Integrating gut-brain axis insights into bundled nutrition care for critically ill patients: From mechanisms to implementation (Review)

LIQI ZHANG[1*], SHUXIA YANG[1*], HUIYAN WU[2] and HONG ZHOU[3]

[1]Department of Critical Care Medicine, Baiyin Central Hospital, Baiyin, Gansu 730900, P.R. China; [2]Department of Nephrology, Baiyin Central Hospital, Baiyin, Gansu 730900, P.R. China; [3]Department of Obstetrics, Baiyin Central Hospital, Baiyin, Gansu 730900, P.R. China

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Abstract. Critical illness induces a marked disruption of the gut-brain axis, which is characterized by systemic inflammation and the rapid collapse of intestinal barrier integrity. These pathological shifts facilitate the translocation of pathogen-associated molecular patterns, thereby driving neuroinflammation and exacerbating intensive care unit-acquired syndromes such as delirium and muscular wasting. Although conventional nutritional strategies emphasize caloric and protein goals, emerging evidence has highlighted the necessity of modulating the host-microbiome interface to preserve neurological and systemic homeostasis. The integration of fermentable fibers, probiotics and specialized lipid mediators into a standardized framework may effectively interrupt the self-perpetuating cycle of dysbiosis and organ failure. The present review uniquely contributes to the field by integrating an implementation science framework for clinical bundle application and discussing artificial intelligence driven precision nutrition advances, which are topics that have not been comprehensively covered in the majority of previous reviews. Therefore, the present review bridges mechanistic insights with practical, scalable strategies to optimize nutritional care and improve recovery trajectories in patients with critical illness.

Correspondence to: Dr Hong Zhou, Department of Obstetrics, Baiyin Central Hospital, 13 Baoci Road, Pingchuan, Baiyin, Gansu 730900, P.R. China
E-mail: 397427726@qq.com

*Contributed equally

Abbreviations: AHR, aryl hydrocarbon receptor; AI, artificial intelligence; BBB, blood-brain barrier; EN, enteral nutrition; ENS, enteric nervous system; GBA, gut-brain axis; HPA, hypothalamic-pituitary-adrenal; ICUAW, intensive care unit-acquired weakness; ICU, intensive care unit; LPS, lipopolysaccharide; PICS, persistent inflammation, immunosuppression and catabolism syndrome; SAE, sepsis-associated encephalopathy; SCFA, short-chain fatty acid; SPM, specialized pro-resolving mediator; TLR4, toll-like receptor 4; TPN, total parenteral nutrition; VAP, ventilator-associated pneumonia; VBF, volume-based feeding

Key words: gut-brain axis, critical illness, intensive care unit, enteral nutrition, dysbiosis, neuroinflammation, intestinal barrier integrity, nutrition care bundles

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1. Introduction

Critical illness represents a marked physiological challenge that is characterized by a systemic inflammatory response and the frequent progression to multiple organ dysfunction syndrome. Historically, the gastrointestinal tract has been viewed as a passive victim of circulatory failure; however, modern evidence has redefined it as the primary engine of systemic sepsis. Wozniak *et al* (1) highlighted the central and biodynamic role of the gut microbiota in orchestrating host responses during critical illness, thus suggesting that intestinal health is closely associated with clinical outcomes. The breakdown of the intestinal barrier allows for the translocation of pathogen-associated molecular patterns, which exacerbates systemic immune activation and promotes distant organ injury (2). This phenomenon is particularly evident in cases of septic shock and major trauma, wherein gut-derived signals propagate damage to the lungs, liver and brain (3,4). Therefore,

an understanding of the gut as a dynamic immune and metabolic hub is key in improving the recovery trajectories of the most vulnerable patient populations.

The bidirectional communication between the enteric environment and the central nervous system, known as the gut-brain axis (GBA), is a key determinant of the host adaptive response to acute stress. During critical illness, this axis is severely disrupted by neuroendocrine shifts and local inflammatory mediators. Wang *et al* (5) recently described how the GBA influences the pathogenesis of sepsis-associated encephalopathy, underscoring the importance of neural and humoral pathways in neuroprotection. These interactions are mediated by a variety of signals, including neurotransmitters, cytokines and microbial metabolites that reach the brain through the vagus nerve or systemic circulation (6). Furthermore, the enteric nervous system (ENS) itself is highly susceptible to oxidative stress and inflammation, which can impair intestinal motility and further compromise barrier function (7,8). Consequently, the GBA serves as an important conduit that associates intestinal integrity with neurological and systemic homeostasis during the acute phase of severe illness.

A hallmark of the critically ill state is the rapid and profound loss of microbial diversity, often referred to as dysbiosis, which notably impacts host defense mechanisms. This microbial collapse is driven by factors such as broad-spectrum antibiotic use, altered nutrient delivery and extreme physiological stress (9,10). Klingensmith and Coopersmith (11) emphasized that the disappearance of commensal organisms and the emergence of pathobionts are key contributors to the persistence of the systemic inflammatory response in the intensive care unit (ICU). The depletion of beneficial species reduces the production of short-chain fatty acids (SCFAs), which are necessary for maintaining the intestinal epithelial lining and regulating immune cell activity (12). In addition, this dysbiosis is not confined to the gut, as the crosstalk between the gut and other organs often leads to secondary complications such as myocardial dysfunction or acute lung injury (13,14). In summary, the maintenance of a healthy and diverse microbiome is a prerequisite for preventing the secondary inflammatory cascades that lead to poor clinical prognoses.

Traditional nutritional therapy in the ICU has primarily focused on meeting caloric and protein targets, but the 2022 American Society for Parenteral and Enteral Nutrition guidelines advocate for a more nuanced approach centered on metabolic and microbial support (15). Despite the established benefits of early enteral nutrition (EN), including reduced infectious complications, preservation of gut barrier function and attenuation of systemic inflammation, many patients still fail to meet their physiological requirements due to feeding intolerance or clinical interruptions, such as diagnostic procedures, surgical interventions, feeding tube-related issues and gastrointestinal intolerance (for example, high gastric residual volumes) (16,17). Furthermore, standard polymeric formulas (for example, Osmolite and Jevity), which provide macronutrients as whole proteins, carbohydrates and fats, typically lack fermentable fiber, probiotics and immunomodulatory nutrients, such as omega-3 fatty acids, arginine and glutamine. The inclusion of dietary fiber and probiotics has been shown to modulate the GBA through multiple mechanisms: Fermentable fibers are metabolized to short-chain fatty acids such as butyrate, which suppress TLR4/NF-κB signaling, reduce pro-inflammatory mediators, and reinforce intestinal epithelial and blood-brain barrier integrity, while probiotics restore microbial diversity, competitively exclude pathogens and enhance tight junction protein expression, thereby attenuating systemic inflammation and endotoxemia. These effects have been demonstrated in various clinical and experimental models (18,19). Abenavoli *et al* (20) suggested that immunonutrition and targeted probiotic therapy could bridge the gap between simple caloric delivery and active immune modulation. Thus, evolving from passive feeding to a strategy that actively protects the gut-brain interface is a necessary progression in modern critical care medicine.

Given the complexity of the gut-brain interaction, a fragmented approach to nutritional therapy is often insufficient, necessitating the development of an integrated 'GBA-informed nutrition care bundle'. This bundled approach combines evidence-based interventions such as early EN, microbial modulation and specialized substrate delivery into a standardized implementation framework (21). By integrating these interventions, clinicians can address gut failure as both a cause and a consequence of critical illness (4). Current research efforts have been increasingly focused on translating these mechanistic insights from the bench to the bedside (namely, the translation of fundamental mechanistic discoveries into routine clinical practice) through structured protocols and multidisciplinary care teams (22,23). Furthermore, the metabolic perspective of critical care nutrition highlights the need for precision interventions that adapt to the individual physiological needs of the patients (24). In summary, the present review aimed to summarize the current understanding of GBA mechanisms and provide a practical, bundled framework for optimizing nutrition care in the critically ill.

2. Mechanisms of GBA disruption in critical illness: From dysbiosis to neuroinflammation

Bidirectional communication between the gastrointestinal tract and the central nervous system, collectively termed the GBA, undergoes marked pathological shifts during critical illness. The present section delineates the multi-layered mechanisms through which initial systemic insults, such as sepsis or trauma, trigger a self-perpetuating cycle of intestinal failure and neurological impairment (Fig. 1). Understanding these mechanisms is key in appreciating how the GBA serves as both a target and a driver of critical illness progression (25,26).

Critical illness-induced 'dysbiosis signature'. In the ICU environment, the stable commensal microbiota is rapidly replaced by a 'dysbiosis signature' characterized by a loss of diversity and the dominance of opportunistic pathogens. This shift is frequently driven by necessary but disruptive clinical interventions. For instance, Shao *et al* (27) recently emphasized that antibiotic-induced dysbiosis notably aggravates cerebral injury, particularly in patients undergoing extracorporeal membrane oxygenation. Such disruptions lead to a marked depletion of protective taxa, such as *Bifidobacterium* and *Lactobacillus*, which are key in maintaining immune homeostasis (28).

