Gut dysbiosis-derived butyrate loss predicts feeding intolerance: Multiomics evidence guiding nurse-driven microbiota-supportive interventions (Review)

LING WEI[1], XIAOHUA KONG[2], YUYING LI[3], HUIXIA WU[1], YIRONG GAN[4] and FANG SUN[5]

[1]Nursing Department, Lanzhou First People's Hospital, Lanzhou, Gansu 730000, P.R. China; [2]Department of Critical Care Medicine, Lanzhou First People's Hospital, Lanzhou, Gansu 730000, P.R. China; [3]Department of Neonatology, Lanzhou First People's Hospital, Lanzhou, Gansu 730000, P.R. China; [4]Cardiovascular Disease Research Institute, Lanzhou First People's Hospital, Lanzhou, Gansu 730000, P.R. China; [5]Department of Obstetrics and Gynecology, Lanzhou First People's Hospital, Lanzhou, Gansu 730000, P.R. China

Received December 24, 2025; Accepted June 3, 2026

DOI: 10.3892/mmr.2026.13958

Abstract. Feeding intolerance (FI) is a common and debilitating challenge among critically ill patients that is linked to a pathway involving the collapse of the gut microbial ecology. The present review synthesizes multiomics evidence supporting a framework whereby critical illness-associated gut dysbiosis results in a functional deficit of a microbially derived short-chain fatty acid butyrate, a pivotal metabolite involved in maintaining intestinal barrier integrity, immuneoregulation and gastrointestinal motility. The loss of butyrate-producing bacteria and their genetic pathways is strongly correlated with FI and may represent a contributory pathogenic mechanism. Key butyrate-producing organisms diminished during this process include *Faecalibacterium prausnitzii* and *Roseburia spp*. Building upon this mechanistic framework, a pragmatic, nurse-driven intervention model aimed at preserving and restoring microbial health in critically ill patients was proposed. This model is founded on four principal strategies: Minimizing iatrogenic harm (such as antibiotic/proton pump inhibitor stewardship), targeted microbiota nourishment (pre/synbiotics), cautious microbial restoration (probiotics/fecal microbiota transplantation) and innovative monitoring approaches. By integrating principles of microbial ecology with clinical nursing science, the present review provides a framework for developing nurse-driven protocols designed to address the underlying pathophysiology of FI and improve patient outcomes.

Correspondence to: Professor Fang Sun, Department of Obstetrics and Gynecology, Lanzhou First People's Hospital, 1 Wujiayuan, Qilihe, Lanzhou, Gansu 730000, P.R. China
E-mail: 13893279949@163.com

Professor Yirong Gan, Cardiovascular Disease Research Institute, Lanzhou First People's Hospital, 1 Wujiayuan, Qilihe, Lanzhou, Gansu 730000, P.R. China
E-mail: gyr0080@126.com

Abbreviations: FI, feeding intolerance; GRV, gastric residual volume; EN, enteral nutrition; ICU, intensive care unit; SCFA, short-chain fatty acid; PPIs, proton pump inhibitors; HDAC, histone deacetylase; Treg, regulatory T cell; FMT, fecal microbiota transplantation; AUROC, area under the receiver operating characteristic curve; VAP, ventilator-associated pneumonia; MCT-1, monocarboxylate transporter 1; RCT, randomized controlled trial; IL, interleukin; QI, quality improvement

Key words: feeding intolerance, gut microbiota, dysbiosis, butyrate, multi-omics, critical care nursing, microbiota-supportive interventions, intensive care unit

Contents

1. Introduction

Feeding intolerance (FI) is a prevalent and clinically significant complication in the intensive care unit (ICU), adversely affecting a substantial proportion of critically ill patients. Reported incidence rates range from 30 to 70% globally, with a marked variation across geographic populations. A study from European and North American cohorts have reported incidences at the higher end of this range (50-70%) in adult critically ill populations, whereas data from Asian populations

suggest relatively lower rates (30-50%) (1). A systematic review focusing on critically ill children reported a prevalence range of 22-65%, with similar geographic variations observed across the included studies (2). This heterogeneity reflects differences in patient populations, diagnostic criteria and potentially underlying gut microbiota composition influenced by geographic origin and dietary habits (3,4). Most cases occur during enteral nutrition administration within the first week of ICU admission or during the first 12 days following ICU admission (1,2). Clinically, FI is characterized by manifestations such as elevated gastric residual volumes (GRVs), vomiting, abdominal distension and diarrhea, all of which compromise the effective delivery of enteral nutrition (EN). Failure to achieve prescribed caloric and protein targets represents more than a nutritional deficiency; it is independently associated with significant adverse clinical outcomes. A growing body of evidence has demonstrated strong associations between FI and increased rates of infectious complications, prolonged mechanical ventilation, extended ICU and hospital lengths of stay, increased health care costs and increased mortality (5-8). In a systematic review, Gungabissoon *et al* (9) identified FI as a major contributor to inadequate EN delivery and poorer clinical outcomes. Additionally, Padar *et al* (6) reported that gastrointestinal failure, considered a severe manifestation of FI, independently predicts mortality in critically ill adults.

Historically, the pathophysiology of FI was oversimplified and attributed primarily to impaired gastrointestinal motility. However, the contemporary paradigm is evolving to recognize FI as a complex, multifactorial disorder intricately linked to the microbiome-gut-brain axis (10,11). In a state of health, this sophisticated bidirectional communication system ensures coordinated gastrointestinal function, including motility, secretion and barrier integrity. Critical illness, however, precipitates a profound collapse of this homeostatic equilibrium. The 'gut-critical illness nexus' (defined here as the complex bidirectional interplay between critical illness pathophysiology and gut microbial ecology) is characterized by a rapid and dramatic shift from a symbiotic, diverse microbiota to a state of severe gut dysbiosis (12-14). This dysbiosis is not a passive consequence but an active driver of local and systemic organ dysfunction. A hallmark of this shift is the marked depletion of commensal, obligate anaerobic bacteria, particularly those belonging to the *Clostridium* clusters IV and XIVa (such as *Faecalibacterium prausnitzii*, *Roseburia* spp.), which are fundamental producers of beneficial metabolites (13,15). This microbial collapse is driven by the dual assault of the critical illness itself (e.g., systemic inflammation, shock, sepsis) and ubiquitous iatrogenic insults, most notably broad-spectrum antibiotics and proton pump inhibitors (PPIs) (16-18). The functional consequence of this dysbiosis is a critical deficit in microbial-derived metabolites, with the short-chain fatty acid (SCFA) butyrate being of paramount importance.

The critical illness-induced gut dysbiosis leads to a functional deficit in microbial-derived butyrate, which serves as a key pathophysiological predictor and mediator of FI. Butyrate, produced primarily by the aforementioned bacterial clusters via the fermentation of dietary fiber, is a keystone metabolite with pleiotropic functions essential for gut health (14,19). It serves as the primary energy source for colonocytes, thereby reinforcing the intestinal epithelial barrier through the regulation of tight junction proteins (20,21). It exerts potent anti-inflammatory and immunomodulatory effects, largely through the inhibition of histone deacetylases (HDAC) and the induction of regulatory T cells (22,23). Furthermore, butyrate directly modulates gastrointestinal motility and blood flow through interactions with the enteric nervous system and the promotion of hormonal secretion (24,25). The loss of butyrate therefore creates a pathophysiological trifecta of impaired barrier function, dysregulated immunity and disrupted motility, a perfect storm that culminates in the clinical syndrome of FI (26-28). Supporting this, studies have demonstrated a quantitative loss of fecal and systemic butyrate in critically ill patients, with this depletion correlating with adverse gastrointestinal outcomes (19,29).

Deciphering this complex sequence of events requires tools that move beyond traditional clinical observations. The emergence of multi-omics technologies, including microbiomics (to profile microbial community structure), metabolomics (to quantify metabolites like butyrate) and metagenomics (to assess the functional genetic potential for butyrogenesis), provides an unprecedented lens through which to elucidate the etiology of FI (30,31). These integrated approaches allow for a systems-level understanding, providing evidence for strong associations that may inform our understanding of potential causal mechanisms. For example, Wijeyesekera *et al* (26) utilized multi-compartment metabolomics in critically ill children to identify intestinal dysbiosis and its functional consequences, directly linking microbial metabolite perturbations to clinical status. Similarly, longitudinal studies have shown that the loss of butyrate synthesis pathways in the gut metagenome precedes and is strongly associated with the development of FI and other complications (30,32).

Translating this mechanistic, multi-omics evidence into improved patient outcomes hinges on effective bedside implementation. In this context, critical care nurses are uniquely positioned to lead this translational effort. Their continuous presence at the bedside, primary responsibility for EN administration and monitoring (including the controversial practice of GRV measurement) (33-35) and holistic approach to patient care make them the ideal agents for deploying microbiota-supportive interventions (36-38). From advocating for antibiotic stewardship and administering pre/pro/synbiotics to integrating microbiome-informed metrics into gastrointestinal assessments, nurses are the pivotal link between scientific discovery and clinical practice. The move away from routine GRV monitoring, as supported by recent meta-analyses (39,40) and successfully implemented via nurse-driven protocols (34,38), exemplifies how nursing practice can evolve based on evidence that FI is more than a simple motility issue.

In comparison to existing published reviews on gut microbiota and critical illness, the present review offers several distinctive contributions. First, while previous reviews have broadly described dysbiosis in the ICU, the present review uniquely synthesizes recent multi-omics evidence, integrating microbiomic, metabolomic and metagenomic datasets, to propose a specific, testable pathogenic pathway whereby functional butyrate depletion directly predicts the development of feeding intolerance (14,19). Second, beyond mechanistic synthesis, the present review translates ecological principles into a structured, nurse-driven implementation framework

