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EDITORIAL

The role of microbiome and metabolomics in personalized ICU nutrition

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Abstract

Personalized nutrition in the intensive care unit (ICU) has evolved from traditional caloric replacement strategies toward a multidimensional, biology-driven model that incorporates microbiome ecology and metabolomic signatures. Critical illness induces profound alterations in gut microbial diversity, metabolite production, epithelial integrity, and systemic immune responses, all of which interact with nutritional therapies. Parallel advances in metabolomics offer real-time insight into mitochondrial function, substrate utilization, and catabolic stress, providing a framework for phase-specific nutritional targets. This review synthesizes current evidence on ICU nutrition guidelines, recent randomized trials, and emerging multi-omics science to propose an integrated approach to personalized feeding. Emphasis is placed on early enteral nutrition, avoidance of early overfeeding, moderated protein delivery, and the selective use of supplemental parenteral nutrition, contextualized within microbiome-host metabolic interactions. Preliminary studies suggest that microbiome-guided and metabolomics-informed nutrition could reduce infection risk, optimize metabolic tolerance, and support organ recovery, but clinical translation requires rigorous validation.

Keywords: critical illness, enteral feeding, metabolomics, personalized nutrition, short-chain fatty acids

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Introduction

During the past decade, critical care medicine has undergone a conceptual transformation in the way nutritional therapy is understood and delivered. Nutrition in the intensive care unit (ICU) is no longer perceived merely as the provision of calories and protein to prevent malnutrition. Instead, it has become a therapeutic tool deeply intertwined with immunologic function, metabolic resilience, mitochondrial performance, gut epithelial integrity, and the ecology of the intestinal microbiome. These elements shape a dynamic physiological landscape where nutrition is not simply a supportive measure but a modifiable determinant of outcomes. Critical illness induces rapid microbial disruption, leading to major consequences for infection risk, inflammatory balance, and nutrient processing. Evidence from metagenomic and metabolomic studies demonstrates that the gut and systemic metabolism shift dramatically in response to illness severity, therapeutic interventions, and nutritional status.[1-3]

This shift in perspective has been driven by converging scientific advances. On one hand, progress in microbiome research has demonstrated that critical illness induces rapid and profound disruption of the intestinal microbial community, with consequences for immune competence, susceptibility to infection, inflammatory tone, and nutrient processing.[1] Parallel advances in metabolomics allow clinicians to monitor mitochondrial stress, substrate utilization, and inflammatory metabolic signatures in real time.[4] Together, these developments suggest that a model of *personalized ICU nutrition*—guided by biological signatures rather than static formulas—may be achievable.

However, personalized nutrition in the ICU requires more than theoretical frameworks. It demands methodologies capable of capturing the status of the microbiome and metabolic phenotype in actionable ways. In this context, fecal diagnostics—including 16S rRNA sequencing, shotgun metagenomics, fecal metabolomics, short-chain fatty acid quantification (SCFA), and qPCR pathogen surveillance—have emerged as tools providing a detailed snapshot of microbial activity and mucosal health.[1-5] When interpreted alongside metabolomic profiles derived from blood, urine, or stool samples, these technologies open a path toward integrated, multi-omic nutritional decision-making.

This extended review examines the mechanistic basis of microbiome and metabolomic disturbances in critical illness; describes the major technologies available for fecal microbiome and metabolite analysis; evaluates evidence-based ICU nutrition strategies in light of these biological insights; and proposes a framework for integrating multi-omic data into a personalized ICU nutrition strategy. The central question addressed is how the gut microbiome and metabolomic phenotype can meaningfully inform nutritional decision-making at the bedside and whether these approaches can be translated into improved patient outcomes.

Methods

This review follows a narrative methodology aimed at synthesizing current knowledge from gastroenterology, critical care medicine, metabolomics, and microbial ecology as they relate to nutrition in critically ill adults. Literature published between 2014 and 2025 was analyzed.