The resulting microbial landscape is often dominated by Proteobacteria, a shift that is associated with increased systemic inflammation. In patients with neuro-critical illness,

this gastrointestinal dysbiosis is also a prognostic indicator of clinical severity (29). Furthermore, the loss of beneficial metabolites, such as SCFAs, impairs the ability of the host to regulate inflammatory responses within the gut lumen (30). From a mechanistic perspective, this loss of SCFAs represents not just the deficiency of metabolic fuel. SCFAs, particularly butyrate and valerate, act as endogenous histone deacetylase inhibitors (HDACs) that selectively target class I HDACs (such as HDAC3), thereby modulating the transcription of pro-inflammatory genes (including IL-1β, IL-6, TNF-α and IFN-γ) and reinforcing the intestinal epithelial barrier through epigenetic mechanisms, such as increased histone H3 acetylation at promoters of anti-inflammatory genes (for example, Foxp3 and occludin) and reduced histone acetylation at promoters of proinflammatory genes (8,12). Consequently, the 'ICU microbiome' becomes a reservoir for virulence, where the overgrowth of pathobionts forms the basis of systemic translocation. In summary, the dysbiosis signature in critical illness represents a key transition from a symbiotic ecosystem to a pathogenic state that fuels systemic and organ-specific complications (29,31).

Breakdown of intestinal barrier integrity. Serving as the primary defense against the translocation of luminal contents, the physical barrier of the gut is composed of a single layer of enterocytes joined by tight junctions. In critical illness, this barrier is compromised through a number of pathways. Alhasson *et al* (32) demonstrated that altered gut microbiomes in stress models cause intestinal injury through the activation of toll-like receptor 4 (TLR4), leading to increased permeability, often referred to as 'leaky gut'. This process is further exacerbated by splanchnic hypoperfusion and the surge of inflammatory cytokines such as TNF-α, which promote enterocyte apoptosis and the disassembly of tight junction proteins (33).

In addition, specific molecular channels serve a role in this disintegration. Previous research by Meena *et al* (34) identified that the transient receptor potential vanilloid 6 channel mediates gut barrier dysfunction and systemic responses during metabolic stress, highlighting a potential target for barrier preservation. When these barriers fail, the influx of pathogen-associated molecular patterns into the portal and systemic circulation becomes uncontrolled (35). Emerging evidence has elucidated the precise molecular hierarchy associating barrier breakdown with neuroinflammation: Translocated lipopolysaccharides (LPS) activates circulating monocytes, triggering TNF-α and IL-1β release, which in turn compromise blood-brain barrier (BBB) integrity by downregulating claudin-5 and occluding (5,7,8,11). This is supported by multi-omics profiling demonstrating that fecal microRNA-gut microbiota interactions (such as miR-30e-3p) are associated with both gut barrier dysfunction and hippocampal neuroinflammation (5). This 'leaky gut' phenomenon is an important juncture in GBA disruption, as it converts a localized intestinal issue into a systemic inflammatory driver. In summary, the breakdown of intestinal integrity in the critically ill is a multifactorial process involving microbial signals, cytokine-mediated injury and ion channel dysregulation, all of which facilitate the dissemination of toxic substances (32,34).

Afferent arm: Gut-derived signals to the brain. Once the intestinal barrier is breached, gut-derived danger signals utilize both humoral and neural pathways to reach the brain. Metabolic endotoxemia, characterized by elevated levels of LPS in the blood, is a major driver of post-ischemic neuroinflammation and cognitive decline (36,37). Singer *et al* (38) provided key evidence that bacterial DNA and even viable bacteria can disseminate to the brain during sepsis, directly challenging the integrity of the BBB. These signals activate resident microglia, the primary immune cells of the brain, shifting them toward a pro-inflammatory M1 phenotype (39,40).

The neural pathway, primarily involving the vagus nerve, also serves as a rapid conduit for gut-derived signals. While the vagus nerve typically mediates anti-inflammatory effects, its afferent fibers can transmit distress signals to the nucleus tractus solitarius, which can either exacerbate neuroinflammation via downstream sympathetic and HPA axis activation or dampen it through the cholinergic anti-inflammatory pathway, depending on the context and the balance of efferent vagal activity (41,42). This neuro-immune crosstalk is particularly evident in sepsis-associated encephalopathy (SAE), whereby gut dysbiosis exacerbates hippocampal amyloid burden and microglial activation (43,44). Consequently, the brain is no longer an 'immune-privileged' site during critical illness (i.e., the blood-brain barrier disruption allows gut-derived inflammatory mediators and pathogens to access the central nervous system) but rather a direct recipient of intestinal distress. Overall, the afferent arm of GBA disruption involves a combination of circulating endotoxins and neural signaling that collectively trigger marked neuroinflammation and cognitive dysfunction (5,45).

Efferent arm: Brain-driven gut dysfunction. GBA disruption is bidirectional, as central nervous system stress markedly impairs gastrointestinal function through efferent pathways. The activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system leads to a state of 'sympathetic overdrive'. Schmidt and Müller-Werdan (46) identified that autonomic dysfunction is a hallmark of patients with critical illness, manifesting as reduced heart rate variability and impaired gastrointestinal motility. This sympathetic hyperactivity, often seen following traumatic brain injury, redirects blood flow away from the mesenteric circulation, causing further mucosal ischemia (47,48).

In addition, the ENS is modulated by these central signals. Sepsis has been shown to induce cholinergic deficits and alter the behavior of calcium channels in mesenteric ganglion neurons, leading to gastroparesis and ileus (49,50). This impairment in motility not only prevents effective enteral feeding but also promotes further stasis and overgrowth of pathogenic bacteria, thus closing the pathogenic loop (41,51). The efferent arm therefore represents the 'top-down' contribution of the brain to gut failure, where stress-induced autonomic shifts exacerbate the dysbiosis and barrier breakdown that initiated the cycle. Recent research shows that efferent sympathetic signals directly suppress HDAC3 expression in intestinal epithelial cells, reducing antimicrobial peptide production and creating a feed-forward loop that impairs barrier function through the same HDAC pathway that SCFAs normally activate to maintain homeostasis (8). Ultimately, the efferent arm reinforces GBA disruption by compromising gut motility, mucosal blood flow and local immune defenses through sustained sympathetic and hormonal stress (52).

Self-perpetuating harmful cycle: Reciprocal amplification between afferent and efferent pathways. Afferent and efferent arms of GBA disruption do not operate in isolation; rather, they engage in a reciprocal amplification loop that transforms an acute insult into a self-sustaining pathological cascade. Gut-derived signals traversing the afferent arm (translocated LPS, pro-inflammatory cytokines and microbial metabolites) trigger neuroinflammation and HPA axis activation, which in turn potentiates the efferent arm through sympathetic overdrive and vagal dysfunction (5,45). This sympathetic hyperactivity exacerbates intestinal hypoperfusion, impairs mucosal barrier integrity and promotes dysmotility, thereby creating a permissive environment for further bacterial overgrowth and translocation (8). The clinical consequence of this bidirectional amplification is a 'brain-gut-brain' cycle, whereby the initial brain-directed inflammatory insult worsens gut function, which subsequently generates additional neurotoxic signals that perpetuate central nervous system injury (1). This self-reinforcing dynamic explains why GBA disruption, once established, often persists despite resolution of the original septic or traumatic trigger. Breaking this cycle therapeutically requires simultaneous targeting of both afferent signals (such as reducing endotoxemia and neuroinflammation) and efferent dysfunction (for example, restoring gut motility and barrier integrity), a principle that underpins the bundled nutritional approach.

3. Clinical sequelae: Associating GBA dysfunction with ICU-acquired syndromes

Transitioning from molecular GBA disruption to clinically observable phenomena represents a key phase in the progression of critical illness. While physiological stress and microbial shifts initiate the cycle, the resulting clinical sequelae manifest as distinct ICU acquired syndromes that notably increase morbidity and mortality. The present section bridges the gap between basic mechanisms and patient outcomes by examining how gut-brain communication failure contributes to musculoskeletal wasting, cognitive impairment, chronic immune dysfunction and respiratory failure. The present section discusses specific microbial and inflammatory biomarkers in association with tangible clinical trajectories, providing a framework for the subsequent therapeutic interventions. The complex interdependencies of these syndromes are summarized in Table I and Figs. 1 and 2, which illustrate the multi-organ impact of GBA failure (6,45). The key clinical studies associating GBA dysfunction with specific ICU-acquired syndromes are summarized in Table I, which outlines the pathological findings and molecular targets across different clinical axes.

ICU-acquired weakness and catabolism. ICU-acquired weakness (ICUAW) and profound muscle wasting are no longer viewed solely as consequences of disuse or malnutrition but are now recognized as products of the 'gut-muscle axis' (53,54). During sepsis and major trauma, systemic inflammation driven by intestinal barrier breakdown triggers skeletal muscle proteolysis through the activation of the ubiquitin-proteasome pathway. A study by Liu *et al* (53) specifically highlighted the potential role of the gut microbiota in sepsis-induced myopathy, suggesting that dysbiosis exacerbates muscle loss by modulating systemic inflammatory mediators, including TNF-α, IL-1β and IL-6 . This catabolic state is further worsened by the loss of beneficial microbial metabolites that normally support anabolic signaling in host tissues (18).