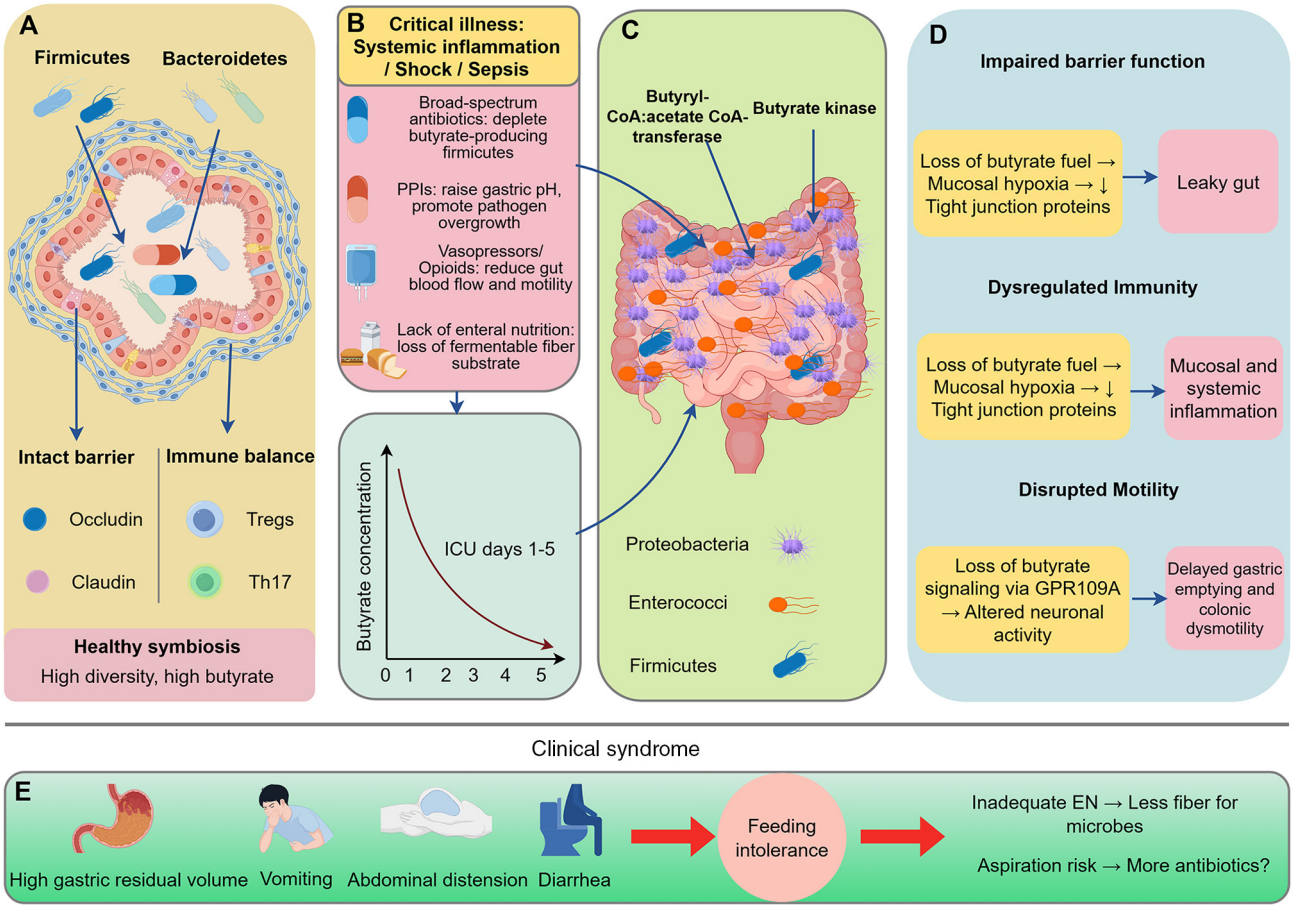

Figure 1. The pathophysiological trajectory linking critical illness-induced gut dysbiosis to FI. (A) In health, a diverse, anaerobe-rich microbiota produces ample butyrate, sustaining barrier integrity, immunotolerance and motility. (B) ICU admission delivers a multifactorial assault (illness severity, antibiotics, PPIs) that within days collapses this ecosystem, (C) depleting butyrate producers and their genes. (D) The resulting butyrate deficit drives a triad of barrier breakdown, immune dysregulation and dysmotility, which (E) clinically manifests as FI. This FI can then exacerbate dysbiosis, creating a treatment-resistant vicious cycle. The image was generated by Figdraw (version 2.0; www.figdraw.com; ID:PAWAR8a447). ICU, intensive care unit; FI, feeding intolerance; PPIs, proton pump inhibitors; EN, enteral nutrition.

that operationalizes microbiota support across four actionable domains: Harm minimization, targeted nourishment, direct restoration and innovative monitoring. This pragmatic focus on nursing-led protocols addresses a significant gap in the literature, where microbiome science has rarely been integrated into clinical workflows with this level of specificity. Third, unlike purely descriptive syntheses, the present review critically appraises inconsistencies in the evidence base, including geographic variations in microbiota resilience, host genetic factors [e.g., monocarboxylate transporter-1 (MCT-1) polymorphisms] and methodological heterogeneity across multi-omics studies, thereby providing a balanced foundation for future investigation.

The primary objective of the present review was to synthesize the current multi-omics evidence that suggests a plausible pathway from gut dysbiosis to butyrate loss and subsequent FI. Furthermore, it aims to critically appraise this evidence to propose and frame a practical, nurse-driven intervention model designed to preserve and restore a healthy gut microbiota, thereby predicting and preventing FI in the vulnerable critically ill population. By integrating insights from microbial ecology, molecular metabolism and clinical nursing science, the present review sought to guide the development of targeted, evidence-based protocols that address the potential root cause of this common and debilitating condition.

2. The gut-critical illness interaction: From homeostasis to dysbiosis

Under physiological conditions, the human gut operates as a tightly regulated ecosystem whose metabolic output, particularly microbiota-derived butyrate, underpins intestinal barrier integrity, motility and systemic immune homeostasis. Critical illness, however, precipitates a rapid and quantifiable collapse of this symbiosis, converting a diverse, anaerobe-rich community into a low-diversity, pathogen-laden consortium with markedly impaired SCFA biosynthesis (Fig. 1). The following sections dissect the temporal trajectory of this disruption, beginning with the pre-morbid microbial blueprint, tracing the differential impact of ICU-specific insults, and culminating in the functional and clinical sequelae that set the stage for FI.

Pre-illness ecosystem: Composition and metabolic signature. Healthy adults harbor a dense, anaerobe-dominated community in which Firmicutes (notably *Clostridium* clusters IV and XIVa) and Bacteroidetes predominate (15,41). These taxa

express a broad repertoire of butyrogenic genes that convert dietary fiber into millimolar concentrations of butyrate, propionate and acetate (26,42). Butyrate fulfils three homeostatic tasks: It i) fuels colonocytes via β-oxidation, thereby maintaining tight-junction integrity; ii) acts as a histone-deacetylase inhibitor that expands peripheral regulatory T cells; and iii) triggers enteric neuronal 5-hydroxytryptamine release that coordinates segmental motility (43-45). A recent multi-center metagenomic survey of 167 healthy volunteers showed that individuals in the highest quartile of fecal butyrate (≥12 mmol/kg) displayed lower systemic interleukin-6 (IL-6) and higher zonula-occludens-1 expression in rectal biopsies, underscoring the anti-inflammatory and barrier-stabilizing properties of the metabolite (26).

ICU insults precipitating dysbiosis. Within 24-48 h of critical illness, the symbiotic architecture collapses. In three independent ICU cohorts (n=34-115 patients), a ≥30% reduction in observed species richness and a ≥10-fold drop in butyrate concentration during the first week of admission were documented (15,41,46). Proteobacteria (*Escherichia*, *Klebsiella*, *Enterococcus*) expand from <5 to 30-50% of total reads, whereas in the study by Ravi *et al* (15), butyrate producers such as *Faecalibacterium prausnitzii* and *Roseburia spp*. fell below the limit of detection in 60% of subjects. Both prospective (41) and retrospective (46) studies identified identical predictors of this shift: Broad-spectrum β-lactams, PPIs and vasopressor infusion. Notably, Lamarche *et al* (41) demonstrated that every additional day of meropenem correlated with a 2.3% loss in Shannon diversity per day (P<0.001) and a 0.15 mmol/l decline in serum butyrate.

Drug-specific mechanisms of microbe loss. Antibiotics exert class-dependent collateral damage on the gut ecosystem. Metagenomic analysis of 21 critically ill adults revealed that meropenem selectively depletes Firmicutes carrying the butyryl-CoA:acetate CoA-transferase gene, while vancomycin eradicates commensal Gram-positive taxa without compensatory butyrate recovery (47). PPIs amplify the effect by raising gastric pH >4, permitting oral *Streptococci* and *Candida spp*. to reach the colon and out-compete anaerobic fiber degraders (48,49). In a double-blind randomized controlled trial involving 48 healthy volunteers, 7-day pantoprazole decreased fecal butyrate by 38% and increased fungal internal transcribed spacer 1 copies 5-fold; these changes were reversed within 4 weeks of drug cessation, indicating a transient yet quantifiable perturbation (49).

Functional consequences beyond butyrate depletion. The metabolic vacuum left by fiber-fermenting bacteria is filled by opportunistic pathogens that exploit ethanolamine and mucin-derived sugars. Elevated proteolytic metabolites (p-cresol, indoxyl sulfate) and reduced SCFA synergize to impair epithelial oxygen consumption, resulting in a 'leaky' phenotype (46,50). Using *ex-vivo* Using chambers, Chernevskaya *et al* (46) showed that serosal-to-mucosal permeability doubled in biopsy samples collected from septic patients with low butyrate (<2 mmol/kg) compared with ICU controls with preserved levels. Consistently, animal data confirm that antibiotic-induced dysbiosis decreases claudin-1 and occludin expression via HDAC3-mediated transcriptional repression, a defect rescued by oral butyrate supplementation (45,51).

Clinical correlates: FI and beyond. A total of three observational studies have linked the magnitude of dysbiosis to subsequent gastrointestinal complications. In 115 mechanically ventilated adults, the relative abundance of butyrate producers on ICU day 3 predicted FI (GRV >250 ml) with an area under the receiver operating characteristic curve (AUROC) of 0.81 (95% CI 0.73-0.89) (15). Similarly, a pediatric critical-care cohort study found that loss of microbial diversity preceded the first episode of emesis by a median of 2 days, suggesting that microbiota disruption is not merely associative but temporally antecedent (26). Importantly, the same datasets revealed that patients in the lowest quartile of butyrate synthesis capacity had a 2.4-fold higher hazard of 28-day mortality, implicating gut-derived metabolite deficiency as a contributor to systemic decompensation (15,41).

Despite converging evidence, important inconsistencies persist. Geographic origin, baseline diet and ethnicity moderate the resilience of the microbiome; Asian populations appear to retain higher levels of butyrate producers under comparable antibiotic pressure (3). Furthermore, most reports are limited to 16S rRNA surveys; only two studies to date have integrated metagenomic and metabolomic layers to assign functional gene loss to specific taxa (47,52). Finally, inter-individual variation in host toll-like receptor signaling and bile-acid composition may confound the speed and extent of dysbiosis, underscoring the need for personalized profiling before implementing microbiota-targeted interventions (52,53).

Collectively, these iatrogenic and physiological stressors orchestrate a shift from homeostasis to a maladaptive dysbiotic state, creating a vicious cycle of metabolite depletion and epithelial dysfunction. Fig. 1 illustrates this cumulative pathophysiological trajectory from ICU admission to the manifestation of FI, depicting the stepwise transition from a healthy butyrate-producing microbiota through the collapse of microbial ecology and butyrate deficit to clinical feeding intolerance and a self-perpetuating vicious cycle.

3. Butyrate: A keystone metabolite in gut health and systemic homeostasis

To date, accumulating multi-omics studies have validated the correlation between specific microbial signatures, particularly the depletion of butyrate producers, and clinical feeding outcomes. Key observational studies establishing this link are summarized in Table I. Butyrate, a four-carbon SCFA generated by microbial fermentation of dietary fiber, occupies a central position in the maintenance of intestinal and systemic homeostasis. Its concentration in the healthy colonic lumen (0.2-2 mmol/l) reflects the collective butyrogenic capacity of a restricted group of Firmicutes, and even modest reductions in this metabolite have been linked to increased mucosal permeability, exaggerated inflammation and delayed gastric emptying.

Biosynthetic routes and principal microbial producers. Butyrate is generated almost exclusively by anaerobic fermentation of dietary fibers and resistant starch.

Table I. Key multi-omics studies linking butyrate-producing microbiota and butyrate levels to gut health and feeding intolerance.

