International Journal of General Medicine

Dovepress
Taylor & Francis Group

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REVIEW

Advances in Intermittent Fasting Applications for Critically Ill Patients

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Abstract: Enteral nutrition remains the standard approach for nutritional support in critically ill patients, with established benefits for immune function and recovery. Intermittent fasting, a dietary strategy characterized by extended fasting intervals, has emerged as a potential adjunctive therapy. IF may induce beneficial metabolic responses such as autophagy activation and ketogenesis, contributing to improved glucose regulation, reduced intestinal permeability, modulation of gut microbiota, enhanced insulin sensitivity, and preservation of muscle mass. Unlike prolonged fasting, IF elicits these effects without causing sustained caloric deprivation. This review summarizes the current evidence regarding the physiological mechanisms, implementation strategies, clinical outcomes, and safety considerations of IF in the intensive care setting to provide a theoretical basis for further validation of the safety efficacy of the intermittent fasting paradigm for use in the ICU.

Keywords: intermittent fasting, critically ill patients, mechanisms of action, research progress

Introduction

Enteral nutrition is widely recognized as the preferred nutritional strategy for critically ill patients, contributing to immune function and clinical recovery.[1] Current guidelines recommend initiating enteral nutrition within 48 hours of admission to the intensive care unit for critically ill patients.[2] Observational data suggest that 60% to 80% of patients receive continuous enteral feeding during their hospital stay.[3] Although this approach ensures consistent energy and nutrient delivery, it may not fully engage intrinsic metabolic processes such as autophagy and metabolic switching, which are believed to facilitate recovery. Moreover, continuous feeding has been associated with potential adverse effects, including dysbiosis and metabolic disturbances.[4] Intermittent fasting (IF), a time-based nutritional intervention, has recently been explored as an alternative or adjunct strategy in critical care. Recent studies suggest that intermittent fasting may exert synergistic effects when combined with probiotics, contributing to enhanced gut barrier function and reduced systemic inflammation. This dual approach may present novel therapeutic advantages for critically ill patients, who often suffer from gut dysbiosis.[5] Additionally, IF may synchronize circadian rhythms and activate cellular pathways that mitigate inflammation and support tissue repair.[6] Importantly, existing studies report that IF does not impair metabolic stability during critical illness and may improve overall nutritional status.[7] Despite these promising findings, robust clinical data on IF in critically ill populations remain limited. This review outlines the conceptual framework of IF, underlying physiological mechanisms, current clinical evidence, potential benefits, and implementation considerations, with the goal of informing future approaches to enteral nutrition in the critical care setting.

Concept of Intermittent Fasting

IF refers to a structured dietary approach involving periodic intervals of minimal or no caloric intake alternating with periods of eating. Common IF patterns include time-restricted feeding, alternate-day fasting, overnight fasting, and periodic fasting.[8] IF is designed to modulate metabolic states by inducing cyclical transitions between fasting and feeding, allowing for the utilization of stored energy and activation of adaptive physiological processes. These processes include autophagy activation, improved insulin sensitivity, and modulation of systemic inflammation. Although IF has

Received: 19 April 2025
Accepted: 6 August 2025
Published: 12 August 2025

Table 1 Comparison of Two Common Intermittent Fasting Regimens

Fasting Regimen	Fasting Period	Eating Period
12:12	8:00 PM - 8:00 AM	8:00 AM - 8:00 PM
16:8	7:00 PM - 11:00 AM (next day)	11:00 AM - 7:00 PM

been primarily studied in the context of metabolic disorders, neurological diseases, and gut microbiota regulation, its potential role in nutritional support for critically ill patients is gaining interest. The core rationale for IF lies in its mimicry of ancestral feeding patterns, aiming to enhance metabolic efficiency and stress adaptation while potentially mitigating cellular damage associated with cardiometabolic diseases.[9,10]

Clinically, two of the most commonly studied IF models are the 12:12 pattern (12 hours fasting, 12 hours feeding)[11] and the 16:8 pattern (16 hours fasting, 8 hours feeding),[12] as summarized in Table 1. Compared with continuous enteral feeding, which distributes nutrient intake evenly over 24 hours, IF introduces defined fasting intervals to elicit metabolic adaptations such as increased fat oxidation and improved insulin sensitivity.[13]