Beyond acute muscle loss, the persistence of a catabolic state contributes to the development of chronic critical illness. Recent experimental evidence has led to new animal models being established to evaluate persistent inflammation, immunosuppression and catabolism syndrome (PICS). Wang *et al* (54) developed a model demonstrating that gut microbiota dysbiosis and subsequent bacterial translocation are foundational to the development of PICS, associating intestinal failure directly with long-term catabolic outcomes. Consequently, the gut serves as a persistent 'motor' for systemic catabolism, hindering physical recovery even after the initial insult has resolved. In summary, ICUAW and catabolic failure in the ICU are rooted in the systemic inflammatory burden generated by a dysfunctional gut-brain-muscle network (53,54).

Delirium and cognitive dysfunction. Clinical manifestation of neuroinflammation in the ICU often appears as delirium or SAE, which are associated with prolonged hospitalization and long-term cognitive decline. This neurological deterioration is closely associated with the influx of gut-derived neurotoxins and the disruption of the BBB. Giridharan *et al* (45) showed that the crosstalk between the gut and brain is a primary driver of sepsis-induced cognitive decline, where intestinal signals directly modulate hippocampal function. Furthermore, metabolic endotoxemia resulting from dietary or stress-induced gut permeability has been identified as a key mechanism associating high-fat intake or critical stress with human cognitive impairments (55,56).

The role of microbial metabolites in mitigating or exacerbating this cognitive decline has become a notable research focus. For instance, SCFAs have been shown to attenuate hippocampal neuroinflammation through the activation of NLRP6 inflammasome pathways, offering a protective effect against SAE (30,40). Conversely, the loss of these metabolites during critical illness leaves the brain vulnerable to microglial overactivation. Huang *et al* (39) recently suggested that gut microbiota-derived 3-indoleacetic acid provides protection against SAE by acting on microglial aryl hydrocarbon receptor (AhR), further proving that specific microbial signatures dictate neurological outcomes. Overall, cognitive dysfunction in patients with critical illness is a direct clinical reflection of GBA-mediated neuroinflammation and the loss of protective microbial signaling (39,45).

Persistent inflammation and immunosuppression. A notable proportion of ICU survivors suffer from a maladaptive immune state characterized by simultaneous hyper-inflammation and immunoparalysis. Approximately 30% of septic patients present with immunoparalysis, defined as failure of circulating mononuclear cells to produce cytokines upon *ex vivo* stimulation, often leading to T-cell exhaustion (2,7). Furthermore, among the ~7.6% of critically ill patients who develop chronic critical illness, 30-50% show evidence of PICS (5,6). The gut microbiota acts as a central regulator of this immunometabolic

Table I. Summary of key studies associating GBA dysfunction with clinical sequelae and multi-organ impairment in patients with critical illness.

First author, year	Study model	Clinical syndrome	Focus axis	Key pathological findings	Molecular targets/biomarkers	(Refs.)
Huang *et al*, 2025	Animal (mice, cecal ligation and puncture)	SAE	Gut-brain	Microbial metabolites provide neuroprotection against encephalopathy.	3-indoleacetic acid; AhR	(39)
Zhao *et al*, 2026	Animal (mice, LPS-induced endotoxemia)	SAE	Gut-brain	SCFAs attenuate hippocampal inflammation via specific inflammasomes.	SCFAs; NLRP6	(40)
Giridharan *et al*, 2022	Systematic review	SAE	Gut-brain	Intestinal signals modulate hippocampal function and neuroinflammation.	BBB	(45)
Liu *et al*, 2023	Clinical cohort + animal model	ICUAW	Gut-muscle	Dysbiosis exacerbates skeletal muscle proteolysis during sepsis.	Ubiquitin-proteasome pathway	(53)
Wang *et al*, 2025	Animal (mice, PICS model)	PICS	Gut-immune	Bacterial translocation drives persistent inflammation and catabolism.	Commensal microbiota	(54)
Cuenca *et al*, 2022	Clinical cohort (COVID-19 ICU patients)	Septic instability	Gut-immune	Specific dysbiosis patterns are associated with uncontrolled inflammation.	Microbial diversity index	(57)
Li *et al*, 2023	Animal (mice, PICS model)	PICS	Gut-immune	Molecular weight of hyaluronan affects post-intensive care progression.	Hyaluronan; inflammatory milieu	(59)
Zakharkina *et al*, 2017	Clinical cohort (mechanically ventilated patients)	VAP	Gut-lung	Pulmonary microbiome dynamics are associated with pneumonia occurrence.	Oropharyngeal bacteria	(61)
Kitsios *et al*, 2020	Clinical cohort (mechanically ventilated patients)	Weaning failure	Gut-lung	Respiratory tract dysbiosis is associated with poor clinical outcomes.	Airway microbiota	(62)
Zhou *et al*, 2023	Clinical cohort (mechanically ventilated patients)	Weaning failure	Gut-lung	Gut microbiome composition serves as a predictor of 28-day mortality.	Fecal microbiota profile	(64)

AHR, aryl hydrocarbon receptor; COVID 19, coronavirus disease 2019; GBA, gut-brain axis; ICUAW, intensive care unit-acquired weakness; ICU, intensive care unit; NLRP6, NLR family pyrin domain containing 6; PICS, persistent inflammation, immunosuppression and catabolism syndrome; SAE, sepsis-associated encephalopathy; SCFAs, short-chain fatty acids; VAP, ventilator-associated pneumonia.

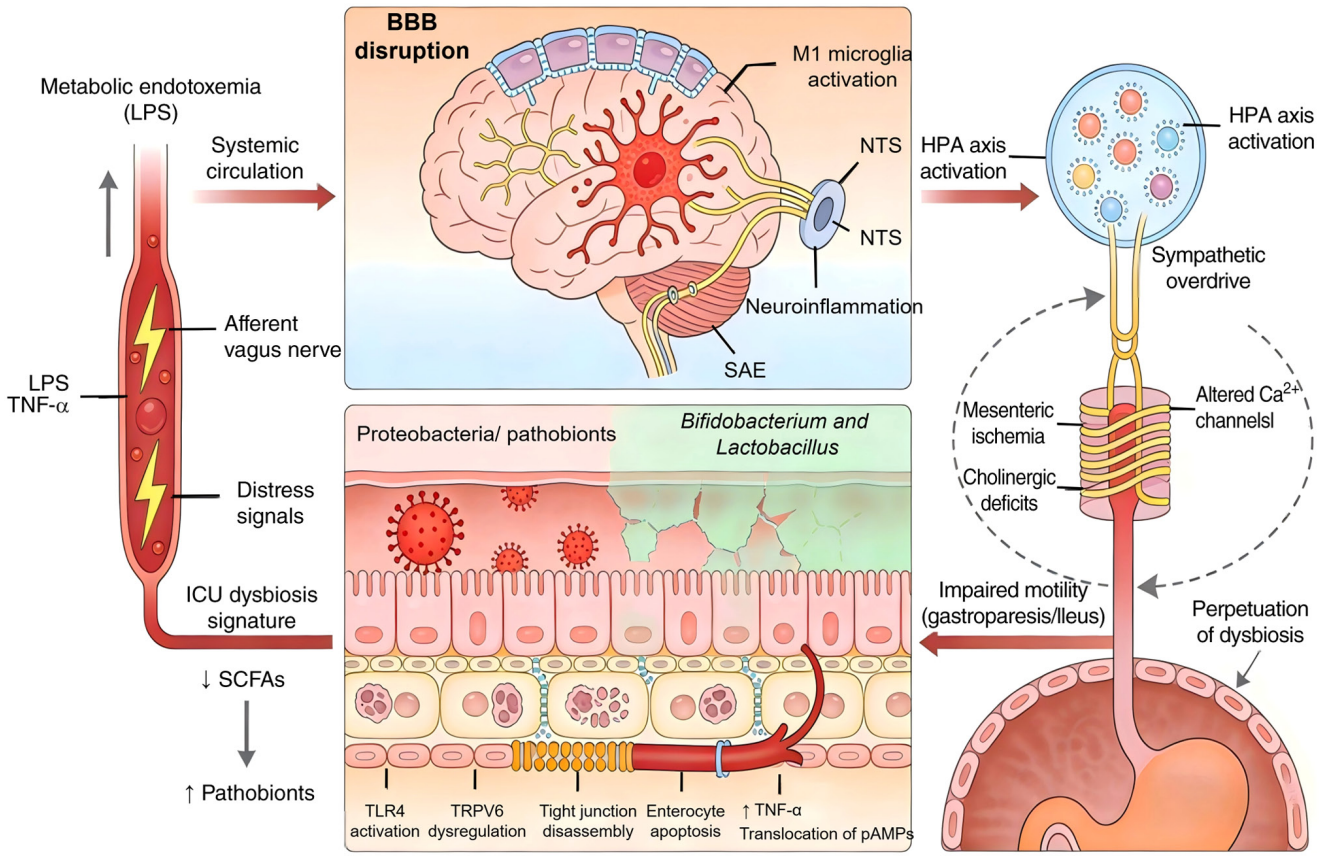

Figure 1. Mechanisms of GBA disruption from dysbiosis to neuroinflammation. Schematic depicting the bidirectional self-perpetuating cycle of GBA dysfunction. Critical illness induces an ICU dysbiosis signature (depletion of beneficial taxa and overgrowth of pathobionts) and reduced SCFAs production, which activates TLR4/TRPV6 pathways to cause intestinal barrier breakdown. Translocated pAMPs and LPS disrupt the BBB and trigger M1 microglial activation, leading to neuroinflammation and SAE. Concurrently, central stress activates the HPA axis and sympathetic overdrive, which signals through the NTS to impair gastrointestinal motility and further exacerbate dysbiosis. BBB, blood-brain barrier; ENS, enteric nervous system; GBA, gut-brain axis; HPA, hypothalamic-pituitary-adrenal; ICU, intensive care unit; LPS, lipopolysaccharides; NTS, nucleus tractus solitarius; pAMPs, pathogen-associated molecular patterns; SAE, sepsis-associated encephalopathy; SCFAs, short-chain fatty acids; TLR4, toll-like receptor 4; TRPV6, transient receptor potential vanilloid 6.

balance and its disruption often leads to clinical severity in conditions such as coronavirus disease-19. Cuenca *et al* (57) identified that specific dysbiosis patterns serve as clear indicators of severity in patients with critical illness, where the loss of microbial diversity is associated with uncontrolled inflammatory responses. This state of 'septic instability' is particularly pronounced in older populations, whereby the gut microbiota fails to maintain overall stability after a septic event compared with their younger counterparts (58).

