A registered observational clinical study (ChiCTR2400090085) aimed to diagnose, predict SAE and differentiate SAE clinical phenotypes via gut microbiota analysis. Furthermore, an ongoing prospective observational clinical investigation (NCT06749483) will evaluate correlations between sepsis-associated clinical outcomes (such as cerebral dysfunction) and the dysregulation of the intestinal microbiota, specifically emphasizing the influence of metabolites derived from the gut microbiota on cognition. Previous studies have focused on the role of gut microbial metabolites in regulating inflammatory responses and oxidative stress, but relatively few have applied them to the treatment of SAE [183–185]. These metabolites can cross the BBB and have demonstrated potential therapeutic efficacy in inhibiting CNS inflammation, which may also benefit the control of neuroinflammation in SAE patients [186–188]. A recent clinical study revealed that a reduction in gut microbiota-derived 3-indoleacetic acid (IAA) was associated with worse clinical outcomes in SAE patients who presented with delirium, and exogenous supplementation with 3-indoleacetic acid (IAA) improved cognitive impairment by activating AhR in microglia [139]. In addition, Xu et al. reported that the clinical drug palmatine can indirectly ameliorate the excessive inflammation and brain dysfunction caused by SAE through promoting the growth of beneficial gut microbiota, inhibiting the proliferation of harmful bacteria, and alleviating intestinal metabolic disorders [189]. To a certain extent, these studies suggest that intestinal microbiota and its derivatives have potential application value in the treatment of clinical SAE.

Conclusions

The pathogenesis of SAE is intricate and multifaceted, which leads to suboptimal clinical outcomes. Inhibiting the progression of SAE with a single treatment approach is challenging. Studies investigating intestinal crosstalk with CNS diseases have highlighted the significant role that gut microbial composition and function may play in the development of various diseases beyond the gastrointestinal tract. Notably, there is interplay between disturbances in the intestinal microbiota and SAE. As SAE progresses, alterations in the composition of the intestinal microbiota potentially promote BBB injury and neuroinflammation, thereby exacerbating SAE pathology. However, the exact mechanisms by which the gut microbiota regulates SAE remain elusive. Given that the gut–brain axis can be influenced by the intestinal microbiota and that interactions exist between the intestinal microbiota and SAE, targeting the intestinal microbiota has been proposed as a novel therapeutic strategy for SAE. Modulating the homeostasis of the intestinal microbiota can help maintain the integrity of the intestinal barrier and immune function, thereby reducing brain cell damage caused by bacterial translocation and systemic circulation of inflammatory factors. However, research on the regulation of the intestinal microbiota for SAE treatment remains limited, and further investigations are needed to explore the specific relationship between SAE and intestinal microbiota disorders. Additionally, translational research focusing on elucidating the mechanisms connecting these two crucial organ systems is necessary to develop targeted gut-based therapies targeting specific microbial components.

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Author contributions

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Ethics approval and consent to participate

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Consent for publication

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