A focused, non-systematic search was conducted in PubMed and Embase using combinations of the following terms: “critical illness,” “intensive care,” “ICU nutrition,” “enteral nutrition,” “parenteral nutrition,” “gut microbiome,” “dysbiosis,”

"metabolomics," "short-chain fatty acids," and "multi-omics." Reference lists of key articles and guidelines were also screened to identify additional relevant publications.

Inclusion criteria were adult critically ill patients (≥18 years); studies addressing nutritional therapy, gut microbiome, or metabolomics in the ICU context; randomized controlled trials, observational clinical studies, major guidelines, and mechanistic or translational work with clear relevance to ICU nutrition. Pediatric-only studies, non-ICU populations, and purely basic science work without a clear translational link to nutrition in critical illness were generally excluded, except when they provided essential mechanistic insight.

Priority was given to seminal works in the fields of critical care nutrition, intestinal microbiology, metabolomics, and critical illness physiology. Key references include the CALORIES trial comparing enteral and parenteral nutrition[6], early and late parenteral nutrition trials [7], ESPEN and ASPEN guidelines[8-9], microbiome studies in critical illness[1,5,10], and metabolomics studies addressing mitochondrial dysfunction.[4] Additional emphasis was placed on technologies for fecal analysis, including sequencing-based and metabolomic approaches.

Because this is a narrative and not a systematic review, formal risk-of-bias tools were not applied. However, randomized trials and guideline documents were considered higher-level evidence than observational or mechanistic studies, and this hierarchy is reflected in how recommendations are framed (established practice vs emerging or hypothesis-generating strategies).

The ICU microbiome and its nutritional implications

The rapid collapse of microbial diversity

Critical illness triggers abrupt dysbiosis, characterized by the loss of up to 90% of commensal anaerobes within the first hours of physiological insult [1]. Beneficial taxa such as *Ruminococcaceae* and *Lachnospiraceae* rapidly diminish, while opportunistic pathogens—including *Enterococcus*, *Enterobacteriaceae*, *Staphylococcus*, and *Pseudomonas*—expand aggressively.[1,10] This extreme microbial shift resembles ecological collapse observed in decomposition, reflecting the severity of physiologic stress.

The consequences extend beyond microbial composition. SCFA producers vanish, reducing production of butyrate—a critical energy source for colonocytes and a regulator of epithelial barrier integrity. Without these protective metabolites, epithelial tight junctions deteriorate, permeability increases, and microbial translocation becomes likely.[1,11]

The implications for nutrition are profound. Enteral feeding depends in part on an intact gut mucosa and a metabolically active microbial community capable of fermenting dietary components. When this ecosystem is disrupted, the gut becomes less tolerant of feeds, more susceptible to bacterial translocation, and less able to metabolize complex nutrients.

Drivers of dysbiosis during critical illness

A combination of direct and indirect insults accelerates dysbiosis in critically ill patients. A Multiple ICU-specific factors exacerbate dysbiosis (See **Table 1**)

Table 1. Multiple ICU-specific factors exacerbate dysbiosis:

ICU-specific factors	• **Broad-spectrum antibiotics** with anti-anaerobic activity, which correlate with mortality, infection, and microbial collapse [12]. • **Vasopressor therapy**, impairing mucosal perfusion. • **Sedatives and opioids**, slowing motility and promoting stasis [1]. • **Prolonged fasting**, removing fermentable substrates required for SCFA production [11]. • **Stress ulcer prophylaxis**, altering gastric pH and modifying microbial ecology [10].

Hemodynamic instability reduces mesenteric perfusion and impairs oxygen delivery to the mucosa. Sedation and opioids slow gastrointestinal motility, leading to stasis and promoting overgrowth of pathogenic bacteria. Stress ulcer prophylaxis modifies luminal pH and alters microbial composition[10] by creating an environment where acid-sensitive organisms can thrive. Broad-spectrum antibiotics—particularly those with anaerobic coverage—disproportionately eliminate beneficial commensals, allowing resistant organisms to dominate.[12]

Fasting itself is also a major contributor to dysbiosis. The absence of fermentable fiber deprives microbes of substrates needed for SCFA production, depriving colonocytes of their primary energy source and reducing mucous layer integrity. Because enteral nutrition stimulates bile acid flow, mucin secretion, and microbial fermentation, delayed feeding exacerbates the deleterious effects of dysbiosis.