Physiological Mechanisms by Which Intermittent Fasting Improves Clinical Outcomes in Critically Ill Patients

Ketogenesis and Autophagy Mechanisms

IF induces a metabolic shift from carbohydrate reliance to lipid metabolism, activating ketogenesis.[14] As fasting continues, ketone bodies become an important alternative energy source and have been associated with improved physical endurance.[15] In addition to their energetic role, ketones exert antioxidant effects, promote autophagy, and activate anti-inflammatory pathways—mechanisms considered critical for recovery in critically ill patients.[16] Autophagy, another key fasting-induced protective mechanism, maintains cellular homeostasis by degrading and recycling intracellular components. It is markedly upregulated under stress conditions such as nutrient deprivation, hypoxia, or oxidative stress. Studies have demonstrated a causal link between autophagy and improved outcomes in critical illness, highlighting its potential role in recovery.[17,18] In sepsis, for example, autophagy activation may help reduce excessive cytokine release and mitigate lung injury.[19] Although pharmacologic inducers of autophagy are not yet available, interest has grown in nonpharmacologic strategies.[20] Modifying nutritional regimens has shown promise, with evidence suggesting that adjusted feeding protocols can activate protective autophagic pathways in critically ill patients.[21] For instance, a randomized controlled trial by Permi[22] reported that IF stimulated autophagy, improving metabolic status and clinical outcomes. Furthermore, autophagy may underlie the benefits of withholding early enteral nutrition, as relative nutrient restriction can activate autophagy in the liver and skeletal muscles, thereby reducing organ injury.[21–23] Similarly, Greet[24] found that early caloric deficits did not worsen muscle atrophy but instead enhanced autophagic quality control of muscle fibers, potentially reducing post–ICU weakness.

The "Biological Clock" Mechanism

The benefits of IF are closely associated with its regulation of circadian rhythms, which govern a range of physiological processes, including the sleep–wake cycle, thermoregulation, cardiovascular activity, gastrointestinal function, and neuroendocrine signaling.[25] Disruption of these rhythms—such as through nighttime eating—can reset peripheral clocks and impair metabolic balance. During fasting, endogenous circadian mechanisms stimulate the liver to synthesize energy-related substrates to maintain metabolic homeostasis.[26] Additionally, feeding–fasting cycles influence the expression of circadian genes, reducing dephosphorylation activity, which may help lower circulating glucose levels, stabilize glycemia, and support vital function in critically ill patients.[27]

Metabolic and Energy Conversion Mechanisms

IF induces a metabolic switch between states of nutrient abundance and deprivation, initiating a series of metabolic and endocrine adaptations. During the feeding phase, glucose serves as the primary energy source, while excess energy and

amino acids promote fat storage and activate anabolic signaling pathways. Once fasting extends beyond approximately 10 to 12 hours, hepatic glycogen stores become depleted, prompting a shift toward lipolysis, fatty acid oxidation, and ketogenesis to meet energy demands.[25] Upon refeeding, anabolic pathways resume, restoring energy reserves and supporting tissue repair. This cyclical metabolic flexibility enhances energy efficiency, improves insulin sensitivity, reduces glycemic variability, and mitigates oxidative stress. Furthermore, IF has been shown to modulate circadian gene expression, reinforcing the alignment between metabolic rhythms and energy homeostasis.[28,29]