Furthermore, the structural components of the intestinal environment, such as hyaluronan, have been shown to affect the progression of PICS by modulating the inflammatory milieu (59). When the gut remains in a dysbiotic state, it continuously primes the immune system toward a state of exhaustion or 'paralysis', rendering the patient susceptible to secondary healthcare-associated infections, such as ventilator-associated pneumonia, bloodstream infections, and urinary tract infections. This clinical trajectory is often driven by the overgrowth of Gram-negative pathogens, which can be predicted through structural equation modeling of gut overgrowth (60). In summary, the persistence of inflammation and the onset of immunosuppression in the ICU are largely dictated by the inability of the hosts to restore a homeostatic gut-microbiome environment (54,57).

Prolonged mechanical ventilation and weaning failure. 'Gut-lung axis' represents a key clinical pathway where intestinal dysfunction complicates respiratory management. Patients who are mechanically ventilated experience rapid shifts in their pulmonary microbiome, which are often influenced by the translocation of bacteria from the oropharynx and gastrointestinal tract. Zakharkina *et al* (61) observed that the dynamics of the pulmonary microbiome during mechanical ventilation are associated with the occurrence of pneumonia, highlighting the lungs as a downstream victim of systemic dysbiosis. Respiratory tract dysbiosis itself has been associated with worse clinical outcomes and higher mortality rates in these populations (62,63).

In addition, the clinical success of weaning from mechanical ventilation is frequently hampered by systemic inflammation that weakens diaphragmatic function. The composition of the gut microbiome has been proposed as a notable predictor of 28-day mortality in patients who are mechanically ventilated, suggesting that the 'health' of the gut-lung axis determines the ability of the patients to liberate from life support (64,65). Interventions such as oral care or probiotic administration have been explored to mitigate these risks, although results vary across clinical trials: One trial found that probiotic oral care with *Lactobacillus plantarum*

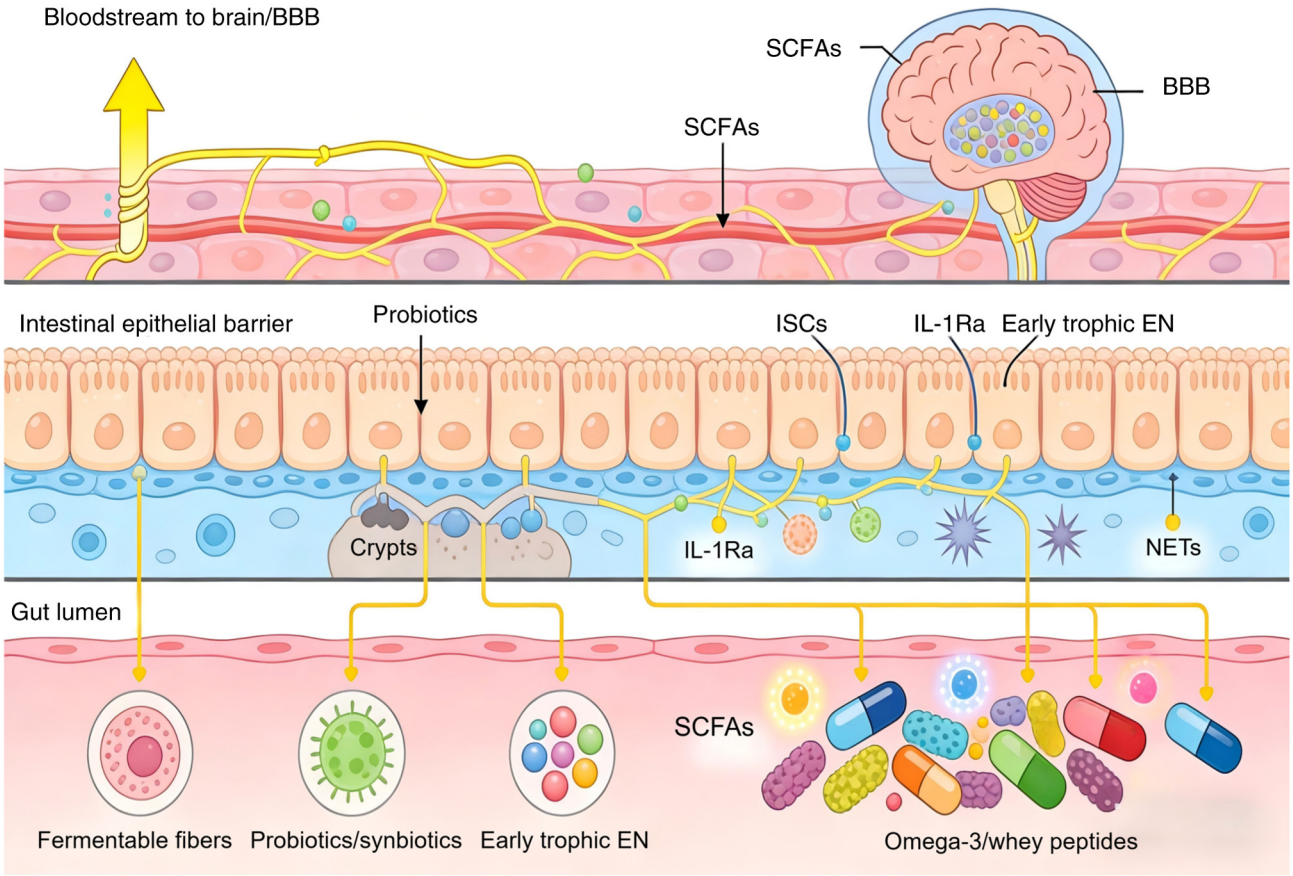

Figure 2. Conceptual framework of GBA-targeted nutrition mechanisms in critical illness. Diagram mapping key nutritional strategies to their mechanistic targets in the GBA disruption cascade. Fermentable fibers enhance SCFAs production to reinforce barrier integrity and attenuate neuroinflammation. Probiotics/synbiotics accelerate ISCs regeneration and deliver anti-inflammatory mediators (such as IL-1Ra). Early trophic EN prevents bacterial mucus foraging and inhibits NET formation. Omega-3 fatty acids generate SPMs to resolve systemic inflammation. Collectively, these interventions interrupt the pathogenic cycle of dysbiosis, barrier failure and neuroinflammation. GBA, gut-brain axis; SCFAs, short-chain fatty acids; BBB, blood-brain barrier; ISCs, intestinal stem cells; IL-1Ra, IL-1 receptor antagonist; EN, enteral nutrition; NETs, neutrophil extracellular traps; SPMs, specialized pro-resolving mediators.

299 was not superior to chlorhexidine in reducing oropharyngeal colonization or improving clinical outcomes in mechanically ventilated patients (66), while another evaluated the impact of a tooth-brushing-based oral hygiene protocol on oral bacteriota and healthcare-associated infections in ventilated COVID-19 patients, reporting changes in microbial composition and safety outcomes (67). Ultimately, prolonged mechanical ventilation and weaning failure are often the result of a feedback loop where gut-derived inflammation impairs respiratory drive and facilitates lung injury. In summary, the gut-lung axis is a decisive factor in the respiratory recovery of patients with critical illness (64).

4. Principles of GBA-targeted nutrition: Moving beyond caloric and protein targets

Current critical care nutrition guidelines, including the 2022 American Society for Parenteral and Enteral Nutrition guidelines, predominately focus on calculating caloric expenditure and protein requirements to mitigate catabolism; however, this macronutrient-centric view often overlooks the metabolic and immunological role of the gastrointestinal tract as a signaling organ (15). A GBA-targeted approach reconceptualizes nutrition therapy not as fuel delivery but as a strategy to modulate the host-microbiome interface, preserve barrier integrity and attenuate neuroinflammation. The principles outlined below shift the clinical paradigm from 'feeding the patient' to 'feeding the GBA', utilizing specific substrates and delivery routes to interrupt the pathogenic cycle of dysbiosis and systemic inflammation. The conceptual framework for these interventions, highlighting the shift from standard care to GBA-focused care, is summarized in Fig. 2, which maps specific nutritional inputs to their neuro-immunological outputs (24,68). Supporting evidence for these foundational principles, drawn from experimental and clinical studies, is summarized in Table II.