Consequences for nutrient handling and feeding tolerance

The metabolic consequences of dysbiosis create a cycle of impaired nutrient utilization and feeding intolerance (See **Table 2**).

Table 2. Consequences for nutrient handling

Dysbiosis impairs:	• SCFA-mediated epithelial repair • Bile acid conversion • Lipid absorption • Carbohydrate fermentation • Gut motility

The absence of SCFAs weakens epithelial barrier function and disrupts metabolic signaling. Butyrate deficiency promotes goblet cell apoptosis, reduces mucus production, and increases epithelial permeability. Propionate and acetate—normally involved in gluconeogenesis and appetite regulation—become deficient, further altering energy homeostasis.

Loss of butyrate-producing organisms compromises the mucous barrier, increases permeability, and reduces tolerance to enteral feeding. Altered bile acid profiles further impair lipid digestion and mucosal immunity.[13]

Thus, fecal analysis of microbial diversity and SCFA production provides actionable information for predicting enteral nutrition tolerance.

For these reasons, understanding the microbial composition and metabolite environment of the gut may be instrumental in selecting nutritional strategies that restore homeostasis

Fecal diagnostic technologies and their role in ICU nutrition

16S rRNA gene sequencing

One of the most widely used and accessible fecal diagnostic techniques is 16S rRNA sequencing, which amplifies bacterial ribosomal genes to identify microbial taxa at the genus or family level. Although it provides limited functional information, it is useful for detecting major dysbiotic changes such as dominance of Enterococcus, depletion of butyrate-producing bacteria, or overgrowth of Proteobacteria. These patterns can guide clinicians in predicting enteral nutrition tolerance, assessing infection risk, and deciding whether fiber, probiotics, or microbial-targeted therapies may be beneficial.[1]

Shotgun metagenomics

Shotgun metagenomics offers higher resolution by sequencing the entire microbial DNA content rather than a single ribosomal region. This allows species-level identification and provides functional insights into metabolic pathways such as SCFA synthesis, mucin degradation, or bile acid transformation.[5] Shotgun metagenomics can determine whether the microbial community retains the capacity to produce butyrate or whether key functional genes have been lost. Such data influence decisions about whether to supplement fermentable fibers, introduce postbiotics (such as butyrate), or adjust lipid delivery.

Fecal metabolomics

Fecal metabolomics evaluates the biochemical output of the microbial ecosystem (**Table 3**).

Table 3. Fecal metabolomics

Fecal metabolomics quantifies:	• SCFAs (butyrate, acetate, propionate) • Primary and secondary bile acids • Amino acid derivatives • Polyamines such as putrescine and cadaverine (markers of protein fermentation)

SCFA levels, bile acid profiles, amino acid derivatives, polyamines, and microbial toxins provide direct evidence of metabolic capacities and deficiencies. Low fecal butyrate levels may signal a need for prebiotic fiber or cautious reintroduction of enteral feeding that suggests impaired epithelial support and poor tolerance of aggressive enteral feeding.[14] Elevated putrescine and cadaverine may indicate protein fermentation associated with catabolic stress or inadequate carbohydrate availability, suggesting review of protein dosing.

qPCR pathogen panels

Quantitative PCR panels offer rapid detection of pathogen overgrowth. High Enterococcus faecium burden, for instance, correlates with risk of bloodstream infection

and mortality[10], and may reflect inadequate microbial diversity. This information alone may alter nutrition; high carbohydrate loads, for example, can fuel Enterococcus expansion, suggesting the need to moderate glucose provision.