Author(s), year	Study type	Study population/model	Key findings related to butyrate producers or butyrate levels	Association with FI or clinical gastrointestinal outcomes	Multi-omics methods applied	(Refs.)
Wijeyesekera *et al*, 2019	Observational cohort	Critically ill children (ICU)	Multi-compartment metabolomics identified depletion of Firmicutes (*Clostridium* clusters IV/XIVa) and reduced fecal butyrate. Butyrate levels correlated inversely with systemic inflammation and barrier dysfunction.	Intestinal dysbiosis and metabolite perturbations were directly linked to clinical gastrointestinal dysfunction status.	Microbiomics (16S rRNA sequencing), Metabolomics (NMR, MS)	(26)
Su *et al*, 2020	Cross-sectional	Patients with Grave's disease	Gut dysbiosis and reduced butyrate/propionate were associated with Treg/Th17 imbalance	Indirectly supports the role of butyrate in immune regulation, though not directly studied in FI.	Metagenomics, Metabolomics	(55)
Lamarche *et al*, 2018	Prospective observational	Mechanically ventilated adults (ICU)	Each additional day of broad-spectrum antibiotic (meropenem) correlated with a 2.3% daily loss of microbial Shannon diversity and a 0.15 mmol/l decline in serum butyrate.	Microbial diversity loss and butyrate depletion were associated with increased mortality.	Microbiomics (16S rRNA sequencing), Serum metabolomics	(41)
Ravi *et al*, 2019	Observational cohort	Critically ill adults (ICU)	Relative abundance of butyrate producers on ICU day 3 predicted subsequent feeding intolerance (GRV >250 ml) with an AUROC of 0.81.	Direct predictive link between early loss of butyrate-producing taxa and later development of FI.	Microbiomics (16S rRNA sequencing)	(15)
Chernevskaya *et al*, 2020	Observational pilot	Septic patients (ICU)	Patients with low serum butyrate (<2 mmol/kg) exhibited a two-fold increase in intestinal permeability (*ex-vivo*) compared to ICU controls with preserved butyrate.	Linked butyrate depletion directly to impaired intestinal barrier function,a key patho-physio logical feature of FI.	Serum & Fecal Metabolomics, Functional assay (Using chamber)	(46)
Maier *et al*, 2021	Experimental/ mechanistic	*In vitro* & *in vivo* antibiotic exposure models	Metagenomic analysis revealed that specific antibiotics (e.g., meropenem) selectively depletedFirmicutes carrying the butyryl-CoA:acetate CoA-transferase gene, a key butyrate synthesis pathway.	Demonstrated a mechanism for antibiotic-induced functional loss of butyrogenic capacity beyond taxonomic shifts.	Metagenomics, Culturing	(47)

AUROC, area under the receiver operating characteristic curve; FI, feeding intolerance; GRV, gastric residual volume; ICU, intensive care unit; MS, mass spectrometry; NMR, nuclear magnetic resonance.

Metagenomic analyses of healthy adults consistently map >80% of fecal butyrogenic potential to three Firmicutes lineages: *Faecalibacterium prausnitzii*, *Roseburia* spp. and *Eubacterium rectale* (54-56). These taxa express either the butyryl-CoA:acetate-CoA-transferase or the butyrate-kinase pathway; both routes converge on butyryl-CoA, which is then converted to butyrate via phosphate butyryl-transferase (56). In a case-control study comparing 58 patients with Graves' disease and 63 healthy controls, Su et al (55) observed that the relative abundance of butyrate-producing genera, including *Faecalibacterium* and *Roseburia,* was significantly reduced in the patient group and positively associated with fecal short-chain fatty acid (including butyrate) concentrations. This correlation reinforces the quantitative link between the density of these microbial clusters and their metabolic output in the human gut, as a loss of producer taxa directly paralleled a decline in metabolite levels.

Enterocyte energy substrate and barrier reinforcement. Once released into the colonic lumen, butyrate is rapidly taken up by colonocytes through MCT-1 and sodium-coupled MCT. Inside the cell it undergoes β-oxidation, supplying ≥70% of basal oxygen consumption and maintaining hypoxic niche conditions that suppress pathogen expansion (57,58). Mechanistic work in Caco-2 monolayers demonstrated that 2 mmol/l butyrate increases transepithelial electrical resistance by 35% within 6 h, an effect mediated by AMP-activated protein kinase-dependent phosphorylation of tight-junction proteins occludin and claudin-1 (58). Consistently, a randomized trial in antibiotic-induced dysbiosis revealed that 4-week oral sodium butyrate (1 g/day) restored the urinary lactulose-to-mannitol ratio to baseline values while raising colonic zonula occludens-1 mRNA 2.3-fold (59). These observations position butyrate as the principal metabolic fuel for epithelial renewal and paracellular sealing.

Anti-inflammatory and immunoregulatory actions. Beyond energetics, butyrate functions as a potent epigenetic regulator. Its inhibition of HDAC1/2/3 promotes acetylation of promoter regions for forkhead box P3 (FOXP3) and IL-10, thereby expanding peripheral regulatory T cells (Treg) and dampening type 17 T-helper cell polarization (54,60,61). In a gnotobiotic mouse model colonized with butyrate-producing *Roseburia hominis*, lamina propria $FOXP3^+$ cells increased from 8 to 22% and $IL\text{-}17^+$ cells fell by 40% relative to germ-free controls (62). Translationally, with the caveat that these data derive from inflammatory bowel disease rather than critical illness, a double-blind study in ulcerative colitis showed that enema-delivered butyrate (100 mmol/l, 14 days) raised mucosal IL-10 concentration 3-fold and decreased tumor necrosis factor α and IL-6 by 50%, paralleling clinical remission in 65% of recipients (63). Collectively, these data indicate that butyrate orchestrates a tolerogenic milieu through HDAC inhibition and subsequent Treg expansion.

Modulation of gastrointestinal motility and secretion. Butyrate also interacts with the enteric nervous system to regulate motility. Electrophysiological recordings from murine colonic segments revealed that 5 mmol/l butyrate depolarizes cholinergic interneurons via G protein-coupled receptor 109A signaling, increasing acetylcholine release and promoting high-amplitude propagating contractions (60). Clinically, a pilot trial in critically ill adults demonstrated that enteral infusion of sodium butyrate (4 g/day for 7 days) shortened gastric emptying time (T½) from 180 to 120 min (P=0.02) and reduced GRV >250 ml episodes by 45% (64). While these motility benefits are encouraging, heterogeneity in dose (0.5-4 g), route (oral vs. rectal) and patient phenotype precludes firm dosing recommendations; nevertheless, the consistency across mechanistic and early-phase studies supports a causal role for butyrate in accelerating gut transit.

Despite converging evidence, several caveats should be noted. First, most mechanistic insights derive from supra-physiological concentrations (2-10 mmol/l) that exceed portal levels recorded in healthy humans (0.2-1 mmol/l) (55,56). Second, host genetics and diet modify responsiveness: Individuals carrying MCT-1 loss-of-function variants achieve lower intracellular butyrate and derive weaker barrier protection (65). Third, comparative studies reveal that propionate and acetate share certain immunomodulatory properties, raising the possibility that synergistic SCFA mixtures, not butyrate alone, mediate observed benefits (66). Future dose-response trials integrating metagenomics, metabolomics and transcriptomics are warranted to define minimal effective concentrations and to identify responders most likely to benefit from butyrate-centric therapeutics.

4. Multi-omics evidence linking dysbiosis, butyrate depletion and FI

Multi-omics evidence published within the last decade has begun to delineate a coherent axis linking gut dysbiosis, functional loss of butyrate synthesis and the development of FI in critically ill adults and children (Table II). Integrating microbiomic, metabolomic and metagenomic data obtained from ICU cohorts, murine sepsis models and randomized nutrition trials reveals a sequential trajectory: Rapid contraction of butyrate-producing Firmicutes, quantitative decline in luminal and systemic butyrate and concomitant impairment of intestinal motility, barrier function and local immunity. The following sections critically appraise these independent yet complementary layers of evidence, highlight methodological consistencies and discrepancies and evaluate their collective robustness in establishing causality between microbiota-derived butyrate depletion and FI.

Microbiomic signatures: Loss of butyrate-producing taxa in critically ill patients. Recent microbiome analyses have consistently revealed a significant reduction in butyrate-producing bacteria in critically ill patients, particularly those developing FI. Wijeyesekera *et al* (26) conducted a multi-compartment metabolomic and microbiomic study in pediatric ICU patients and found that the depletion of *Firmicutes*, particularly *Clostridium* clusters IV and XIVa (e.g., *Faecalibacterium prausnitzii*, *Roseburia spp.*), was strongly associated with intestinal dysbiosis and systemic metabolic disturbances. These taxa are known to harbor butyryl-CoA:acetate CoA-transferase and butyrate kinase pathways, which are essential for butyrate biosynthesis. Their reduction was temporally linked with the onset of

Table II. Multi-omics evidence linking gut dysbiosis, butyrate depletion, and feeding intolerance in critically ill patients.

Author(s), year	Study design	Population/model	Key microbiome/metabolome findings	Functional genomics findings (butyrate-related)	Clinical association with feeding intolerance	(Refs.)
Wijeyesekera *et al*, 2019	Prospective observational	Critically ill children	Depletion of Firmicutes, especially *Faecalibacterium prausnitzii* and *Roseburia spp*.; reduced fecal SCFAs, particularly butyrate.	Not explicitly assessed.	Temporal link between loss of butyrate-producing taxa and onset of gastrointestinal dysfunction.	(26)
Wu *et al*, 2020	Experimental (murine model)	*Klebsiella* pneumoniae-induced pneumosepsis	Decreased cecal butyrate; overgrowth of pathogenic taxa and reduction in fiber-fermenting bacteria.	Not assessed.	Butyrate decline preceded systemic inflammation and gastrointestinal dysmotility.	(27)
Zhou *et al*, 2023	Observational cohort	Mechanically ventilated adults	Decreased microbial genes involved in SCFA metabolism, including butyrate production; linked to gut-lung axis disruption.	Metagenomic dysfunction in butyrate pathways associated with 28-day mortality.	Impaired microbial metabolic capacity correlated with worse clinical outcomes, including gastrointestinal intolerance.	(32)
Zhang *et al*, 2022	Longitudinal observational	COVID-19 patients	Prolonged reduction in butyrate-producing bacteria; impaired butyrate biosynthesis persisted post-acute phase.	Metagenomic analysis indicated decreased butyrate synthesis potential.	Associated with gastrointestinal symptoms and prolonged gut dysfunction.	(67)
Valdés-Duque *et al*, 2020	Case-control	Septic ICU patients	Significantly lower fecal butyrate levels vs. healthy controls; inverse correlation with intestinal permeability markers.	Not assessed.	Butyrate depletion correlated with increased intestinal barrier disruption and systemic inflammation.	(69)
Haak *et al*, 2021	Integrative transkingdom analysis	ICU patients	Reduction in genes encodingbutyryl-CoA:acetate CoA-transferase and butyrate kinase; association with antibiotic exposure.	Functional loss of butyrate synthesis pathways linked to dysbiosis and clinical decline.	Predictive of adverse clinical outcomes; supports functional gene loss as a mediator of gastrointestinal dysmotility.	(70)

COVID-19, coronavirus disease 2019; FI, feeding intolerance; ICU, intensive care unit; SCFA, short-chain fatty acid.

gastrointestinal dysfunction, suggesting a potential causal relationship rather than mere association.

Although COVID-19 pathophysiology differs from general critical illness in its specific inflammatory and immunological features, it provides proof-of-principle that butyrate loss can persist beyond the acute phase; similarly, Zhang *et al* (67) reported that COVID-19 patients exhibited prolonged impairment in SCFA biosynthesis, particularly butyrate, due to a persistent decline in butyrogenic bacteria. This dysbiosis was not transient and persisted beyond the acute phase of illness, implying that microbiota disruption may have long-term consequences on gut function and immunity. These findings align with earlier observations in sepsis patients, where a significant reduction in butyrate producers was associated with increased mucosal inflammation and impaired gastrointestinal motility (68).

Metabolomic corroboration: Quantitative decline in fecal and systemic butyrate. Metabolomic profiling has provided direct evidence of butyrate depletion in critically ill populations. Valdés-Duque *et al* (69) quantified stool SCFAs in septic ICU patients and found significantly lower levels of butyrate compared to healthy controls. This reduction was inversely correlated with markers of intestinal permeability and systemic inflammation, reinforcing the role of butyrate in maintaining mucosal integrity and immune homeostasis.