Role of fermentable fiber and SCFAs. Dietary fiber is frequently underutilized in the ICU due to concerns regarding bowel distension or incompatibility with enteral feeding tubes; however, the exclusion of fermentable substrates deprives the microbiota of key nutrients required for homeostasis. The primary mechanism by which fiber exerts neuroprotective effects is through the production of SCFAs, particularly butyrate and acetate. These metabolites serve as potent histone deacetylase inhibitors that downregulate inflammatory cytokines and reinforce the BBB. Fan *et al* (69) demonstrated that prebiotic fibers notably enhance SCFA production in

Table II. Summary of evidence-based nutritional strategies targeting the GBA in critical illness.

First author, year	Study model/setting	Nutritional intervention	Target GBA mechanism	Key systemic or neurological outcomes	Clinical/mechanistic importance	(Refs.)
Fan *et al*, 2021	Endotoxemic murine model (LPS-induced)	Prebiotic fibers	Enhancement of SCFA production	Reduction in bacterial translocation and systemic inflammation	Highlights fiber as a metabolic signal to suppress encephalopathy drivers	(69)
Morowitz *et al*, 2017	Murine sepsis model (cecal ligation and puncture)	Nonfermentable fiber	Modulation of microbiota composition	Notable protection against sepsis induced mortality	Demonstrates the role of fiber structure in enhancing physical barrier integrity	(70)
Chen *et al*, 2023	Septic murine model	*L. rhamnosus* GG	Regeneration of intestinal stem cells	Acceleration of colonic barrier recovery	Identifies a specific cellular pathway for mucosal repair during severe stress	(77)
Safabakhsh *et al*, 2025	Pediatric clinical trial (septic ICU patients)	Probiotic supplementation	Reduction in intestinal permeability	Improved clinical stability in children with sepsis	Validates GBA integrity preservation across different age demographics	(78)
Yao *et al*, 2025	Septic lung injury murine model	SpyTag-PEGylated probiotics	Delivery of IL-1Ra	Modulation of gut-lung crosstalk and lung injury mitigation	Represents the frontier of precision pharmaconutrition using engineered microbes	(79)
Ralls *et al*, 2016	Murine enteral nutrient deprivation model	Enteral nutrient deprivation	Prevention of bacterial mucus foraging	Reduced risk of gut-derived sepsis	Proves that trophic feeding is essential to prevent microbiome-driven barrier damage	(84)
Hu *et al*, 2020	Clinical cohort (surgical ICU patients)	Early enteral nutrition	Inhibition of neutrophil extracellular traps	Preservation of intestinal barrier function	Links early feeding to the modulation of innate immune signaling pathways	(87)
Tsutsumi *et al*, 2015	Experimental sepsis model (LPS-induced)	Whey peptides with Omega-3	Vagal anti-inflammatory reflex	Attenuation of LPS-mediated inflammatory cascades	Suggests lipid-rich formulas trigger protective neuro-immune pathways	(91)

EEN, early enteral nutrition; GBA, gut-brain axis; IL-1Ra, IL-1 receptor antagonist; ISC, intestinal stem cell; LPS, lipopolysaccharide; NETs, neutrophil extracellular traps; SCFA, short-chain fatty acid.

endotoxemic models, leading to a reduction in gut commensal translocation and systemic inflammation. Consequently, the reintroduction of fermentable fibers acts as a key signal to suppress the systemic inflammatory response syndrome that drives encephalopathy.

Furthermore, non-fermentable fibers, such as cellulose, may possess distinct immunomodulatory properties beyond fermentation (70-72). Morowitz *et al* (70) showed that dietary supplementation with nonfermentable fiber alters the gut microbiota composition and confers notable protection in murine models of sepsis. This suggests that the physical structure of fiber may provide a scaffold for beneficial bacteria or mechanically stimulate mucus production, thereby enhancing the physical barrier against pathogen invasion. In addition, the administration of specific cellulose supplements has been observed to modulate immune responses in endotoxemia by reducing the production of pro-inflammatory cytokines (including TNF-α, IL-1β and IL-6), attenuating NF-κB pathway activation, and decreasing neutrophil infiltration, thereby preventing the apoptosis of intestinal epithelial cells (71,72). Therefore, fiber supplementation should be viewed as a 'prebiotic pharmaceutical' that maintains the functional integrity of the GBA rather than an optional additive for bowel regularity.

In addition to direct barrier support, the metabolic byproducts of fiber fermentation serve an important role in systemic immune regulation. Chancharoenthana *et al* (73) recently demonstrated that modulation of sepsis by *Lacticaseibacillus rhamnosus* is associated with the levels of SCFAs in feces and blood. At the molecular level, SCFAs exert effects through two complementary mechanisms: Activation of G-protein-coupled receptors (GPR41/43) on immune cells and inhibition of class I HDACs. Butyrate and valerate increase histone acetylation at promoters of anti-inflammatory genes (Foxp3 and occludin) and recent evidence from an SAE murine model has demonstrated that SCFA supplementation activates NOD-like receptor family pyrin domain containing 6 (NLRP6) inflammasomes, restores intestinal barrier [Zonula Occludens-1 (ZO-1): 1.8-fold increase] and ameliorates cognitive deficits [escape latency: cecal ligations and puncture (CLP) 48 sec vs. SCFA + CLP 32 sec; $P<0.01$] (11). Thus, providing adequate fermentable substrates represents the basic principle of GBA-targeted nutrition, ensuring that the microbiome retains the capacity to synthesize neuroprotective metabolites (74,75).

Probiotics, synbiotics and postbiotics: Direct microbial modulation. Restoring microbial diversity through the direct administration of live biotherapeutics represents a proactive strategy to reverse the 'ICU dysbiosis signature'. While the use of probiotics in patients with critical illness has previously been controversial due to safety concerns, emerging evidence supports their efficacy in specific phenotypes to reduce infection and modulate immunity. Shimizu *et al* (76) reviewed the application of synbiotics in critical care, highlighting their role in normalizing gut immunity and preventing the overgrowth of pathogenic bacteria that trigger systemic inflammation. By competitively excluding pathogens and enhancing the expression of tight junction proteins, probiotics act as a 'living shield' for the intestinal mucosa.

The mechanistic basis for these benefits involves complex signaling pathways between the microbe and the host immune system. Chen *et al* (77) highlighted that *Lactobacillus rhamnosus* GG promotes the recovery of the colon barrier in septic mice specifically by accelerating the regeneration of intestinal stem cells. This regenerative capacity is important for patients suffering from ischemia-reperfusion injury or antibiotic-associated mucosal damage. Beyond established barrierrepair mechanisms, including upregulation of tight junction proteins (for example, occludin, claudins and ZO-1), suppression of pro-inflammatory cytokines, inhibition of NF-κB and MLCK signaling, activation of TLR-2, and modulation of autophagy, specific gut microbial metabolites have been shown to directly modulate neuroinflammation through the GBA (77). Indole derivatives, particularly 3-indoleacetic acid (IAA), produced by tryptophan-metabolizing bacteria, act as ligands for the AhR expressed on microglia. Huang *et al* (39) demonstrated that patients with sepsis and SAE exhibit markedly reduced fecal IAA levels. In a murine CLP model, exogenous IAA supplementation was shown to activate microglial AhR, suppress the secretion of proinflammatory cytokines (including TNF-α, IL-1β and IL-6), and improve cognitive performance. This protective effect was shown to be abolished by co-administration of the AhR antagonist CH223191, demonstrates that IAA confers neuroprotection in an AhR-dependent manner. In addition, recent trials have explored the use of synbiotics, which combine probiotics with prebiotic substrates, to enhance the survival and colonization of beneficial strains. Safabakhsh *et al* (78) reported preliminary results from a double-blind trial indicating that probiotic supplementation effectively reduces intestinal permeability in critically ill children with sepsis, suggesting that early intervention can preserve GBA integrity across different age groups.

Beyond established probiotics, the field is advancing toward precision engineering and postbiotics. Yao *et al* (79) developed an innovative approach using SpyTag-PEGylated probiotics to deliver IL-1 receptor antagonists, which successfully modulated gut-lung crosstalk and mitigated septic lung injury. This illustrates the potential of 'pharmaconutrition' where genetically or chemically modified microbes serve as vehicles for targeted anti-inflammatory therapy. Furthermore, the administration of specific microbial metabolites, or postbiotics, allows for the benefits of bacterial signaling without the risk of administering live organisms to patients who are immunocompromised (80). In summary, direct microbial modulation through probiotics and synbiotics offers a potent mechanism to stabilize the enteric environment and dampen the vagal and humoral signals that drive neuroinflammation (81,82).

Enteral vs. parenteral route. Nutrient delivery route is a decisive factor in maintaining the functional architecture of the GBA. Total parenteral nutrition (TPN), while life-saving in cases of intestinal failure, is associated with mucosal atrophy and the loss of gut-associated lymphoid tissue function. Ikeda *et al* (83) demonstrated that the lack of enteral feeding leads to a pathological upregulation of intestinal TLRs and pro-inflammatory cytokines, sensitizing the gut to endotoxin. This 'disuse atrophy' creates a permissive environment for bacterial translocation, fueling the systemic inflammation that ultimately affects the brain. Conversely, the physical presence of nutrients in the lumen stimulates the release of incretins (for example, glucose-dependent insulinotropic polypeptide

and glucagon-like peptide-1) and trophic factors (for example, glucagon-like peptide-2, insulin-like growth factor-1 and epidermal growth factor) that maintain enterocyte health.