Fecal markers of epithelial integrity

Markers such as fecal calprotectin, zonulin, alpha-1 antitrypsin, and mucin fragments provide indirect information on epithelial damage and permeability. Elevated levels suggest a fragile mucosa that may poorly tolerate aggressive enteral feeding or hyperosmolar formulas.

Translating fecal analysis into nutritional decisions

Although fecal microbiome and metabolomic analyses offer rich biological information, their current use in routine ICU practice is limited by cost, turnaround time, and the need for specialized laboratory infrastructure and bioinformatic expertise. In most centers, rapid qPCR panels for key pathogens and a small set of fecal markers (such as calprotectin) are more feasible than full shotgun metagenomics or comprehensive fecal metabolomics.

For this reason, the decision examples provided in this section should be interpreted as conceptual pathways illustrating how future multi-omic data might inform nutrition, rather than as prescriptive protocols. At present, such strategies are best applied within research settings or as adjuncts to guideline-based care, rather than as stand-alone indications to change feeding practices. Interpretation of fecal data necessitates a structured decision-making approach (See **Table 4**).

Table 4. How fecal results guide nutrition

Examples:	• **Low butyrate** → cautious fiber introduction; consider postbiotics. • **High Enterococcus** → reduce simple carbohydrates; avoid overfeeding. • **Preserved SCFA pathways** (shotgun metagenomics) → safer progression to full enteral nutrition. • **Elevated bile acids** → adjust lipid delivery. • **High polyamines** → review protein load; risk of proteolytic fermentation

When butyrate-producing bacteria are depleted, introducing fermentable fibers may be beneficial, provided the patient's motility allows it. If fecal metabolomics indicates elevated secondary bile acids, reducing lipid infusion or modifying lipid composition may prevent further dysregulation. In cases of pathogen dominance, restricting simple carbohydrates and avoiding early high-caloric loads may reduce pathogenic expansion. Shotgun metagenomic evidence of preserved SCFA biosynthesis can support more ambitious enteral feeding strategies.
Thus, fecal analysis becomes not an academic exercise but a clinically actionable tool capable of informing feed type, macronutrient distribution, and progression of feeding.

Metabolomics in critical illness

Metabolomic signatures of metabolic stress

Metabolomics allows real-time characterization of metabolic pathways that are altered in critical illness. Elevated lactate, pyruvate, and acylcarnitine species signal mitochondrial

dysfunction and impaired oxidative phosphorylation [4]. Such patterns suggest caution in carbohydrate provision, as the patient may rely heavily on glycolysis and be unable to efficiently utilize glucose.

Altered branched-chain amino acids (BCAAs), and increased aromatic amino acids indicate skeletal muscle breakdown, highlighting the need to modulate protein provision based on catabolic status. The tryptophan–kynurenine ratio reflects immune activation[15] and predicts poor outcomes in sepsis, while lipidomic markers signal changes in fatty acid oxidation and phospholipid metabolism.

Metabolomics and substrate selection

These metabolic signatures can inform substrate allocation in nutritional prescriptions. For example, if fatty acid oxidation is impaired, clinicians may temporarily limit lipid administration to avoid lipid accumulation. Conversely, if glucose oxidation is suppressed, modestly increasing lipids and reducing carbohydrates may be preferable.

Protein requirements may be modulated based on amino acid turnover. Excessive early protein can impair autophagy and worsen outcomes, while insufficient protein during recovery phases may exacerbate muscle wasting.

Integration of metabolomics and microbiome data

Metabolomics and microbiome data are inherently complementary. Fecal SCFA levels reflect the metabolic activity of the microbiome, while plasma metabolomics represents whole-body metabolism. When combined, clinicians can differentiate between microbial-driven metabolic deficiencies (e.g., butyrate deficiency) and host-driven metabolic dysfunction (e.g., mitochondrial failure), guiding integrated nutritional interventions.

The integration of microbiome and metabolomic data is therefore attractive but remains largely investigational in critically ill adults. Most available studies are observational, with limited interventional data showing that altering nutrition based on specific metabolomic signatures improves hard clinical outcomes such as mortality, length of stay, or functional recovery.