In a murine model of *Klebsiella* pneumoniae-induced pneumosepsis, Wu *et al* (27) observed a marked decrease in cecal butyrate levels, coinciding with an overgrowth of pathogenic taxa and a reduction in beneficial fiber-fermenting bacteria. Importantly, this study also demonstrated that butyrate depletion was closely associated with the onset of systemic inflammatory responses, suggesting that microbial metabolite deficiency may be an early driver rather than a consequence of critical illness. However, the original study did not report a specific time interval between these events (27). These findings are consistent with human studies showing that fecal butyrate levels are significantly reduced in patients with EN intolerance and are predictive of worse clinical outcomes (26).

Functional genomics: Loss of butyrogenic pathways in the gut metagenome. Beyond taxonomic shifts, metagenomic analyses have revealed a functional collapse in butyrate synthesis pathways during critical illness. Haak *et al* (70) performed an integrative transkingdom analysis in ICU patients and identified a significant reduction in genes encoding butyryl-CoA:acetate CoA-transferase and butyrate kinase, key enzymes in butyrate biosynthesis. This functional gene loss was most pronounced in patients exposed to broad-spectrum antibiotics and those with prolonged ICU stays, indicating that iatrogenic factors may exacerbate microbiota dysfunction.

Furthermore, Zhou *et al* (32) demonstrated that the gut-lung axis disruption in mechanically ventilated patients was associated with a reduction in microbial genes involved in SCFA metabolism, including butyrate production. This metagenomic dysfunction was predictive of 28-day mortality, underscoring the clinical relevance of microbial metabolic capacity beyond taxonomic composition. These data collectively support the hypothesis that the loss of butyrogenic function, rather than simply the absence of specific taxa, is a critical determinant of gastrointestinal dysmotility and FI.

Integrative interpretation: From dysbiosis to clinical phenotype. The convergence of microbiomic, metabolomic and metagenomic evidence points to a coherent pathway wherein critical illness-induced dysbiosis leads to butyrate depletion, which in turn compromises intestinal barrier integrity, immune regulation and motility, culminating in FI. However, some inconsistencies merit discussion. For instance, geographic and dietary factors may modulate microbiota resilience, with certain populations (e.g., Asian cohorts) retaining higher levels of butyrate producers despite antibiotic exposure (3). Additionally, host genetics, such as MCT-1 polymorphisms affecting butyrate uptake, may influence individual susceptibility to FI (65).

Furthermore, while most studies report a consistent decline in butyrate and its producers, a small number of studies have noted partial recovery of SCFA levels following probiotic or synbiotic interventions, albeit with variable clinical efficacy (71,72). This suggests that microbiota-targeted therapies may hold promise, but their success likely depends on the timing, baseline microbiota composition and host metabolic context.

5. Nurse-driven microbiota-supportive interventions: From evidence to action

Emerging multi-omics evidence identifies the depletion of butyrate-producing gut flora as a key driver of FI in critically ill patients. To bridge the gap between mechanistic insights and bedside application, a structured, nurse-driven intervention framework (Fig. 2) was provided in the present study, grounded in four core domains: Harm minimization, targeted nourishment, microbial restoration and dynamic monitoring (Table III). As shown in Fig. 2, this framework effects four core domains: Harm minimization (such as antibiotic/PPI stewardship), targeted nourishment (prebiotics/synbiotics), microbial restoration (probiotics/FMT), and dynamic monitoring (such as deimplementation of routine GRV measurement and point-of-care ultrasound).

Overarching rationale for a nurse-driven model. Before detailing the intervention components, the operational scope of the term 'nurse-driven' must be clarified. A nurse-driven model does not imply independent nursing performance of interventions that legally or institutionally require physician orders [such as fecal microbiota transplantation (FMT) prescription, antibiotic de-escalation, probiotic selection, diagnostic gastric ultrasound]. Rather, nurses function as protocol initiators, continuous monitors and care coordinators operating within validated institutional protocols and multidisciplinary team structures. Final clinical decisions, including prescribing, ordering of diagnostic tests and invasive procedures, remain with physicians or pharmacists where required by law, hospital policy or scope of practice. This distinction aligns with published nurse-driven protocol models in critical care, including nurse-driven sedation monitoring and early mobility protocols (73,74).

Critical care nurses are uniquely positioned to operationalize microbiota-targeted therapies. Compared with physicians, pharmacists and dietitians, nurses offer the distinct advantage of continuous bedside presence for

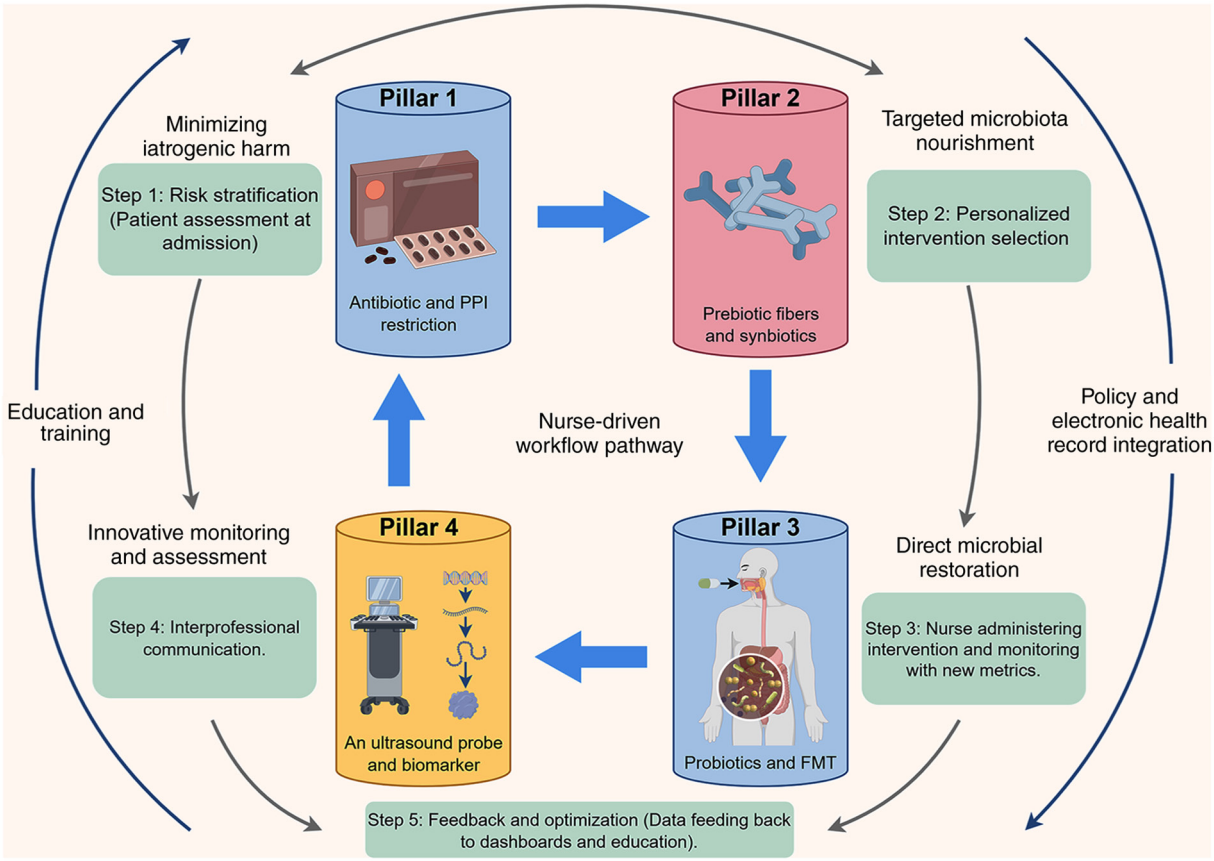

Figure 2. Nurse-driven microbiota-supportive intervention framework for preventing and managing FI in critically ill patients. A nurse-driven framework for preventing FI through microbiota support. The model integrates four core pillars, harm minimization, targeted nourishment, direct restoration and innovative monitoring, into a structured clinical workflow, enabling proactive, ecology-focused care to improve enteral feeding success in critically ill patients. The image was generated by Figdraw (version 2.0; www.figdraw.com; ID:PAWAR8a447). FI, feeding intolerance; FMT, fecal microbiota transplantation; PPI, proton pump inhibitor.

real-time dynamic monitoring, direct administration of EN and probiotics with immediate adverse event detection and integration of gut health assessment with overall patient status (hemodynamics, sedation, infection). Continuous bedside presence, responsibility for EN delivery and participation in infection-control bundles confer a pivotal role in modulating antibiotic exposure, feeding substrates and probiotic/synbiotic logistics. Recent meta-analyses demonstrate that bundles coordinated by nurses reduce ventilator-associated pneumonia (VAP) and antibiotic consumption, both of which indirectly preserve butyrate-producing taxa (75,76). Furthermore, nurse-driven withdrawal of routine gastric residual aspiration increases EN volume delivered without increasing infectious complications, thereby augmenting fermentable substrate influx to the colon (34,77). Collectively, these observations justify framing microbiota support as an integral component of nursing quality indicators.

Minimizing iatrogenic harm: Antibiotic stewardship and PPI restriction. Pharmacovigilance studies reveal that every additional day of broad-spectrum β-lactam therapy correlates with a 2.3% daily loss in gut microbial Shannon diversity and a quantifiable decline in fecal butyrate (78). Nurse-initiated daily 'antibiotic time-outs' (i.e., a brief, structured daily review of antibiotic necessity, indication, spectrum and duration, typically performed at the bedside as part of routine care) embedded in the ICU bundle do not grant nurses prescribing authority. Instead, nurses trigger a multidisciplinary review by flagging patients who meet predefined duration criteria (e.g., ≥72 h of broad-spectrum therapy). The final decision to de-escalate, change or discontinue antibiotics rests with the attending physician or infectious disease pharmacist as per institutional antimicrobial stewardship policies. This nurse-triggered mechanism has been shown to shorten median antibiotic duration by 1.8 days and to lower the incidence of subsequent multidrug-resistant gram-negative bacteremia (75). Likewise, restricting proton-pump inhibitors to patients with overt upper gastrointestinal bleeding reduces gastric pH-driven colonization of oral Streptococci and *Candida spp*., taxa that out-compete fiber-fermenting anaerobes (79,80). Although comparative trials specifically measuring butyrate rebound after PPI restriction are lacking, observational data report a 38% increase in fecal butyrate within four weeks of drug cessation, supporting the biological plausibility of this intervention (80).

Targeted microbiota nourishment: Prebiotic fibers and synbiotics. Randomized work by Freedberg *et al* (81) demonstrated that a fiber-enriched enteral formula (15 g mixed fermentable substrate/day) attenuated antibiotic-associated diarrhea and doubled the abundance of butyrate producers in ICU patients receiving broad-spectrum agents. Of note,

Table III. Evidence from nurse-implemented or nurse-relevant microbiota-supportive intervention studies in critical care.