A key concept in understanding TPN-induced dysfunction is the phenomenon of bacterial adaptation to starvation. Ralls *et al* (84) provided insight into the gut origin of sepsis by showing that during enteral nutrient deprivation, commensal bacteria switch their transcriptional profile to 'forage' on the host mucus layer. This degradation of the protective mucus barrier allows bacteria to come into direct contact with the epithelium, triggering inflammation and barrier failure. Therefore, even minimal amounts of EN, often termed 'trophic feeding', are key in satisfying the metabolic demands of the microbiota and prevent them from consuming the defensive layers of the host (85,86).

In addition, early EN has been associated with specific cellular protective mechanisms. Hu *et al* (87) found that early EN preserves intestinal barrier function by reducing the formation of neutrophil extracellular traps in critically ill surgical patients. By minimizing local neutrophil activation, enteral feeding breaks the cycle of local inflammation that leads to systemic organ dysfunction. This evidence supports the principle that the enteral route should be prioritized not just for caloric delivery, but as a therapeutic maneuver to maintain the physiological barrier between the gut lumen and the systemic circulation (87,88).

Trophic versus. full feeding: Balancing GBA integrity and metabolic stress. While enteral stimulation is important, the volume and composition of nutrition must be carefully titrated to avoid metabolic overload during the acute phase of critical illness. Aggressive full feeding can induce hyperglycemia and suppress autophagy, a cellular cleaning process important for clearing intracellular pathogens and damaged organelles. Hadley and Hinds (89) discussed anabolic strategies, noting that pushing calories in the early phase of critical illness often fails to halt catabolism and may exacerbate metabolic stress. A GBA-targeted approach advocates for trophic feeding, delivering small volumes to sustain mucosal integrity and microbial diversity, without overwhelming the compromised mitochondrial function of the host.

Specific nutrient compositions also serve a role in modulating the inflammatory response during feeding. Luyer *et al* (90) observed that pretreatment with high-fat EN reduces endotoxin and TNF-α levels, preserving gut barrier function after hemorrhagic shock. This suggests that lipid-rich formulas may stimulate the cholecystokinin-vagal pathway, triggering an anti-inflammatory reflex that protects the gut. However, the type of lipid is key; omega-3 fatty acids and whey peptides have been shown to offer improved protection against LPS-mediated sepsis compared with standard lipids (91).

The goal of titrating feeding strategies is to maintain a 'metabolic peace' between the host and the microbiome. Oami *et al* (24) reviewed critical care nutrition from a metabolic point of view, suggesting that nutritional interventions must align with the dynamic phases of critical illness. By initiating trophic feeding early, clinicians can prevent the 'starving gut' phenomenon and support the GBA, while gradually advancing to full caloric targets as the patient stabilizes. Consequently, the principle of GBA-targeted nutrition prioritizes the biological impact of the feed over the immediate achievement of caloric goals, ensuring that nutrition supports rather than hinders the resolution of inflammation (24,92).

5. Proposed GBA-informed nutrition care bundle: Components and evidence

Clinical application of GBA insights necessitates a structured, multimodal approach known as the 'GBA-informed nutrition care bundle'. Unlike a combination of separate interventions, this framework is designed as an integrated system where each component targets a distinct mechanistic node in the GBA disruption cascade. Fermentable fibers restore SCFA-mediated HDAC inhibition and barrier integrity; probiotics supply AhR-activating indole derivatives for microglial immunomodulation; and specialized pro-resolving mediators engage resolution pathways. Their concurrent application produces synergistic repair of gut-brain communication beyond any single intervention alone. By summarizing evidence from randomized controlled trials and meta-analyses, the present section defines the key components of the bundle. Table III summarizes the clinical and mechanistic evidence supporting each component of the proposed care bundle, highlighting key outcomes across diverse patient populations.

Microbial modulation through probiotics and synbiotics. Probiotics and synbiotics constitute a hallmark of the GBA-informed bundle by restoring microbial diversity and inhibiting the translocation of pathogens. Extensive research has focused on their role in preventing healthcare-associated infections, particularly ventilator-associated pneumonia (VAP) (93,94). For example, an early clinical trial has demonstrated that probiotic prophylaxis could markedly reduce the incidence of VAP in pediatric populations (93). Similarly, a meta-analysis of adult patients in the ICU have indicated that synbiotic therapy effectively modulates gut microbiota and reduces both enteritis and pneumonia rates (94).

However, evidence remains nuanced regarding mortality and universal application. Johnstone *et al* (95) conducted a large-scale randomized trial which demonstrated that *Lactobacillus rhamnosus* GG did not notably decrease VAP incidence compared with placebo in a broad critically ill population. This finding has been further determined in recent systematic reviews and trial sequential analyses, which suggest that while probiotics may reduce infection rates, their impact on overall mortality remains unremarkable (96,97). A systematic analysis of heterogeneity across these trials has revealed a number of key factors that may explain the conflicting results. Strain specificity is important: The negative trial used a single strain without prebiotics, whereas positive trials often used multi-strain synbiotics (94). Dosage and timing also vary markedly, with earlier initiation (within 48 h) exhibiting greater benefits. Patient population differences are also important, as benefits appear more notable in surgical patients compared with medical ICU populations (96). These sources of heterogeneity suggest that a standardized probiotic protocol is unlikely to succeed across all patients in the ICU. Despite these challenges, certain strains have shown specific promise. Panigrahi *et al* (98) demonstrated in a landmark study that a synbiotic preparation markedly reduced neonatal sepsis in

Table III. Clinical and mechanistic evidence supporting the components of the GBA-informed nutrition care bundle.

First author, year	Study population	Bundle component	GBA target/ mechanism	Primary outcomes	Main findings	(Refs.)
Banupriya *et al*, 2015	Critically ill children (n=120)	Probiotics (*L. acidophilus*)	Pathogen exclusion; gut barrier	VAP incidence	Notable reduction in the occurrence of VAP	(93)
Shimizu *et al*, 2018	Adult septic ICU patients (n=100)	Synbiotics (*Bifidobacterium* + GOS)	Microbiota stability; SCFA production	VAP and enteritis	Reduced incidence of infectious complications	(94)
Johnstone *et al*, 2021	Mixed adult ICU patients (n=2650)	Probiotics (*L. rhamnosus* GG)	Microbial diversity modulation	VAP incidence	No notable difference versus placebo	(95)
Panigrahi *et al*, 2017	Rural neonates (n=4556)	Synbiotics (*L. plantarum* + FOS)	Innate immunity; barrier restoration	Sepsis and mortality	40% reduction in sepsis and death rates	(98)
Serbanescu *et al*, 2025	Critically ill trauma patients (n=40)	Fiber-containing EN	SCFA enrichment; taxa diversity	Microbial dynamics	Enhanced abundance of beneficial commensals	(103)
Karimi *et al*, 2022	Adult septic ICU patients (n=60)	Nano-curcumin	Oxidative stress; neuro-inflammation	Inflammatory markers	Improved endothelial function and lower CRP	(112)
Seifi *et al*, 2022	Critically ill adults (n=60)	Synbiotics	Protein homeostasis; GBA signaling	Feeding tolerance	Improved nitrogen balance and muscle mass	(117)
Zhang *et al*, 2025	Neurological ICU patients (n=128)	Protocolized EN	Delivery timing; motility support	Neurological recovery	Improved clinical prognosis and GBA stability	(118)
Yao *et al*, 2025	Critically ill adults (n=80)	Sequential vs. continuous EN	Circadian rhythm; diversity	Microbiome composition	Sequential feeding preserved microbial diversity	(119)

EN, Enteral nutrition; FOS, Fructo-oligosaccharides; GBA, Gut-brain axis; GOS, Galacto-oligosaccharides; ICU, Intensive care unit; SCFA, Short-chain fatty acids; VAP, Ventilator-associated pneumonia.

a rural setting, highlighting the potential for targeted GBA modulation.

In addition to infectious outcomes, probiotics appear to influence the systemic inflammatory response and organ function. Probiotic administration has been associated with the modulation of serum cytokine levels, including proinflammatory cytokines (TNFα, IL6 and IL8) and antiinflammatory cytokines (IL10), and endotoxin concentrations in various critical and chronic illness models, such as clinical trials in pediatric sepsis, animal models of sepsis, and studies in acute pancreatitis and liver cirrhosis (99). Furthermore, multispecies probiotics have been shown to attenuate dysbiosis and improve clinical markers, including disease severity scores (SOFA and APACHE II), inflammatory markers (CRP and PCT), and endotoxin levels, in the early stages of sepsis (81). Collectively, these findings have suggested that while probiotics are a beneficial tool for GBA modulation, their efficacy is likely strain-specific and timing-dependent and systematic assessment of trial heterogeneity is key before generalizing results.

Prebiotics and fiber for barrier integrity. Prebiotics and dietary fibers serve as important substrates for the production of SCFAs, which are key in maintaining the intestinal epithelial barrier. Systematic reviews have highlighted that fiber and prebiotic supplementation in EN can improve gastrointestinal tolerance and reduce the duration of diarrhea in patients with critical illness (100,101). By fostering the growth of beneficial bacteria such as *Bifidobacterium*, prebiotics mitigate the metabolic endotoxemia often observed in systemic inflammation (102).