Timing of Intermittent Fasting in Critically Ill Patients

Currently, there is no consensus on the optimal duration or frequency of IF protocols in critically ill populations. However, preliminary data suggest that modified feeding regimens, such as cyclic enteral nutrition (eg, 12–16 hour fasting windows), may stimulate protective autophagic responses without compromising energy balance. Recent studies suggest that circadian-aligned IF cycles—particularly those confined to daytime hours—may offer physiological advantages.[30] Potential benefits include adequate caloric delivery, fewer feeding interruptions, improved glycemic control, reduced infection risk, preservation of muscle mass, and enhanced sleep quality. Currently, no formal guidelines exist regarding the ideal fasting duration for critically ill patients. However, circadian rhythms and patient-specific factors should inform decision-making. Investigations have examined fasting intervals ranging from 8 to 18 hours,[31] with some evidence indicating that restricting fasting to within 10 hours may help regulate blood pressure and lower atherogenic lipid levels.[32] In a randomized crossover trial involving 70 ICU patients, Lisa[33] alternated 12-hour feeding and fasting periods over at least 8 days, demonstrating that a 12-hour fasting window can activate a fasting response, reduce insulin requirements, and maintain metabolic stability in critically ill adults. Similarly, a study in pediatric intensive care unit (PICU) patients found that nighttime fasting and prolonged daily fasting periods stimulated ketone metabolism and autophagy, supporting recovery in critically ill children.[34] A 20-day IF intervention in 72 patients with type 2 diabetes by Wei-nan Yu[35] reported no serious adverse events, further suggesting that IF is safe under close clinical supervision. In summary, the development of standardized protocols that define fasting duration and timing is critical. Continuous monitoring of patient tolerance, particularly regarding intermittent enteral nutrition and complications such as aspiration, is essential to ensure safety and optimize outcomes.

Current Clinical Research Status of Intermittent Fasting in Critically Ill Patients

Tailoring IF protocols requires consideration of patients' metabolic reserve, baseline nutritional status, comorbidities (eg, diabetes, renal dysfunction), and organ support needs. For example, patients with high catabolic stress or low BMI may require shorter fasting durations or continuous monitoring to avoid exacerbating muscle wasting. Personalized strategies could involve "metabolically adapted IF", where the fasting duration is dynamically adjusted based on metabolic markers, insulin sensitivity, or inflammatory status. In a randomized trial involving 62 critically ill patients, RENC[36] compared IF with continuous feeding and found a significantly higher incidence of hyperglycemia in the continuous feeding group ($P < 0.05$). Rates of feeding intolerance were also significantly elevated in the continuous group. These findings suggest that IF may represent a more physiologically compatible nutritional strategy in critical care. Intermittent feeding allows for phased delivery of hypertonic nutritional solutions to the jejunum, which may reduce the metabolic burden on the small intestine and limit excessive jejunal fluid accumulation. Additionally, IF has been studied across diverse populations, including critically ill pediatric patients.[34,37–39] Notably, these studies reported no severe or refractory hypoglycemic events, nor significant gastrointestinal complications attributable to the intervention. Despite these promising findings, current evidence is constrained by several limitations. Most clinical studies on IF in critically ill populations involve small sample sizes and short-term follow-up. Long-term outcomes remain underexplored, and the generalizability of results is limited. As such, further large-scale, high-quality randomized controlled trials are needed to establish the safety, efficacy, and optimal protocols of IF in this patient population. The core significance of intermittent fasting in clinical practice and policy lies in its potential to drive revisions of current critical care nutrition guidelines. It is recommended that, in patients who are hemodynamically stable and free of intestinal ischemia risk, time-restricted feeding (such as the 12:12 model) be considered as an alternative to continuous enteral nutrition. Additionally, personalized monitoring protocols (eg, assessing blood glucose fluctuations and muscle wasting) should be developed,

and safety of implementation should be ensured through multidisciplinary collaboration (physicians, dietitians, nursing teams). Future large-scale randomized controlled trials are necessary to clarify the effects of various IF regimens on circadian gene expression and long-term functional outcomes, thereby providing evidence for the standardization of such protocols.