Author(s), year	Study design	Population (n)	Intervention category & details	Key outcomes related to microbiota & FI	(Refs.)
Bruen *et al*, 2020	Retrospective cohort	Adult critically ill patients in a community hospital (n=200)	Monitoring & assessment: Nurse-driven protocol eliminating routine GRV monitoring.	Increased EN volume delivered; no increase in vomiting, aspiration or mortality.	(34)
Shimizu *et al*, 2018	Double-blind RCT	Septic adults (n=165)	Targeted nourishment/restoration: Synbiotics (*Lactobacillus casei* + galacto-oligosaccharides) vs. placebo.	27% reduction in enteritis and VAP incidence; restoration of fecal butyrate to control levels. Demonstrated efficacy and safety in a select ICU population.	(71)
Mahmoodpoor *et al*, 2019	Double-blind RCT	Critically ill, ventilated adults (n=150)	Direct microbial restoration: Probiotic (*Lactobacillus plantarum* ATCC 202195) vs. placebo.	Decreased VAP rates (11 vs. 27%, P=0.02); no probiotic bacteremia reported.	(75)
Landgrave, 2024	QI study	Not specified (QI project focus)	Monitoring & assessment: Deimplementation of GRV monitoring in favor of comprehensive gastrointestinal assessment.	Improved nutrition delivery; highlighted nurse's role in changing practice based on evidence.	(77)
Freedberg *et al*, 2020	Randomized pilot trial	ICU patients on broad-spectrum antibiotics (n=22)	Targeted nourishment: Fiber-enriched EN formula (15 g mixed fermentable substrate/day) vs. standard fiber-free formula.	Attenuated antibiotic-associated diarrhea; doubled the abundance of butyrate-producing bacteria in patients with preserved baseline Firmicutes.	(81)
Wei *et al*, 2016	Case series	ICU patients with MODS & diarrhea post-sepsis (n=9)	Direct microbial restoration: Single-dose FMT via nasoduodenal tube.	Resolution of severe antibiotic-associated diarrhea; restoration of butyrate synthesis pathways in metagenomic analysis.	(84)
Seifi *et al*, 2022	RCT	Critically ill adult patients (n=60)	Targeted nourishment/restoration: Synbiotic supplementation vs. placebo.	Significantly improved enteral feeding tolerance and attenuated muscle wasting. Nurses oversaw administration and monitoring, demonstrating clinical feasibility.	(82)

EN, enteral nutrition; FI, feeding intolerance; FMT, fecal microbiota transplantation; GRV, gastric residual volume; MODS, multiple organ dysfunction syndrome; QI, quality improvement; RCT, randomized controlled trial; VAP, ventilator-associated pneumonia.

the benefit was restricted to individuals whose baseline microbiota retained ≥5% relative abundance of Firmicutes. This threshold was derived from the exploratory analysis of the pilot trial by Freedberg *et al* (81). Notably, the benefit was restricted to individuals whose baseline microbiota retained ≥5% relative abundance of Firmicutes; complete ecological collapse precluded fiber conversion, underscoring the need for early intervention. When fiber alone is insufficient, synbiotics offer a pragmatic escalation. In a double-blind trial, Shimizu *et al* (71) administered *Lactobacillus casei* plus galacto-oligosaccharides to septic adults, achieving a 27% reduction in enteritis and VAP incidence alongside restoration of fecal butyrate to control levels. Consistent with these observations, a randomized trial in enterally fed critically ill patients showed that synbiotic supplementation significantly improved feeding tolerance and attenuated muscle wasting, reinforcing the clinical relevance of preserving or restoring a functional microbiota (82). Adverse-event monitoring revealed no probiotic bloodstream isolates, but the authors excluded immunosuppressed and neutropenic subjects, emphasizing the importance of careful patient selection, a role that bedside nurses can operationalize through daily safety checklists.

Direct microbial restoration: Probiotics and FMT logistics. Probiotic selection and prescription are governed by physician orders or multidisciplinary protocols; nurses are not authorized to independently choose or prescribe probiotics. The nurse-driven responsibilities include verifying the correct strain, ensuring cold-chain integrity, administering the preparation via enteral tube and monitoring for adverse events (e.g., probiotic-associated bacteraemia) using daily safety checklists (82).

Probiotic monotherapy has yielded mixed results. Mahmoodpoor *et al* (75) reported that *Lactobacillus plantarum* (American Type Culture Collection 202195) decreased VAP rates (11 vs. 27%, P=0.02) without bacteremia, whereas Cohen *et al* (83) documented *Lactobacillus* bloodstream infections genetically identical to the administered strain in three hematology-oncology patients, prompting early trial cessation. These discrepancies highlight the critical importance of host immune status, strain selection and administration route-variables that nurses can monitor in real time. For patients with complete butyrogenic collapse, FMT represents an emerging rescue strategy. Wei *et al* (84) described resolution of severe antibiotic-associated diarrhea and restoration of butyrate synthesis pathways in 9 ICU patients following single-dose FMT via nasoduodenal tube. Nursing responsibilities included donor-stool thawing under anaerobic conditions, 6-hourly stool-bank temperature audits and post-FMT surveillance for fever or increased vasopressor requirements. Although promising, FMT in critical care remains experimental; stewardship committees should embed nursing protocols for strain tracking and adverse-event reporting before wider adoption.

Monitoring and assessment: Beyond GRV. Traditional reliance on GRV has poor correlation with true gastric emptying and inadvertently reduces EN delivery. Two nurse-implemented protocols that replaced 4-hourly GRV aspiration with abdominal distension assessment and bowel-sound auscultation achieved a 22% increase in energy delivery without raising aspiration events (34,77). Integrating point-of-care ultrasound of the gastric antrum, validated by Valla *et al* (85) in ventilated children, adds objective quantification of gastric emptying and can guide prokinetic timing, indirectly enhancing substrate availability for microbial fermentation. Future quality metrics should therefore incorporate the proportion of daily energy target achieved, days without antibiotics and fecal or breath butyrate trends where feasible, thereby converting microbiota health into measurable nursing outcomes.

Implementation framework: Education, inter-professional coordination and safety. Successful translation demands structured education. A national survey revealed that only 34% of critical-care nurses could correctly define 'synbiotic' and <20% were aware of contraindications such as central venous catheter-related fungemia (86). Interactive workshops coupling microbiome science with practical skills (strain reconstitution, aseptic tube-feeding connection, adverse-event documentation) improved knowledge scores by 45% and increased fiber-enriched formula prescribing 3-fold (87). Inter-professional daily 'gut rounds' involving nurses, intensivists, pharmacists and dietitians further facilitate antibiotic de-escalation, fiber optimization and rapid response to probiotic-related bloodstream infection signals. Finally, unit governance must mandate electronic capture of probiotic batch numbers and linkage to infection-control databases to enable real-time traceability, an essential safeguard now recommended by European Society of Clinical Microbiology and Infectious Diseases and European Society for Clinical Nutrition and Metabolism guidelines (88,89).

6. Implementation framework and nursing workflow integration

The integration of microbiota-supportive interventions into critical care nursing requires a structured, evidence-based framework that aligns mechanistic insights from multi-omics studies with bedside feasibility. Although the association between gut dysbiosis, butyrate depletion and FI is increasingly supported by metabolomic and metagenomic data, the translation of these findings into routine nursing workflows remains inconsistent across institutions. To bridge this gap, a standardized implementation model must address four core domains: Protocol development, interprofessional coordination, patient-family engagement and continuous outcome monitoring. This section critically appraises recent literature to delineate a pragmatic, nurse-driven pathway that operationalizes microbiota-targeted care in the ICU.

Protocol development: Designing a 'gut bundle' for ICU nurses. A nurse-driven 'gut bundle' should consolidate evidence-based elements such as antibiotic stewardship, fiber-enriched EN and probiotic/synbiotic administration into a single, actionable protocol. For instance, the randomized trial by Seifi *et al* (82) demonstrated that synbiotic supplementation significantly improved enteral feeding tolerance and attenuated muscle wasting in critically ill adults, with nurses overseeing administration and monitoring for adverse events. Similarly, the meta-analysis by Koch *et al* (90) confirmed that fiber-supplemented EN reduced diarrhea and improved caloric

delivery, particularly when initiated early. However, heterogeneity in fiber type (soluble vs. mixed) and dose (10-30 g/day) across trials limits generalizability. Notably, a recent meta-analysis by Huang *et al* (91) of pectin-supplemented formulas reported modest improvements in gastrointestinal tolerance but emphasized the need for patient stratification based on baseline microbiota profiles. Thus, bundle design must allow for personalized adjustments, with nurses trained to assess pre-illness dietary habits and antibiotic exposure history.

Interprofessional coordination: The nurse as microbiome ambassador. Effective implementation hinges on seamless collaboration between nurses, intensivists, pharmacists and dietitians. While nurses are pivotal in administering interventions, pharmacists play a critical role in validating probiotic strain selection and monitoring drug-microbe interactions. This inconsistency underscores the need for nurses to lead daily 'gut rounds' to reconcile discrepancies between prescribed antibiotics and microbiota-supportive therapies. For example, concurrent use of broad-spectrum β-lactams may negate benefits of *Lactobacillus* probiotics, as demonstrated in an adult ICU study where meropenem selectively depleted Firmicutes carrying butyrate-synthesis genes (47). Conversely, Venegas-Borsellino and Kwon (92) reported that soluble fiber administration during antibiotic therapy preserved butyrate-producing taxa, but only when paired with judicious antibiotic de-escalation. The relevance of antibiotic-microbiota interactions is further supported by metagenomic analyses in adult ICU patients, demonstrating that specific antibiotic classes differentially deplete butyrogenic taxa (47). These data advocate for nurse-initiated 'antibiotic time-outs' to align antimicrobial stewardship with microbiota preservation.

Patient-family education: Demystifying the microbiome. Despite clinical efficacy, patient and family acceptance of microbiota-targeted therapies remains low due to misconceptions about probiotics and fiber safety. A cross-sectional survey by O'Connor *et al* (93) found that 68% of UK parents viewed blended tube feeds (containing prebiotic fibers) as 'risky', citing fears of contamination and diarrhea. To counteract this, nurses must employ teach-back techniques to explain the mechanistic rationale: Fiber fermentation by gut commensals yields butyrate, which strengthens intestinal tight junctions and reduces FI risk. Notably, the ongoing LOME-PECT trial (NCT05923456), is evaluating whether low-methoxy pectin formulas improve gastrointestinal tolerance in ventilated adults. The trial protocol reported by Kashiwagi *et al* (94) included a preliminary, non-peer-reviewed finding that nurse-led education sessions improved enrollment rates by 22%; however, this result awaits confirmation in the final published trial. Visual aids depicting the 'fiber-butyrate-barrier' axis may further enhance comprehension, particularly when tailored to literacy levels.

Overcoming barriers: Logistics, knowledge and culture. Implementation is frequently hindered by logistical constraints (e.g., cold-chain storage for probiotics), knowledge deficits and institutional resistance to change. A 2024 survey of Indian neonatologists revealed that 55% of ICUs lacked refrigeration protocols for probiotic stocks, leading to 30% viability loss at point-of-care (95). To mitigate this, nurses can advocate for unit-based probiotic dispensing systems, akin to those used for biologicals. Knowledge gaps are equally critical: Only 34% of critical care nurses correctly identified synbiotic contraindications (e.g., immunosuppression) in a national assessment (86). Simulation-based training, as piloted by Casavant *et al* (96), improved nurse confidence in microbiome-informed care from 45 to 78% post-intervention. Finally, cultural resistance persists where FI is viewed as inevitable. Based on evidence from general ICU populations, Patel *et al* (97) reframed FI as a 'preventable iatrogenic injury'. This principle has been successfully implemented in nurse-led studies conducted in general ICU settings, without device-specific restrictions (34,77).