However, clinical evidence on fiber interventions shows marked heterogeneity. The type and fermentability of fiber differ: Soluble fiber blends reduce diarrhea more effectively compared with nonfermentable fibers. Doses range from 10-30 g/day, with higher doses increasing intolerance. Patient populations have been shown to respond differently; trauma patients show favorable microbial shifts (103), while medical patients in the ICU with ileus may not tolerate fiber. Timing is also important; early fiber may help stable patients but could exacerbate shock states. These factors may explain contradictory trial outcomes. Recent evidence has suggested that the inclusion of fiber in enteral formulas can dynamically shift the microbial community in patients with trauma (103). This shift is key in GBA health, as it promotes the production of butyrate, which has known neuroprotective and anti-inflammatory properties. A clinical trial has also indicated that prebiotic supplementation may improve sleep quality and metabolic markers through the GBA in patients with chronic metabolic disturbances, which may have implications for ICU delirium and recovery (102). In summary, prebiotics are not passive nutrients but active modulators of the gut environment. Despite this, heterogeneity in fiber type, dose, patient selection and timing must be addressed in future trials to establish standardized recommendations.

Specialized pro-resolving mediators and lipid modulation. Resolution of inflammation is an active process mediated by specialized pro-resolving mediators (SPMs) derived from omega-3 polyunsaturated fatty acids. Dalli *et al* (104) identified novel pro-resolving pathways that are key in tissue regeneration and the termination of acute inflammatory responses. In the context of sepsis, the temporal profile of these lipid mediators is closely associated with clinical survival and the resolution of organ dysfunction (105).

Experimental and clinical studies have shown that omega-3 fatty acids such as docosahexaenoic acid and eicosapentaenoic acid can attenuate septic shock-induced arterial dysfunction and neuroinflammation (106,107). Furthermore, specific SPMs such as maresin-1 have been found to ameliorate microglial activation and cognitive decline in septic models by modulating inflammatory signaling pathways, including inhibition of p38 MAPK phosphorylation and activation of the PPARγ/STAT6 signaling pathway (108,109). These findings suggest that incorporating omega-3 fatty acids into the care bundle may facilitate the transition from systemic inflammation to homeostatic resolution through the GBA. Therefore, lipid-based GBA modulation represents an emerging frontier for protecting the central nervous system during critical illness.

Polyphenols and antioxidant micronutrients. Polyphenols such as curcumin and resveratrol offer potent antioxidant and anti-inflammatory benefits that reinforce the GBA. Research has shown that curcumin can alleviate LPS-induced lung and liver failure by suppressing oxidative stress and NF-κB signaling (110,111). In addition, nano-curcumin supplementation in patients with sepsis has been associated with improvements in endothelial function and the reduction of inflammatory biomarkers (112).

Resveratrol has similarly demonstrated protective effects against sepsis-induced cardiac and renal dysfunction in a number of experimental models, including cecal ligation and puncture-induced sepsis in rats and mice (113). These compounds appear to work by activating sirtuin-1 and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, which are key in maintaining mitochondrial dynamics and cellular homeostasis during severe stress (114,115). Recent advances have also explored the use of resveratrol-loaded nanoparticles to enhance efficacy in addressing acute lung injury (116). Ultimately, the integration of polyphenol-rich compounds into nutrition care provides an additional layer of neuro-metabolic protection for the critically ill.

Implementation of feeding strategies and protocols. Effectiveness of the GBA-informed bundle depends on the delivery method and the timing of EN. Research into feeding tolerance has indicated that the early initiation of EN, potentially supplemented with synbiotics, can improve protein homeostasis and reduce muscle wasting (117,118). Notably, the choice between sequential and continuous feeding may also influence the composition of the gut microbiota and the overall metabolic response (119).

Structured EN protocols have been shown to improve nutritional indicators and clinical prognosis in neurological patients in the ICU (118). Furthermore, the duration of oral care using maternal milk or other biological substrates can modulate the oral microbiota composition and reduce the incidence of healthcareassociated infections, thereby positively affecting the oralgut microbial axis and improving clinical outcomes in vulnerable populations (120). These strategies underscore the importance of not only what is delivered but how it is

administered to optimize GBA communication. In summary, a standardized approach to feeding delivery is important in the successful implementation of the GBA-informed nutrition care bundle.

Subpopulation-specific considerations. While the proposed GBA-informed bundle provides a standardized framework, minor evidence-based adjustments may enhance its applicability to specific critically ill subpopulations. For patients with sepsis, probiotic initiation should be deferred until hemodynamic stabilization (norepinephrine ≤0.5 μg/kg/min) due to translocation risks (96,121). For patients with major trauma, early synbiotic administration (within 24-48 h) combined with higher protein targets (1.5-2.0 g/kg/day) may better address hypercatabolism and reduce infectious complications. For patients with neurocritical illness, protocolized EN with prebiotic-fortified formulas has been associated with improved nutritional indicators, including serum albumin, prealbumin and nitrogen balance, as well as lower diarrhea rates (118). These adaptations do not alter the core components of the bundle but refine their timing and implementation across distinct pathophysiological contexts.

6. From bench to bedside: Implementation science and a practical framework

Translation of theoretical GBA mechanisms into routine clinical practice requires a robust implementation science framework. The present section delineates the practical strategies for integrating GBA-informed nutrition bundles into the ICU workflow. By addressing organizational barriers and utilizing protocolized delivery systems, clinicians can optimize nutrient provision and microbial health in the critically ill. The following discussion provides a structured approach to personalized nutritional therapy, which is further summarized in the accompanying Fig. 2 and Table IV detailing the practical implementation workflow.

Protocolized delivery and implementation science. Adoption of standardized protocols is a key component of effective nutritional management in the ICU. Heyland *et al* (122) demonstrated that implementation of the Enhanced Protein-Energy Provision via the enteral Route (PEP uP) protocol, which emphasizes volume-based feeding (VBF) and nurse-driven adjustments, notably improves the delivery of EN compared with traditional hourly rate-based feeding methods. This approach has been further validated in surgical and neuroscience populations, where VBF protocols have been shown to effectively enhance protein and energy provision (123,124). A systematic review has further determined that such protocolized systems demonstrate an improved performance with regard to reaching nutritional goals and minimizing caloric deficits in patients who are mechanically ventilated (125).

Furthermore, the application of early EN protocols based on enhanced recovery after surgery concepts has shown promise in improving clinical outcomes and shortening ICU stays (23). Recent studies have highlighted that the success of these protocols depends on adherence and the use of clinical decision support tools (126,127). Ventura and Waitzberg (128) suggested that while protocols are necessary, their effectiveness

Table IV. Simplified bedside protocol for the GBA-informed nutrition care bundle.

Component	Patient stratification	Contraindications	Dynamic adjustment	Safety monitoring
Probiotics	mNUTRIC ≥5; sepsis/trauma; no vasopressor at start	CVC, neutropenia (<500/μl), short bowel, high-dose vasopressors (norepi >0.5)	Start day 3-5 after vasopressor wean; stop if new fever, fungemia	Daily blood culture if fever; stop at first sign of *Saccharomyces* infection
Prebiotic fiber	All critically ill receiving EN; no ileus	Bowel obstruction, severe ileus, abdominal compartment syndrome	Start day 3 (10 g/d); advance to 20 g/d if GRV <250 ml and no distension	Abdominal exam q8h; hold if GRV >500 ml or distension
SPMs (omega-3)	Stable phase (day 5-7); sepsis survivors	Bleeding diathesis, triglycerides >500 mg/dl	Start after enteral tolerance achieved (≥60% target)	Check triglycerides q3d; monitor for bleeding
Polyphenols	Persistent inflammation (CRP >100 mg/dl day 5)	None specific; caution in liver dysfunction	Consider after day 5 if no improvement	Monitor LFTs weekly

CVC, central venous catheter; EN, enteral nutrition; GRV, gastric residual volume; LFTs, liver function tests; mNUTRIC, Modified Nutrition Risk in Critically Ill score; SPMs, specialized pro-resolving mediators.

is associated with the education of the multidisciplinary team. Collectively, these findings suggest that structured, protocol-driven strategies are key in the consistent delivery of GBA-targeted interventions across diverse clinical settings.

Addressing barriers to nutritional success. Despite the availability of protocols, achieving nutritional targets remains challenging due to frequent interruptions for medical procedures and perceived gastrointestinal intolerance. Kuslapuu *et al* (17) identified that a notable proportion of EN interruptions in the ICU lack a clear evidence-based justification, leading to suboptimal feeding. To mitigate this, specific protocols designed to avoid tube feed interruptions during procedures such as tracheostomies have been implemented with high success rates (129). In addition, managing common complications such as diarrhea is important in maintaining bundle adherence.

Research has indicated that the development of predictive models for diarrhea can help clinicians identify patients at high-risk and preemptively adjust nutritional strategies (130). Studies have also explored the impact of feeding patterns, noting that while intermittent feeding may more closely mimic physiological states, continuous feeding remains a standard in numerous protocols to ensure volume delivery (131,132). Furthermore, addressing constipation through prophylactic laxative regimens is an often overlooked but key aspect of GBA health (133). In summary, identifying and systematically removing practical barriers is a prerequisite for achieving the physiological benefits of GBA modulation at the bedside.