Clinical Significance of Intermittent Fasting on Outcomes in Critically Ill Patients

Gastrointestinal Function

The clinical relevance of IF in critically ill patients is particularly evident in its effects on gastrointestinal physiology. Early enteral nutrition is known to help maintain gastrointestinal integrity, thereby reducing complications, infection rates, and mortality in this population.[2] However, gastrointestinal dysfunction is common in critically ill patients, resulting from underlying disease processes and interventions such as mechanical ventilation and sedative use. These factors contribute to symptoms including gastric retention, diarrhea, and dysbiosis.[40] By introducing scheduled periods of fasting, IF may provide physiologic rest to the gastrointestinal tract, facilitating the recovery of motility and barrier function.[24] Preclinical and clinical studies suggest that fasting promotes intestinal epithelial repair and enhances mucus layer regeneration, potentially reducing bacterial translocation and systemic inflammatory responses.[41] Additionally, IF may modulate gut microbiota composition by promoting the proliferation of beneficial bacteria (eg, *Lactobacillus, Bifidobacterium*) while inhibiting pathogenic species, thereby improving microbial balance. Restoration of gastrointestinal function may indirectly contribute to improved outcomes, such as reduced ventilator-associated pneumonia, decreased infection rates, and shorter ICU length of stay.[42] The DC-SCENIC trial is currently the only randomized controlled trial systematically evaluating the application of intermittent fasting (IF) principles in ICU patients.[29] This study compared 10 hours of cyclic enteral nutrition (simulating 14 hours of fasting) with standard 24-hour continuous feeding in critically ill patients requiring mechanical ventilation, aiming to induce early metabolic shifts (such as ketogenesis) to reduce organ dysfunction. The design distinctly differentiates itself from traditional "interrupted feeding", using a standardized feeding window and monitoring of metabolic markers, thus providing the first clinical model to replicate the rhythmic and metabolic characteristics of IF in critically ill populations. Nonetheless, further high-quality clinical trials are needed to clarify the precise impact of IF on gastrointestinal function and long-term outcomes.

Muscle Protein Catabolism and Metabolism

Excessive skeletal muscle catabolism is a hallmark of critical illness and is associated with poor recovery.[43] Muscle wasting is exacerbated by systemic inflammation, immobility, and metabolic dysregulation. IF may influence protein metabolism by alternating periods of feeding and fasting, potentially restoring anabolic-catabolic balance.[44] Evidence suggests that IF can generate postprandial amino acid peaks, stimulating muscle protein synthesis and improving metabolic efficiency.[45] However, the protective effect of IF on muscle mass remains uncertain. For example, fasting windows limited to 4 hours were shown to enhance protein utilization but did not prevent loss of thigh muscle mass in critically ill patients.[46] While IF may theoretically optimize protein utilization, evidence from non-critically ill populations raises concerns. Isocaloric IF regimens (eg, 16:8 TRE) have been associated with 2–4% reductions in lean mass, possibly due to prolonged catabolic states during fasting windows.[28] In critically ill patients already experiencing hypercatabolism, extended fasting (>12h) could exacerbate muscle loss. Therefore, IF protocols must include rigorous muscle mass monitoring and protein supplementation (≥1.5 g/kg/day) during feeding phases to mitigate this risk. These findings suggest that although IF may optimize feeding efficiency, it may not be sufficient to prevent acute muscle atrophy. Further investigation is needed to determine optimal fasting durations and feeding strategies for preserving muscle function in critical care settings.

Organ Function Protection

From an evolutionary viewpoint, prolonged fasting represents a stress adaptation rather than an optimal state. While preclinical studies suggest IF may activate protective mechanisms, human data in critical illness remain limited. Continuous energy delivery may better support organs under high metabolic demand by ensuring substrate availability. IF's potential benefits must be weighed against risks of substrate deprivation in hemodynamically unstable patients. IF

may confer organ-protective effects through multiple biological mechanisms. During fasting periods, reliance on lipid metabolism leads to increased ketone production, which serves as an alternative energy substrate for organs such as the brain and heart. This metabolic shift may reduce oxidative stress and inflammation, thereby protecting neuronal and myocardial function.[47] IF also induces autophagy, promoting the clearance of damaged cellular components and facilitating tissue repair and regeneration.[48] Furthermore, fasting modulates inflammatory signaling pathways, potentially mitigating systemic inflammation and its detrimental effects on organ systems.[41] Renal function may also benefit from IF. Preliminary data suggest that IF may reduce the incidence of acute kidney injury by improving metabolic homeostasis and attenuating inflammatory responses.[49,50] While these findings are promising, additional clinical studies are required to validate these organ-protective effects and to delineate the underlying mechanisms in critically ill populations.