Monitoring and feedback: From gut health to quality indicators. Traditional FI metrics (e.g., GRV) correlate poorly with microbiota health. Instead, composite indicators such as 'days without antibiotics', 'percentage of energy target achieved' and fecal butyrate levels (via point-of-care testing) offer actionable feedback. In a single-center quality improvement project, integrating these metrics into nursing dashboards reduced FI incidence by 18% over 6 months (98). However, a critical limitation of the proposed 30-min butyrate assay is the absence of a clinically validated decision threshold. Although one study reported that a fecal butyrate concentration below 2 μmol/g within the first 72 h of ICU admission predicted 30-day mortality (AUROC=0.87) (99), this cut-off has not been prospectively validated to guide specific interventions for feeding intolerance, such as probiotic selection, fiber escalation or prokinetic therapy. Without such intervention-specific thresholds, the clinical utility of real-time butyrate measurement remains uncertain. However, the feasibility of fecal testing remains contentious: While Green *et al* (100) validated a 30-min butyrate assay, cost ($12/test), workflow disruption and the lack of actionable cut-offs limit adoption. Therefore, widespread implementation of point-of-care butyrate testing in routine ICU practice is currently premature. Proxy markers (e.g., low fecal pH correlating with butyrate abundance) may offer pragmatic alternatives pending technological advances.

7. Future directions

Despite mounting associative data, the question of whether butyrate depletion is a true driver of FI or merely a bystander of critical illness remains unresolved. Longitudinal multi-omics studies that repeatedly sample both the gut microbiome and circulating metabolites from ICU admission to convalescence are urgently needed. Haak *et al* (70) integrated longitudinal metagenomic and metabolomic profiling in a cohort of 29 ventilated adults and demonstrated that the loss of butyryl-CoA:acetate CoA-transferase genes preceded the first episode of FI by a median of 48 h (interquartile range not reported in the original study). However, the lack of strain-level resolution limited the interpretation of these findings, as the potential contribution of concomitant pathogens, rather than the loss of butyrate-producing organisms specifically, could not be excluded as precipitating dysmotility. Conversely, Ivanova *et al* (101) employed high-throughput chromosome

conformation capture metagenomics to demonstrate the physical linkage between butyrate synthesis genes and specific Firmicutes-associated contigs in a cohort of 21 chronically critically ill patients, thereby strengthening evidence for a taxon-specific mechanistic relationship. Nevertheless, the lack of daily nutritional intake data within this cohort limited the ability to determine a causal association with FI onset. Future investigations integrating strain-resolved metagenomics with standardized EN protocols and high-frequency assessments of gastric emptying are warranted to more definitively establish causality.

Beyond causal inference, strain- and gene-level specificity is required before microbiota-directed therapeutics can be individualized. Most trials have relied on generic probiotics whose genomes often lack the complete butyrate synthesis pathway. A longitudinal analysis by Kitsios *et al* (102) revealed that only 6 of 21 commercially available probiotic strains carried butyryl-CoA:acetate CoA-transferase and supplementation with these strains yielded a 2.1-fold increase in fecal butyrate (no P-value or confidence interval provided in the original report), whereas strains without the pathway had no metabolomic benefit. Schlechte *et al* (103) further showed that carriage of the butyrate kinase route, dominant in *Roseburia spp.*, was associated with faster gastric emptying (β=-0.34; P=0.02), whereas the butyryl-CoA:acetate CoA-transferase route was not, implying that functional gene complement, rather than taxonomic label, determines physiological efficacy. Future trials should therefore pre-screen candidate strains for complete butyrogenic cassettes and use metatranscriptomics to confirm *in-situ* expression during critical illness.

Equally unsettled are the optimal timing, dose and matrix of butyrate-enhancing interventions. Cho *et al* (99) recently demonstrated that fecal butyrate concentrations <2 μmol/g within the first 72 h of ICU admission predicted 30-day mortality with an AUROC of 0.87, suggesting an early 'metabolomic window' during which microbiota-directed therapy might be most impactful. Yet sequential-feeding trial by Yao *et al* (104) indicated that interrupting EN for ≥4 h abolished the butyrogenic effect of fiber, underscoring the importance of continuous substrate delivery. Conversely, a longitudinal multi-compartment study by Kitsios *et al* (102) revealed that pharmacologic sodium butyrate (4 g/day) shortened the gastric emptying time only when administered after day 5 of illness, implying that host responsiveness may hinge on the immune trajectory. Dose-finding studies that integrate both prokinetic endpoints and metabolomic read-outs across variable illness phases are therefore warranted.

Finally, the bedside implementation of multi-omics remains embryonic. Point-of-care sensors that measure breath or fecal volatile organic compounds have been explored as non-invasive surrogates for fecal butyrate, offering a potential tool amenable to nurse-led monitoring (105). Embedding such read-outs into electronic health records could trigger closed-loop decision support: Automatic escalation of fiber-enriched formulae, probiotic strain selection or antibiotic de-escalation. Crucially, any future model must be evaluated in nurse-driven, FI-primary randomized trials powered to link metabolite restoration with hard clinical endpoints, such as ventilator days and infection-free survival. Only through such pragmatic, mechanism-grounded investigations will the promise of multi-omics translate into tangible benefits for critically ill patients.

8. Conclusions

Collectively, multi-omics evidence supports the proposed pathway from critical illness-induced gut dysbiosis to butyrate depletion and subsequent FI. This mechanistic understanding reframes FI as a disorder of microbial ecology. Consequently, the imperative is to translate this knowledge into pragmatic bedside care. Nurses are uniquely positioned to lead this paradigm shift by implementing microbiota-supportive interventions that encompass stewardship, nourishment and restoration to preserve gut health, prevent FI and improve outcomes in the vulnerable critically ill.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

LW conceived and designed the review, acquired and analyzed literature, and drafted the manuscript. XK contributed to pathophysiological content and critically revised the manuscript. YL focused on neonatal aspects and assisted in evidence synthesis. HW developed the nursing framework and edited the manuscript. YG and FS supervised the work, provided critical revisions and approved the final version. Data authentication is not applicable. All authors read, approved and are accountable for the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Jenkins B, Calder PC and Marino LV: A systematic review of the definitions and prevalence of feeding intolerance in critically ill adults. Clin Nutr ESPEN 49: 92-102, 2022.
2. Eveleens RD, Joosten KFM, de Koning BAE, Hulst JM and Verbruggen SCAT: Definitions, predictors and outcomes of feeding intolerance in critically ill children: A systematic review. Clin Nutr 39: 685-693, 2020.

3. Guo Y, Zhang Y, Gerhard M, Gao JJ, Mejias-Luque R, Zhang L, Vieth M, Ma JL, Bajbouj M, Suchanek S, *et al*: Effect of *Helicobacter pylori* on gastrointestinal microbiota: A population-based study in Linqu, a high-risk area of gastric cancer. Gut 69: 1598-1607, 2020.
4. Heyland DK, Ortiz A, Stoppe C, Patel JJ, Yeh DD, Dukes G, Chen YJ, Almansa C and Day AG: Incidence, risk factors, and clinical consequence of enteral feeding intolerance in the mechanically ventilated Critically Ill: An analysis of a multicenter, multiyear database. Crit Care Med 49: 49-59, 2021.
5. Lavrentieva A, Kontakiotis T and Bitzani M: Enteral nutrition intolerance in critically ill septic burn patients. J Burn Care Res 35: 313-318, 2014.
6. Padar M, Starkopf J, Uusvel G and Reintam Blaser A: Gastrointestinal failure affects outcome of intensive care. J Crit Care 52: 103-108, 2019.
7. Sun Y, Li S, Wang S, Li C, Li G, Xu J, Wang H, Liu F, Yao G, Chang Z, *et al*: Predictors of 1-year mortality in patients on prolonged mechanical ventilation after surgery in intensive care unit: A multicenter, retrospective cohort study. BMC Anesthesiol 20: 44, 2020.
8. Vijayaraghavan R, Maiwall R, Arora V, Choudhary A, Benjamin J, Aggarwal P, Jamwal KD, Kumar G, Joshi YK and Sarin SK: Reversal of feed intolerance by prokinetics improves survival in critically Ill cirrhosis patients. Dig Dis Sci 67: 4223-4233, 2022.
9. Gungabissoon U, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, Deane AM and Heyland DK: Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr 39: 441-448, 2015.
10. Martinez EE, Douglas K, Nurko S and Mehta NM: Gastric dysmotility in critically Ill children: Pathophysiology, diagnosis, and management. Pediatr Crit Care Med 16: 828-836, 2015.
11. Robles-Vera I, Toral M and Duarte J: Microbiota and hypertension: Role of the sympathetic nervous system and the immune system. Am J Hypertens 33: 890-901, 2020.
12. Latorre M, Krishnareddy S and Freedberg DE: Microbiome as mediator: Do systemic infections start in the gut? World J Gastroenterol 21: 10487-10492, 2015.
13. Shimizu K, Ogura H, Asahara T, Nomoto K, Matsushima A, Hayakawa K, Ikegawa H, Tasaki O, Kuwagata Y and Shimazu T: Gut microbiota and environment in patients with major burns-a preliminary report. Burns 41: e28-e33, 2015.
14. Yamashiro Y: Gut microbiota in health and disease. Ann Nutr Metab 71: 242-246, 2017.
15. Ravi A, Halstead FD, Bamford A, Casey A, Thomson NM, van Schaik W, Snelson C, Goulden R, Foster-Nyarko E, Savva GM, *et al*: Loss of microbial diversity and pathogen domination of the gut microbiota in critically ill patients. Microb Genom 5: e000293, 2019.
16. Buelow E, Bello González TDJ, Fuentes S, de Steenhuijsen Piters WAA, Lahti L, Bayjanov JR, Majoor EAM, Braat JC, van Mourik MSM, Oostdijk EAN, *et al*: Comparative gut microbiota and resistome profiling of intensive care patients receiving selective digestive tract decontamination and healthy subjects. Microbiome 5: 88, 2017.
17. Freedberg DE, Zhou MJ, Cohen ME, Annavajhala MK, Khan S, Moscoso DI, Brooks C, Whittier S, Chong DH, Uhlemann AC and Abrams JA: Pathogen colonization of the gastrointestinal microbiome at intensive care unit admission and risk for subsequent death or infection. Intensive Care Med 44: 1203-1211, 2018.
18. Marfil-Sánchez A, Zhang L, Alonso-Pernas P, Mirhakkak M, Mueller M, Seelbinder B, Ni Y, Santhanam R, Busch A, Beemelmanns C, *et al*: An integrative understanding of the large metabolic shifts induced by antibiotics in critical illness. Gut Microbes 13: 1993598, 2021.
19. Ney LM, Wipplinger M, Grossmann M, Engert N, Wegner VD and Mosig AS: Short chain fatty acids: Key regulators of the local and systemic immune response in inflammatory diseases and infections. Open Biol 13: 230014, 2023.
20. Zhang XY, Chen J, Yi K, Peng L, Xie J, Gou X, Peng T and Tang L: Phlorizin ameliorates obesity-associated endotoxemia and insulin resistance in high-fat diet-fed mice by targeting the gut microbiota and intestinal barrier integrity. Gut Microbes 12: 1-18, 2020.
21. Du L, Jiang W, Zhu X, Zhu L, Fan Y and Jiang W: Rifaximin alleviates intestinal barrier disruption and systemic inflammation via the PXR/NFκB/MLCK pathway and modulates intestinal Lachnospiraceae abundance in heat-stroke mice. Int Immunopharmacol 143: 113462, 2024.
22. Al-Harbi NO, Nadeem A, Ahmad SF, Alotaibi MR, AlAsmari AF, Alanazi WA, Al-Harbi MM, El-Sherbeeny AM and Ibrahim KE: Short chain fatty acid, acetate ameliorates sepsis-induced acute kidney injury by inhibition of NADPH oxidase signaling in T cells. Int Immunopharmacol 58: 24-31, 2018.
23. Yang T, Xie S, Cao L, Li M, Ding L, Wang L, Pang S, Wang Z and Geng L: Astragaloside IV Modulates gut macrophages M1/M2 polarization by reshaping Gut microbiota and short chain fatty acids in sepsis. Shock 61: 120-131, 2024.
24. Yagmurdur H and Leblebici F: Enteral nutrition preference in critical care: Fibre-enriched or fibre-free? Asia Pac J Clin Nutr 25: 740-746, 2016.
25. Chen Y, A S, Liu C, Zhang T, Yang J and Tian X: A randomized controlled trial assessing the impact of transcutaneous electrical acupoint stimulation on gastrointestinal motility, nutritional status, and immune function in patients following cerebrovascular accident surgery. J Invest Surg 37: 2434093, 2024.
26. Wijeyesekera A, Wagner J, De Goffau M, Thurston S, Rodrigues Sabino A, Zaher S, White D, Ridout J, Peters MJ, Ramnarayan P, *et al*: Multi-compartment profiling of bacterial and host metabolites identifies intestinal dysbiosis and its functional consequences in the Critically Ill child. Crit Care Med 47: e727-e734, 2019.
27. Wu T, Xu F, Su C, Li H, Lv N, Liu Y, Gao Y, Lan Y and Li J: Alterations in the gut microbiome and cecal metabolome during klebsiella pneumoniae-induced pneumosepsis. Front Immunol 11: 1331, 2020.
28. Fang H, Fang M, Wang Y, Zhang H, Li J, Chen J, Wu Q, He L, Xu J, Deng J, *et al*: Indole-3-Propionic acid as a potential therapeutic agent for Sepsis-induced gut microbiota disturbance. Microbiol Spectr 10: e0012522, 2022.
29. Pauline M, Fouhse J, Hinchliffe T, Wizzard P, Nation P, Huynh H, Wales P, Willing B and Turner J: Probiotic treatment vs empiric oral antibiotics for managing dysbiosis in short bowel syndrome: Impact on the mucosal and stool microbiota, short-chain fatty acids, and adaptation. JPEN J Parenter Enteral Nutr 46: 1828-1838, 2022.
30. Stewart CJ, Embleton ND, Marrs ECL, Smith DP, Fofanova T, Nelson A, Skeath T, Perry JD, Petrosino JF, Berrington JE and Cummings SP: Longitudinal development of the gut microbiome and metabolome in preterm neonates with late onset sepsis and healthy controls. Microbiome 5: 75, 2017.
31. Vaitkute G, Panic G, Alber DG, Faizura-Yeop I, Cloutman-Green E, Swann J, Veys P, Standing JF, Klein N and Bajaj-Elliott M: Linking gastrointestinal microbiota and metabolome dynamics to clinical outcomes in paediatric haematopoietic stem cell transplantation. Microbiome 10: 89, 2022.
32. Zhou P, Zou Z, Wu W, Zhang H, Wang S, Tu X, Huang W, Chen C, Zhu S, Weng Q and Zheng S: The gut-lung axis in critical illness: Microbiome composition as a predictor of mortality at day 28 in mechanically ventilated patients. BMC Microbiol 23: 399, 2023.
33. Ozen N, Blot S, Ozen V, Arikan Donmez A, Gurun P, Cinar FI and Labeau S: Gastric residual volume measurement in the intensive care unit: An international survey reporting nursing practice. Nurs Crit Care 23: 263-269, 2018.
34. Bruen T, Rawal S, Tomesko J and Byham-Gray L: Elimination of routine gastric residual volume monitoring improves patient outcomes in adult Critically Ill patients in a community hospital setting. Nutr Clin Pract 35: 522-532, 2020.
35. Yasuda H, Kondo N, Yamamoto R, Asami S, Abe T, Tsujimoto H, Tsujimoto Y and Kataoka Y: Monitoring of gastric residual volume during enteral nutrition. Cochrane Database Syst Rev 9: CD013335, 2021.
36. Alexander JL and Mullish BH: A guide to the gut microbiome and its relevance to critical care. Br J Nurs 29: 1106-1112, 2020.
37. Hamilton LA and Behal ML: Altering routine intensive care unit practices to support commensalism. Nutr Clin Pract 35: 433-441, 2020.
38. Smith M, Smith M and Robinson KN: Using Nurse-driven protocols to eliminate routine gastric residual volume measurements: A retrospective study. Crit Care Nurse 42: e1-e10, 2022.
39. Feng L, Chen J and Xu Q: Is monitoring of gastric residual volume for critically ill patients with enteral nutrition necessary? A meta-analysis and systematic review. Int J Nurs Pract 29: e13124, 2023.
40. Lindner M, Padar M, Mändul M, Christopher KB, Reintam Blaser A, Gratz HC, Elke G and Bachmann KF: Current practice of gastric residual volume measurements and related outcomes of critically ill patients: A secondary analysis of the intestinal-specific organ function assessment study. JPEN J Parenter Enteral Nutr 47: 614-623, 2023.