Consequently, metabolomics-informed substrate selection should, at present, be viewed as a hypothesis-generating framework layered on top of established nutrition principles, rather than a replacement for guideline-based caloric and protein targets.

Evidence-based foundations of ICU nutrition

This section summarizes aspects of ICU nutrition that are currently supported by guidelines and large randomized trials and therefore can be considered standard of care, independent of microbiome or metabolomic testing.

Although biological signatures guide personalization, standard nutritional principles remain essential. Early enteral nutrition, if tolerated, supports microbial activity, prevents villus atrophy, and modulates inflammation. Clinical trials—including the CALORIES trial—demonstrate that the enteral route is not inferior to parenteral nutrition, provided caloric delivery is comparable.[6] Similarly, EPaNIC showed harm related to early supplemental PN, largely driven by overfeeding and impaired autophagy.[7]

Energy provision should be conservative during the acute phase, ESPEN recommends 70% of measured caloric requirements during early critical illness to prevent

overfeeding.[8] Indirect calorimetry is the gold standard for determining caloric requirements and prevents overfeeding. Predictive equations are unreliable during early critical illness.

Protein dosing remains controversial. High-dose early protein (>1.5 g/kg/day) may impair autophagy and worsen outcomes; moderate protein 1.0–1.3 g/kg/day is preferred until resolution of inflammation.[9] Higher doses may be introduced during recovery phases supporting anabolic rebuilding. ASPEN recommends delaying SPN until after day 7 in well-nourished patients.[9] Early SPN offers no mortality benefit and may worsen metabolic stress.

Taken together, early enteral nutrition (when hemodynamically feasible), avoidance of early overfeeding, moderate early protein delivery, and delayed initiation of supplemental parenteral nutrition in well-nourished patients represent core, guideline-supported pillars of ICU nutrition. Multi-omic data may refine these strategies in the future, but they should not currently displace these evidence-based foundations.

Integrating multi-omic data into personalized nutrition

The following framework is intentionally conceptual and reflects an emerging, biologically informed approach to ICU nutrition. It is built on associations between microbiome patterns, metabolomic signatures, and clinical outcomes, and extrapolates from existing physiological and mechanistic knowledge.

Personalizing ICU nutrition requires an integrated model that synthesizes microbiome analysis, fecal metabolomics, systemic metabolomics, clinical status, and organ function.

Fecal analysis guiding enteral feeding tolerance

When fecal SCFA levels are low, the gut may be poorly equipped to metabolize fiber-rich formulas. Introducing small volumes of fermentable fiber may stimulate microbial recovery, but large boluses may cause intolerance. If Enterococcus or Proteobacteria dominate, carbohydrate-rich feeds may promote pathogenic growth. Thus, fiber type, carbohydrate load, and formula osmolarity must be adapted based on microbial patterns.

Metabolomics guiding macronutrient allocation

If metabolomic evidence indicates mitochondrial dysfunction, clinicians should avoid aggressive carbohydrate infusion that may worsen lactate accumulation. Lactate elevation or mitochondrial stress markers merit reduction of carbohydrate load. Impaired β-oxidation suggests limiting lipid intake and adjusting lipid emulsions.

Multi-phase algorithmic feeding

Critical illness evolves through phases (**Table 5**).

Table 5. Phase-based algorithm

Phase-based algorithm	• **Early acute phase**: trophic EN; hypocaloric feeding; moderate protein; avoid early PN; avoid excessive carbs. • **Late acute phase**: gradual advance when SCFAs increase; adjust based on metabolomics. • **Recovery phase**: higher protein; increased energy; support anabolic rehabilitation.

During the early acute phase, permissive underfeeding, moderate protein dosing, reduced carbohydrate load, and microbiome-supportive strategies (such as cautious fiber introduction) may be optimal. As inflammation resolves, caloric intake is progressively increased to reach full requirement, guided by indirect calorimetry and metabolomics. In the recovery phase, anabolic support through increased protein provision becomes essential.