Safety monitoring and risk stratification. Safety is an important consideration when implementing specialized GBA-targeted nutrients, particularly in patients who are hemodynamically unstable. The results of large-scale trials such as REducing Deaths due to OXidative Stress (REDOXS) and METAPLUS have suggested that high-dose glutamine and antioxidant supplementation might increase mortality in patients with multi-organ failure (134,135). However, Wischmeyer (136) argued that these findings should not lead to the total abandonment of glutamine, especially in populations such as burn patients where recent evidence continues to show benefit (137). This underscores the necessity of a risk-stratified approach rather than a universal application of all bundle components.

To enhance clinical operability for high-risk populations, a refined risk stratification has been proposed. For probiotics, absolute contraindications include: Central venous catheter (CVC) *in situ* due to fungemia risk, particularly with *Saccharomyces boulardii*, with an associated mortality of 36.1% (138,139). Additional contraindications comprise neutropenia (<500/μl), short bowel syndrome and high-dose vasopressor support (norepinephrine >0.5 μg/kg/min) indicating hemodynamic instability (96,121). Patients who are immunocompromised (active chemotherapy, solid organ transplant on intensive immunosuppression) should generally not receive live probiotics (96). For glutamine and high-dose antioxidants, evidence from the REDOXS trial has demonstrated harm in patients with multiorgan failure (especially renal dysfunction) and those in shock (140). Thus, in patients with multiorgan failure or ongoing shock, high-dose glutamine should be withheld. For stable patients without these risk factors, the full GBA-informed bundle may be safely initiated.

The use of probiotics also requires careful safety monitoring, as rare cases of *Saccharomyces fungemia* have been reported in patients with critical illness receiving these supplements (138,139). Clinicians must weigh the proven benefits of probiotics in reducing VAP against the potential for infectious complications in severely immunocompromised individuals (96,121). Therefore, a nuanced understanding of patient-specific contraindications is important for the safe implementation of microbial modulation strategies. Ultimately, safety protocols must be integrated into the GBA-informed bundle to protect vulnerable ICU populations from potential adverse effects.

Technological integration and multidisciplinary care. Modern implementation strategies have increasingly incorporated advanced technology to guide and monitor nutritional therapy. Ultrasound-guided protocols for assessing gastric residual volume and intestinal motility offer a non-invasive and reliable method to evaluate feeding tolerance at the bedside (141,142). These technological advances allow for real-time adjustments to the nutrition bundle, ensuring that delivery is optimized according to the changing physiological status of the patient. In addition, the involvement of a dedicated nutrition support team has been shown to notably improve the administration and monitoring of EN (143).

In the future, the integration of biomarkers and metabolomics may allow for even more precise GBA-informed care (144). For example, monitoring fecal calprotectin or microbial metabolites could provide early warnings of intestinal barrier failure or dysbiosis (145). The coordination between dietitians, nurses and physicians remains important in successful bundle implementation, ensuring that each component of the GBA-informed care is delivered accurately (22). Overall, the synergy between technological innovation and multidisciplinary collaboration is key in the global adoption and long-term success of the GBA-centric nutrition framework.

A simplified bedside protocol for the GBA-informed nutrition care bundle. To address the lack of standardization and stratification, the present section provides a concise, ready-to-use protocol (Table IV). Population stratification is based on the modified Nutrition Risk in the Critically Ill (NUTRIC) score (≥5 indicates high risk) combined with disease category (sepsis/septic shock, trauma or neuro-critical illness) (21,118). Explicit contraindications for probiotics include CVC, neutropenia (<500/μl), short bowel syndrome and concurrent high-dose vasopressors (norepinephrine >0.5 μg/kg/min) (96,138). Dynamic adjustment follows three phases: i) Acute phase (days 1-3), trophic EN (10-20 ml/h) and no probiotics; ii) stabilization phase (days 3-7), gradual volume increase and initiate prebiotic fiber (10-15 g/day) and probiotics after vasopressor weaning; and iii) recovery phase (>day 7), full bundle including omega-3 (5-10 g/day) if tolerated (24,68). Hold parameters include new-onset diarrhea (>3 episodes/24 h), gastric residual volume >500 ml or signs of bowel ischemia. Standard operating procedures are summarized in Table IV.

7. Knowledge gaps and future directions

Despite the integration of GBA insights into bundled nutrition care offering a promising therapeutic frontier, a number of notable knowledge gaps persist that hinder universal clinical adoption. The transition from current supportive care to proactive GBA-modulation requires a clear roadmap for future research priorities to progress beyond empirical treatments. To enhance the guidance for future research, the following priorities are structured around three critical care scenarios: i) The early warning of GBA disruption; ii) microbiome-guided personalization; and iii) dynamic risk prediction.

First, a marked gap is the lack of specific, non-invasive biomarkers for the early warning of GBA disruption at the bedside. Instead of general omics profiling, future research should focus on validating a panel of circulating markers that reflect distinct pathophysiological nodes: Intestinal barrier injury [such as intestinal fatty acid-binding protein (iFABP)], microbial translocation (such LPS) and protective metabolite depletion (such as SCFAs) (12,34,45). For example, elevated iFABP and LPS levels could serve as an early trigger to initiate the 'GBA-informed bundle' before clinical signs of sepsis or delirium manifest. Studies on acute ischemic stroke have demonstrated that integrating such gut-derived biomarkers with clinical scores markedly enhances prediction accuracy for post-stroke infection and cognitive outcomes, a framework directly applicable to the ICU setting (36,37). Similarly, the temporal profiles of SCFAs in feces and blood could be monitored to assess the efficacy of prebiotic interventions in real-time (73).

Second, the current 'one-size-fits-all' bundle requires refinement into personalized nutrition formulas based on microbiome typing or metabolomic signatures. Future research should therefore aim to stratify patients with critical illness into distinct metabotypes or enterotypes to guide specific interventions. For instance, patients with a severe depletion of SCFA-producing taxa (such as *Lachnospiraceae* or *Ruminococcaceae*) may derive greater benefit from high-dose, fermentable fiber blends, while those with an overgrowth of Proteobacteria might require targeted synbiotics or even specific phage therapies (11,29,103). This concept is supported by data showing that the efficacy of nutritional interventions is strongly dependent on baseline microbiota composition. For patients with trauma, fiber-containing enteral formulas dynamically shift microbial communities; future trials should use this principle to assign specific fiber types (such as psyllium for butyrate enhancement versus inulin for bifidogenesis) based on a rapid stool metagenomic screen (103).

Third, the application of artificial intelligence (AI) should move beyond general concepts to focus on dynamic risk prediction and adaptive bundle adjustment. The foundational role of AI in clinical nutrition has been established through early work on machine learning applications for risk prediction and decision support in nutritional assessment (146,147). Limketkai *et al* (148) systematically outlined how digital technologies, including machine learning algorithms, can be integrated into clinical nutrition practice for real-time data collection, risk prediction and diet optimization. Belkhouribchia and Pen (149) further provided an accessible framework for understanding core AI concepts, including machine learning, deep learning and large language models and their practical applications in clinical nutrition, demonstrating the importance of clinician preparedness for responsible AI integration. Building on these frameworks, the goal should be to develop explainable machine learning models that integrate real-time data, including daily microbiome profiles (through rapid 16S ribosomal RNA (rRNA) sequencing), serum metabolomics and clinical variables (such as feeding tolerance and vasopressor dose), to predict the individual patient response to the bundle (146,147). For example, an AI algorithm could analyze the trajectory of a patient over the first 72 h and recommend advancing from trophic to full feeding, or adding a specific probiotic strain, thereby functioning as a 'clinical decision support tool' for GBA management (126,127). This aligns with the 'AI-guided precision nutrition' paradigm, where computational models simulate microbiome dynamics and predict the optimal timing and composition of nutritional interventions (150).

Finally, the validation of GBA-informed bundles requires large-scale, well-designed randomized controlled trials that progress beyond the testing of single components in isolation. These trials must incorporate the aforementioned stratified approaches by using biomarker enrichment strategies to enroll patients who are most likely to receive benefits (for example those with elevated iFABP/LPS). Research must also focus on individualized precision therapy for patients with complex organ failure by utilizing indirect calorimetry and bioenergetic balance to define energetic needs (151). Addressing the long-term impact of GBA-targeted nutrition on post intensive care syndrome remains a priority, as the current data primarily focus on short-term ICU outcomes. Overall, bridging the current knowledge gaps through technological innovation and clinical validation will transform the GBA-informed nutrition care bundle into a standard of care. This will improve the multidimensional recovery trajectories of the most vulnerable critically ill populations.

8. Conclusions

In conclusion, GBA serves as a key determinant of systemic homeostasis and recovery trajectories in the ICU. Shifting from conventional caloric targets toward GBA-informed nutrition bundles allows for targeted modulation of the host-microbiome interface and neuroinflammatory cascades. Standardizing the integration of biotherapeutics and specialized substrates within clinical protocols is important for mitigating multi-organ dysfunction. Future precision-based strategies will hopefully refine these frameworks to optimize survival and long-term functional outcomes.

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Authors' contributions

LZ and SY conceptualized the review and made marked contributions to the conception and design. HW performed the literature search, analysis and interpretation of the retrieved studies. HZ contributed to the interpretation of the literature and was a major contributor in drafting the manuscript. All authors were involved in revising the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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