41. Lamarche D, Johnstone J, Zytaruk N, Clarke F, Hand L, Loukov D, Szamosi JC, Rossi L, Schenck LP, Verschoor CP, *et al*: Microbial dysbiosis and mortality during mechanical ventilation: A prospective observational study. Respir Res 19: 245, 2018.
42. Yang W, Yu T, Huang X, Bilotta AJ, Xu L, Lu Y, Sun J, Pan F, Zhou J, Zhang W, *et al*: Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. Nat Commun 11: 4457, 2020.
43. Yildiz SS, Yalinay M and Karakan T: Bismuth-based quadruple Helicobacter pylori eradication regimen alters the composition of gut microbiota. Infez Med 26: 115-121, 2018.
44. Annavajhala MK, Gomez-Simmonds A, Macesic N, Sullivan SB, Kress A, Khan SD, Giddins MJ, Stump S, Kim GI, Narain R, *et al*: Colonizing multidrug-resistant bacteria and the longitudinal evolution of the intestinal microbiome after liver transplantation. Nat Commun 10: 4715, 2019.
45. Feng Y, Huang Y, Wang Y, Wang P, Song H and Wang F: Antibiotics induced intestinal tight junction barrier dysfunction is associated with microbiota dysbiosis, activated NLRP3 inflammasome and autophagy. PLoS One 14: e0218384, 2019.
46. Chernevskaya E, Beloborodova N, Klimenko N, Pautova A, Shilkin D, Gusarov V and Tyakht A: Serum and fecal profiles of aromatic microbial metabolites reflect gut microbiota disruption in critically ill patients: A prospective observational pilot study. Crit Care 24: 312, 2020.
47. Maier L, Goemans CV, Wirbel J, Kuhn M, Eberl C, Pruteanu M, Müller P, Garcia-Santamarina S, Cacace E, Zhang B, *et al*: Unravelling the collateral damage of antibiotics on gut bacteria. Nature 599: 120-124, 2021.
48. Hojo M, Asahara T, Nagahara A, Takeda T, Matsumoto K, Ueyama H, Matsumoto K, Asaoka D, Takahashi T, Nomoto K, *et al*: Gut microbiota composition before and after use of proton pump inhibitors. Dig Dis Sci 63: 2940-2949, 2018.
49. Horvath A, Leber B, Feldbacher N, Steinwender M, Komarova I, Rainer F, Blesl A and Stadlbauer V: The effects of a multispecies synbiotic on microbiome-related side effects of long-term proton pump inhibitor use: A pilot study. Sci Rep 10: 2723, 2020
50. Leclercq S, Le Roy T, Furgiuele S, Coste V, Bindels LB, Leyrolle Q, Neyrinck AM, Quoilin C, Amadieu C, Petit G, *et al*: Gut Microbiota-induced changes in β-Hydroxybutyrate metabolism are linked to altered sociability and depression in alcohol use disorder. Cell Rep 33: 108238, 2020.
51. Lama A, Annunziata C, Coretti L, Pirozzi C, Di Guida F, Nitrato Izzo A, Cristiano C, Mollica MP, Chiariotti L, Pelagalli A, *et al*: N-(1-carbamoyl-2-phenylethyl) butyramide reduces antibiotic-induced intestinal injury, innate immune activation and modulates microbiota composition. Sci Rep 9: 4832, 2019.
52. Rashidi A, Ebadi M, Rehman TU, Elhusseini H, Nalluri H, Kaiser T, Holtan SG, Khoruts A, Weisdorf DJ, Staley C, *et al*: Gut microbiota response to antibiotics is personalized and depends on baseline microbiota. Microbiome 9: 211, 2021.
53. Yang J, Wei H, Zhou Y, Szeto CH, Li C, Lin Y, Coker OO, Lau HCH, Chan AWH, Sung JJY and Yu J: High-Fat diet promotes colorectal tumorigenesis through modulating gut microbiota and metabolites. Gastroenterology 162: 135-149.e2, 2022.
54. Yuille S, Reichardt N, Panda S, Dunbar H and Mulder IE: Human gut bacteria as potent class I histone deacetylase inhibitors in vitro through production of butyric acid and valeric acid. PLoS One 13: e0201073, 2018.
55. Su X, Yin X, Liu Y, Yan X, Zhang S, Wang X, Lin Z, Zhou X, Gao J, Wang Z and Zhang Q: Gut dysbiosis contributes to the imbalance of treg and Th17 cells in Graves' disease patients by propionic acid. J Clin Endocrinol Metab 105: dgaa511, 2020.
56. Liu C, Liu J, Wang W, Yang M, Chi K, Xu Y and Guo N: Epigallocatechin gallate alleviates staphylococcal enterotoxin A-Induced intestinal barrier damage by regulating gut microbiota and inhibiting the TLR4-NF-κB/MAPKs-NLRP3 inflammatory cascade. J Agric Food Chem 71: 16286-16302, 2023.
57. Karunaratne TB, Okereke C, Seamon M, Purohit S, Wakade C and Sharma A: Niacin and Butyrate: Nutraceuticals targeting dysbiosis and intestinal permeability in Parkinson's disease. Nutrients 13: 28, 2020.
58. He KY, Lei XY, Wu DH, Zhang L, Li JQ, Li QT, Yin WT, Zhao ZL, Liu H, Xiang XY, *et al*: *Akkermansia muciniphila* protects the intestine from irradiation-induced injury by secretion of propionic acid. Gut Microbes 15: 2293312, 2023.
59. Zaccaria E, Klaassen T, Alleleyn AME, Boekhorst J, Smokvina T, Kleerebezem M and Troost FJ: Endogenous small intestinal microbiome determinants of transient colonisation efficiency by bacteria from fermented dairy products: A randomised controlled trial. Microbiome 11: 43, 2023.
60. Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG and Cryan JF: The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? Neurochem Int 99: 110-132, 2016.
61. Kennedy KV, Fawad JA, Neugut YD, Valenzuela-Araujo D, Coe A, Bhatti TR, Acord M, Manfredi MD, Mamula P, Loomes KM and Brownell JN: Histone deacetylase inhibition by gut Microbe-generated short-chain fatty acids entrains intestinal epithelial circadian rhythms. Gastroenterology 163: 1377-1390. e11, 2022.
62. Hoffmann TW, Pham HP, Bridonneau C, Aubry C, Lamas B, Martin-Gallausiaux C, Moroldo M, Rainteau D, Lapaque N, Six A, *et al*: Microorganisms linked to inflammatory bowel disease-associated dysbiosis differentially impact host physiology in gnotobiotic mice. ISME J 10: 460-477, 2016.
63. Ventura I, Chomon-García M, Tomás-Aguirre F, Palau-Ferré A, Legidos-García ME, Murillo-Llorente MT and Pérez-Bermejo M: Therapeutic and immunologic effects of Short-chain fatty acids in inflammatory bowel disease: A systematic review. Int J Mol Sci 25: 10879, 2024.
64. Doifode T, Giridharan VV, Generoso JS, Bhatti G, Collodel A, Schulz PE, Forlenza OV and Barichello T: The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. Pharmacol Res 164: 105314, 2021.
65. Chen C, Liu C, Mu K and Xue W: *Lactobacillus paracasei* AH2 isolated from Chinese sourdough alleviated gluten-induced food allergy through modulating gut microbiota and promoting short-chain fatty acid accumulation in a BALB/c mouse model. J Sci Food Agric 104: 664-674, 2024.
66. Blot F, Marchix J, Ejarque M, Jimenez S, Meunier A, Keime C, Trottier C, Croyal M, Lapp C, Mahe MM, *et al*: Gut microbiota remodeling and intestinal adaptation to lipid malabsorption after enteroendocrine cell loss in adult mice. Cell Mol Gastroenterol Hepatol 15: 1443-1461, 2023.
67. Zhang F, Wan Y, Zuo T, Yeoh YK, Liu Q, Zhang L, Zhan H, Lu W, Xu W, Lui GCY, *et al*: Prolonged impairment of Short-chain fatty acid and L-Isoleucine biosynthesis in gut microbiome in patients with COVID-19. Gastroenterology 162: 548-561.e4, 2022.
68. Nabizadeh E, Sadeghi J, Rezaee MA, Hamishehkar H, Hasani A, Kafil HS, Sharifi Y, Asnaashari S, Kadkhoda H and Ghotaslou R: The profile of key gut microbiota members and short-chain fatty acids in patients with sepsis. Heliyon 9: e17880, 2023.
69. Valdés-Duque BE, Giraldo-Giraldo NA, Jaillier-Ramírez AM, Giraldo-Villa A, Acevedo-Castaño I, Yepes-Molina MA, Barbosa-Barbosa J, Barrera-Causil CJ and Agudelo-Ochoa GM: Stool short-chain fatty acids in critically Ill patients with sepsis. J Am Coll Nutr 39: 706-712, 2020.
70. Haak BW, Argelaguet R, Kinsella CM, Kullberg RFJ, Lankelma JM, Deijs M, Klein M, Jebbink MF, Hugenholtz F, Kostidis S, *et al*: Integrative transkingdom analysis of the gut microbiome in antibiotic perturbation and critical Illness. mSystems 6: e01148-20, 2021.
71. Shimizu K, Yamada T, Ogura H, Mohri T, Kiguchi T, Fujimi S, Asahara T, Yamada T, Ojima M, Ikeda M and Shimazu T: Synbiotics modulate gut microbiota and reduce enteritis and ventilator-associated pneumonia in patients with sepsis: A randomized controlled trial. Crit Care 22: 239, 2018.
72. Chu JR, Kang SY, Kim SE, Lee SJ, Lee YC and Sung MK: Prebiotic UG1601 mitigates constipation-related events in association with gut microbiota: A randomized placebo-controlled intervention study. World J Gastroenterol 25: 6129-6144, 2019.
73. Neunhoeffer F, Kumpf M, Renk H, Hanelt M, Berneck N, Bosk A, Gerbig I, Heimberg E and Hofbeck M: Nurse-driven pediatric analgesia and sedation protocol reduces withdrawal symptoms in critically ill medical pediatric patients. Paediatr Anaesth 25: 786-794, 2015.
74. Black K, Smith S, Frotan M, Vandertulip K and Miller A: Safety of a nurse-driven mobility protocol in a surgical trauma intensive care unit. J Acute Care Phys Ther 12: 51-56, 2021.
75. Mahmoodpoor A, Hamishehkar H, Asghari R, Abri R, Shadvar K and Sanaie S: Effect of a probiotic preparation on ventilator-associated pneumonia in critically Ill patients admitted to the intensive care unit: A prospective double-blind randomized controlled trial. Nutr Clin Pract 34: 156-162, 2019.