Importantly, these multi-phase, multi-omic algorithms have not yet been validated in randomized clinical trials. Their role at present is to guide hypothesis generation and protocol design for future studies, while day-to-day bedside practice should remain anchored in established guideline recommendations and individualized clinical judgment.

Clinical scenarios

The clinical scenarios presented illustrate how microbiome and metabolomic data might eventually refine nutrition strategies in specific ICU phenotypes such as sepsis, ARDS, and AKI. However, most of the microbiota-targeted interventions described (for example, specific prebiotics, postbiotics, strain-selected probiotics, and detailed substrate shifts based on omics) should currently be implemented, if at all, within clinical trials or structured quality-improvement programs with predefined safety and outcome monitoring.

Sepsis and septic shock

Sepsis produces profound dysbiosis, with diminished SCFA production and increased pathogenic expansion. Fecal metabolomics often shows low butyrate and altered bile acid profiles. Nutritional strategies should emphasize early trophic feeding, controlled carbohydrate delivery, and restoration of microbial fermentation capacity through fermentable fiber. Excess protein should be avoided during early shock, as metabolomic data reveal impaired amino acid oxidation.[14]

Acute respiratory distress syndrome (ARDS)

ARDS is characterized by systemic inflammation, increased catabolism, and impaired mitochondrial function. Metabolomics often shows elevated lactate and acylcarnitines, suggesting reduced tolerance to high carbohydrate loads. Moderate lipid-based calories may be beneficial, but total energy should remain conservative early on.[4]

Acute kidney injury (AKI)

Acute kidney injury alters nitrogen handling and amino acid clearance. Fecal metabolomics may reveal increased uremic toxins and changes in microbial fermentation patterns. Protein dosing should be carefully titrated, balancing the need to prevent catabolism with avoidance of nitrogen overload. Fiber that supports microbial nitrogen salvage may be beneficial.[15]

Challenges and future directions

Despite the promise of microbiome- and metabolomics-guided nutrition, substantial methodological, logistical, and economic challenges currently limit their widespread adoption. Fecal diagnostics and metabolomics platforms are not standardized across institutions, require specialized laboratory and bioinformatic capabilities, and often have turnaround times that are not yet compatible with real-time ICU decision-making in many settings. Moreover, while associations between microbiome patterns and outcomes are increasingly recognized, interventional evidence remains limited.

The cost and logistical complexity of sequencing and metabolomics limit widespread adoption, particularly in resource-limited settings. Moreover, while associations between microbiome patterns and outcomes are increasingly recognized, interventional evidence remains limited.

Future research priorities include pragmatic randomized trials comparing standard guideline-based nutrition with multi-omic–guided algorithms. These studies should evaluate not only biological endpoints (microbiome diversity, SCFA levels, metabolomic profiles) but also patient-centered outcomes such as infections, organ failure scores, ICU and hospital length of stay, mortality, and functional recovery. Decision-support tools, including artificial intelligence models, will need prospective validation to ensure that they provide clinically meaningful and safe recommendations that augment, rather than replace, clinician judgment.

Conclusion

Personalized ICU nutrition has entered a new era influenced by advances in microbiome science and metabolomics. Critical illness induces rapid dysbiosis and metabolic alterations that reshape nutrient handling and feeding tolerance. Fecal diagnostics and metabolomic profiling offer powerful tools to tailor nutrition to biological needs, supporting epithelial integrity, modulating immune responses, and optimizing substrate utilization.

The challenge now is to integrate these biological insights into routine clinical practice in a way that is methodologically rigorous and operationally feasible, particularly outside highly specialized centers. As multi-omic analysis becomes more accessible and is tested in well-designed clinical trials, nutrition therapy may evolve from a largely standardized intervention toward a more dynamic, biology-responsive strategy, while remaining grounded in established guideline-based principles of ICU nutrition.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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