Considerations for Intermittent Fasting

IF may interact with pharmacotherapy and other nutritional strategies in complex ways. For instance, timing-dependent drug absorption (eg, insulin, corticosteroids) could be altered by prolonged fasting intervals, necessitating careful scheduling. Moreover, the intermittent absence of caloric intake may reduce the efficacy of enterally administered medications or probiotics. Additionally, integration with parenteral nutrition or early goal-directed feeding protocols may introduce logistical and metabolic conflicts that need further investigation. Although IF has been explored in critically ill populations, existing studies vary in design, objectives, and outcomes. Therefore, careful clinical monitoring is essential during implementation to ensure adequate nutrient delivery and minimize potential complications. One major concern is glycemic variability; fasting periods may increase the risk of hypoglycemia, particularly in patients with type 2 diabetes. IF protocols should be managed by healthcare professionals, with appropriate adjustments in medication, increased frequency of glucose monitoring, and close attention to fluid balance. Inadequate nutrient intake during feeding windows can result in malnutrition, especially if patients fail to meet protein, vitamin, and mineral requirements. Nutritional planning must align with the duration and frequency of fasting to prevent deficiencies. Maintaining adequate hydration is also critical, regardless of the fasting regimen employed. Gastrointestinal function should be assessed prior to initiating IF, given the high prevalence of gastrointestinal dysfunction in critically ill patients. Fasting may exacerbate issues such as gastric retention, diarrhea, or even ischemic injury if not properly managed. Tolerance should be evaluated on an individual basis. Successful implementation of IF requires multidisciplinary coordination among physicians, dietitians, and nursing staff to ensure safe and evidence-based practices. Finally, the long-term safety and efficacy of IF remain uncertain, as most available studies focus on short-term outcomes. Further research is needed to evaluate the sustainability and clinical relevance of IF over extended periods in critically ill populations.

Conclusions

In summary, while preclinical evidence suggests intermittent fasting (IF) may enhance metabolic flexibility and attenuate organ injury in critical illness through ketogenesis and autophagy activation, clinical translation remains constrained by significant knowledge gaps. Current human studies are predominantly limited to small-scale trials with heterogeneous protocols, wherein purported benefits on glycaemic control and gastrointestinal function lack robust validation. Critically, emerging data from non-ICU populations indicate that even isocaloric IF regimens (eg, 16:8 TRE) may accelerate muscle catabolism—a risk potentially amplified in critically ill patients with pre-existing sarcopenia. Therefore, IF cannot be routinely recommended until large, methodologically rigorous RCTs establish its safety profile, particularly regarding long-term functional outcomes and muscle mass preservation. Future research must prioritize: (1) Standardized IF protocols (≥12h fasting) stratified by patient phenotypes (eg, sepsis vs trauma); (2) Real-time monitoring of catabolic markers (eg, urea-to-creatinine ratio, β-hydroxybutyrate); and (3) Head-to-head comparisons against continuous feeding with clinically relevant endpoints (eg, ventilator-free days, ICU-acquired weakness incidence). Until such evidence emerges, IF implementation should be restricted to hemodynamically stable, well-nourished patients under rigorous metabolic surveillance within controlled trial settings.

Institutional Review Board Statement

Ethical review and approval were waived for this review because it did not involve new animal or human-subjects research; all data had been previously published.

Data Sharing Statement

Please refer to the individual studies cited for information on data availability.

Informed Consent Statement

Informed consent was obtained from all subjects in the studies cited herein.

Author Contributions

All authors made substantial contributions to conception, design, data acquisition, analysis, or interpretation; drafted or critically revised the manuscript; approved the final submitted version; agreed on the journal to which the article was submitted; and accept accountability for all aspects of the work.

Funding

This work was supported by the Guangdong Provincial Medical Science and Technology Research Fund(grant number B2025095).

Disclosure

The authors report no conflicts of interest in this work.

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