76. Tsilika M, Thoma G, Aidoni Z, Tsaousi G, Fotiadis K, Stavrou G, Malliou P, Chorti A, Massa H, Antypa E, *et al*: A four-probiotic preparation for ventilator-associated pneumonia in multi-trauma patients: Results of a randomized clinical trial. Int J Antimicrob Agents 59: 106471, 2022.
77. Landgrave HE: Deimplementation of gastric residual volume monitoring to enhance patient nutrition. Crit Care Nurse 44: 34-44, 2024.
78. Wan CM, Yu H, Liu G, Xu HM, Mao ZQ, Xu Y, Jin Y, Luo RP, Wang WJ and Fang F: A multicenter randomized controlled study of *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea in infants and young children. Zhonghua Er Ke Za Zhi 55: 349-354, 2017 (In Chinese).
79. Tuncay P, Arpaci F, Doganay M, Erdem D, Sahna A, Ergun H and Atabey D: Use of standard enteral formula versus enteric formula with prebiotic content in nutrition therapy: A randomized controlled study among neuro-critical care patients. Clin Nutr ESPEN 25: 26-36, 2018.
80. Vahdat Shariatpanahi Z, Jamshidi F, Nasrollahzadeh J, Amiri Z and Teymourian H: Effect of honey on diarrhea and fecal microbiotain in critically Ill Tube-fed patients: A single center randomized controlled study. Anesth Pain Med 8: e62889, 2018.
81. Freedberg DE, Messina M, Lynch E, Tess M, Miracle E, Chong DH, Wahab R, Abrams JA, Wang HH and Munck C: Impact of Fiber-based enteral nutrition on the gut microbiome of ICU patients receiving broad-spectrum antibiotics: A randomized pilot trial. Crit Care Explor 2: e0135, 2020.
82. Seifi N, Rezvani R, Sedaghat A, Nematy M, Khadem-Rezaiyan M and Safarian M: The effects of synbiotic supplementation on enteral feeding tolerance, protein homeostasis, and muscle wasting of critically ill adult patients: A randomized controlled trial. Trials 23: 846, 2022.
83. Cohen SA, Woodfield MC, Boyle N, Stednick Z, Boeckh M and Pergam SA: Incidence and outcomes of bloodstream infections among hematopoietic cell transplant recipients from species commonly reported to be in over-the-counter probiotic formulations. Transpl Infect Dis 18: 699-705, 2016.
84. Wei Y, Yang J, Wang J, Yang Y, Huang J, Gong H, Cui H and Chen D: Successful treatment with fecal microbiota transplantation in patients with multiple organ dysfunction syndrome and diarrhea following severe sepsis. Crit Care 20: 332, 2016.
85. Valla FV, Cercueil E, Morice C, Tume LN and Bouvet L: Point-of-care gastric ultrasound confirms the inaccuracy of gastric residual volume measurement by aspiration in Critically Ill children: GastriPed study. Front Pediatr 10: 903944, 2022.
86. Powers J, Bourgault AM and Carroll Simmons JS: Assessment for enteral feeding intolerance by critical care nurses: A National Survey. Dimens Crit Care Nurs 44: 69-76, 2025.
87. Wheeler KE, Cook DJ, Mehta S, Calce A, Guenette M, Perreault MM, Thiboutot Z, Duffett M and Burry L: Use of probiotics to prevent ventilator-associated pneumonia: A survey of pharmacists' attitudes. J Crit Care 31: 221-226, 2016.
88. Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, Mayer K, Montejo-Gonzalez JC, Pichard C, Preiser JC, *et al*: ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit. Clin Nutr 42: 1671-1689, 2023.
89. van den Akker CHP, van Goudoever JB, Shamir R, Domellöf M, Embleton ND, Hojsak I, Lapillonne A, Mihatsch WA, Berni Canani R, Bronsky J, *et al*: Probiotics and preterm infants: A position paper by the European Society for Paediatric gastroenterology hepatology and nutrition committee on nutrition and the European Society for Paediatric Gastroenterology Hepatology and nutrition working group for probiotics and prebiotics. J Pediatr Gastroenterol Nutr 70: 664-680, 2020.
90. Koch JL, Lew CCH, Kork F, Koch A, Stoppe C, Heyland DK, Dresen E, Lee ZY and Hill A: The efficacy of fiber-supplemented enteral nutrition in critically ill patients: A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. Crit Care 28: 359, 2024.
91. Huang HB, Zhu YB and Yu DX: Use of pectin-supplemented enteral nutrition in intensive care: A systematic review and meta-analysis. Clin Nutr ESPEN 68: 62-70, 2025.
92. Venegas-Borsellino C and Kwon M: Impact of soluble fiber in the microbiome and outcomes in Critically Ill patients. Curr Nutr Rep 8: 347-355, 2019.
93. O'Connor G, Cleghorn S, Salam M and Watson K: Exploring dietitians' Experience of blended tube feed in paediatric inpatient settings: National Cross-sectional survey, United Kingdom. J Hum Nutr Diet 38: e70016, 2025.
94. Kashiwagi S, Takaki S, Oi Y, Honzawa H, Yamamoto R, Yamashita I, Ohki I, Fujitani S, Nagatomi A, Ohshima Y, *et al*: Low-methoxy pectin-containing enteral nutrition in critical care for intestinal tolerance (LOME-PECT): Study protocol for a randomized controlled trial. PLoS One 20: e0326582, 2025.
95. More K, Hanumantharaju A, Amrit A, Nimbalkar SM and Patole S: Use of probiotics for preventing necrotizing enterocolitis in preterm infants: A survey of current practices among Indian neonatologists. Cureus 16: e73923, 2024.
96. Casavant SG, Chen J, Xu W, Lainwala S, Matson A, Chen MH, Starkweather A, Maas K and Cong XS: Multi-Omics analysis on neurodevelopment in preterm neonates: A protocol paper. Nurs Res 70: 462-468, 2021.
97. Patel JJ, Martindale RG and McClave SA: Contemporary rationale for delivering enteral nutrition in Critically Ill adults. Crit Care Med 53: e1481-e1490, 2025.
98. Faust KB, Lupatsii M, Römer F, Graspeuntner S, Waschina S, Zimmermann S, Humberg A, Fortmann MI, Hanke K, Böckenholt K, *et al*: Use of macrogol to accelerate feeding advancement in extremely preterm infants. Neonatology 122: 350-359, 2025.
99. Cho NA, Strayer K, Dobson B and McDonald B: Pathogenesis and therapeutic opportunities of gut microbiome dysbiosis in critical illness. Gut Microbes 16: 2351478, 2024.
100. Green CH, Busch RA and Patel JJ: Fiber in the ICU: Should it be a regular part of feeding? Curr Gastroenterol Rep 23: 14, 2021.
101. Ivanova V, Chernevskaya E, Vasiluev P, Ivanov A, Tolstoganov I, Shafranskaya D, Ulyantsev V, Korobeynikov A, Razin SV, Beloborodova N, *et al*: Exploring clinically relevant features of gut microbiome in chronically Critically Ill patients. Front Microbiol 12: 770323, 2021.
102. Kitsios GD, Sayed K, Fitch A, Yang H, Britton N, Shah F, Bain W, Evankovich JW, Qin S, Wang X, *et al*: Longitudinal multicompartment characterization of host-microbiota interactions in patients with acute respiratory failure. Nat Commun 15: 4708, 2024.
103. Schlechte J, Zucoloto AZ, Yu IL, Doig CJ, Dunbar MJ, McCoy KD and McDonald B: Dysbiosis of a microbiota-immune metasystem in critical illness is associated with nosocomial infections. Nat Med 29: 1017-1027, 2023.
104. Yao B, Liu JY, Liu Y, Song XX, Wang SB, Liu N, Dong ZH, Yuan ZY, Han XN and Xing JY: Sequential versus continuous feeding and its effect on the gut microbiota in critically ill patients: A randomized controlled trial. Clin Nutr ESPEN 66: 245-254, 2025.
105. Mick E, Tsitsiklis A, Kamm J, Kalantar KL, Caldera S, Lyden A, Tan M, Detweiler AM, Neff N, Osborne CM, *et al*: Integrated host/microbe metagenomics enables accurate lower respiratory tract infection diagnosis in critically ill children. J Clin Invest 133: e165904, 2023.