

Translational perspectives on precision nutrition, microbiome modulation, and muscle remodeling in critical illness

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INTRODUCTION

The comprehensive review by Patel and McClave in *The New England Journal of Medicine* delineates a crucial paradigm shift in critical care nutrition. During the acute phase, intense catabolism, inflammation, and gut dysfunction fundamentally reshape nutritional needs. Because endogenous hepatic gluconeogenesis persistently drives glucose production, superimposing early full-dose calories may contribute to "relative overfeeding" and exacerbate metabolic and gastrointestinal complications. We strongly endorse the transition from historically pursuing 80% to 100% of energy targets to an early restrictive or trophic feeding approach (providing approximately 25% of the target, though this is context- and phase-dependent). This restrained strategy aims to minimize overfeeding while prioritizing intestinal barrier integrity and commensal microbiome health.¹

However, building upon this macroscopic clinical framework, the next frontier requires a microscopic focus. Caloric adjustments alone are insufficient; true precision nutrition must be systematically decoded at the cellular level, explicitly targeting host-microbiome metabolic crosstalk and the molecular drivers of skeletal muscle anabolic resistance.

TIMING AND ROUTE OF NUTRITION: A PRECISION STRATEGY BASED ON CLINICAL PHENOTYPES

In their analysis, the authors affirm early enteral nutrition (EN) as the primary modality to preserve gut barrier function and microbiome diversity. Concurrently, they highlight a fundamental shift in clinical practice: when EN is contraindicated or unfeasible, early short-term parenteral nutrition (PN) serves as a feasible alternative. Importantly, major trials addressed different questions: CALORIES directly compared early EN with early PN,² whereas EPaNIC³ evaluated early versus delayed supplemental PN in patients already receiving early EN. Collectively, available evidence suggests no clear mortality advantage of one early feeding strategy across all critically ill patients. However, this should not be interpreted as universal equivalence or safety. In hemodynamically unstable patients, aggressive early EN may increase the risk of severe gastrointestinal complications, including bowel ischemia.¹

These findings highlight that the profound heterogeneity of critically ill adults renders a uniform nutrition approach suboptimal. Consequently, patients must be stratified by their distinct clinical phenotypes, metabolic reserves, and splanchnic perfusion statuses (Table 1).

Precision is crucial after major abdominal surgery, where gastrointestinal dysmotility often limits EN. For high-risk patients unable to achieve adequate enteral energy targets, supplemental parenteral nutrition (SPN) serves to bridge the caloric gap. To safely balance caloric deficits against the risks of premature overfeeding, SPN timing must be strictly individualized—introduced only when enteral tolerance remains persistently inadequate and advanced as clinical stability permits.

THE "METABOLIC COST" OF PARENTERAL NUTRITION AND GUT MICROBIOME REMODELING

Furthermore, the NEJM article highlights the central role of intestinal dysfunction—characterized by the breakdown of epithelial barrier defenses and the rapid development of gut dysbiosis—in the pathogenesis of critical illness. The authors explicitly highlight the "gut-lung axis of inflammation," illustrating how virulent bacteria and disrupted intestinal cross-talk signaling bypass normal clearance mechanisms to drive systemic inflammation, effectively serving as a pathogenic bridge from the gut to distant organs.¹

When enteral feeding is precluded, we must critically evaluate the hidden "metabolic cost" of exclusive PN (traditionally referred to as TPN). Beyond merely providing passive intravenous energy, prolonged TPN actively exacerbates intestinal dysbiosis, driving profound metabolic and immunological consequences.

Microbiome homeostasis—conceptualized through candidate features like microbial diversity and short-chain fatty acids rather than validated ICU biomarkers—is frequently disrupted in the ICU, though interpretations must account for confounders like antibiotics, acid suppression, and sampling methodology. For TPN-dependent patients, restoring lost microbial metabolic signals represents a hypothesis-generating therapeutic target. Preclinical intestinal failure models indicate that microbiota-derived tryptophan metabolites can orchestrate intestinal immunity by modulating Group 3 innate lymphoid cells (ILC3s).⁴ These micro-ecological hypotheses may evolve into future precision therapies for gut-derived sepsis.

BREAKING ANABOLIC RESISTANCE: SYNERGY OF PROTEIN INTAKE, SATELLITE CELLS, AND REHABILITATION TRAINING

Another pivotal observation from the review is that providing high-dose protein (> 2.0 g/kg/day) fails to improve clinical outcomes in critically ill adults and has raised safety concerns, with trial subgroup analyses suggesting a potential risk of harm in patients with acute kidney injury, though confirmed nephrotoxic mechanisms remain under investigation. A moderate protein target (e.g., 1.2–1.3 g/kg/day) is not a universal prescription for AKI. Protein provision must be highly individualized—particularly for patients not receiving renal replacement therapy (RRT)—and dynamically adjusted for catabolic state, RRT status, tolerance, and illness phase. The clinical paradigm must fundamentally shift from merely "providing protein" to explicitly "overcoming anabolic resistance."¹

Addressing intensive care unit-acquired weakness (ICU-AW) requires distinct evaluations of muscle mass, structural strength, and functional capacity. To stimulate muscle regeneration, preclinical murine models highlight the succinate–SUCNR1 axis—where succinate promotes satellite cell differentiation⁵—as a candidate translational pathway for skeletal muscle remodeling.

Ultimately, reversing continuous cellular muscle loss demands the synergy of "nutrition plus exercise." During the recovery phases, nutritional interventions must integrate hemodynamically safe resistance training. Addressing a "key research gap," future large-scale randomized controlled trials must validate whether combining substrate-level metabolic modulators with structured rehabilitation improves anabolic responsiveness and patient-centered functional outcomes in ICU survivors.

CONCLUSION AND FUTURE DIRECTIONS

Realizing these paradigms faces inherent translational hurdles. ICU cohorts exhibit profound heterogeneity, while foundational insights into microbiome and satellite cell dynamics derive primarily from preclinical models. Furthermore, methodological inconsistencies in microbiome profiling and the absence of large-scale intervention trials currently constrain bedside application.

Nutrition therapy must evolve into a phase-calibrated, biomarker-driven strategy spanning the entire care continuum. Integrating multi-omics monitoring with targeted physical rehabilitation provides a translational roadmap to improve long-term functional recovery and quality of life for ICU survivors.

Table 1. Operational framework for precision nutrition in critically ill adults.

Disease Phase	Patient Phenotype	Current Standard of Care	Candidate Biomarker / Indicator	Precision Intervention	Timing	Safety Criteria	Evidence Level	Intended Outcome
Early acute	Circulatory shock with vasopressor support	Early EN after hemodynamic stabilization	Vasopressor requirement, lactate, perfusion	Trophic/restricted EN; avoid early full-dose feeding	First 24–72 h; reassess with stabilization	Escalating vasopressors, worsening perfusion, GI intolerance/ ischemia	RCT-supported (e.g. NUTRIREA trials, summarized in Ref. 1); biomarker thresholds unvalidated	Safe feeding; reduce GI complications
Early acute	High refeeding risk or preexisting malnutrition	Cautious caloric initiation	Phosphate, Mg, K; nutritional risk	Thiamine, electrolyte correction, slow caloric advancement	Before and during early feeding	Electrolyte decline, fluid overload, arrhythmia	Trial/guideline-supported (e.g., REFEEDING trial, summarized in Ref. 1)	Prevent refeeding complications
Late acute	AKI, especially without RRT	Moderate protein provision	Creatinine, urine output, AKI/RRT status	Avoid high-dose protein; consider moderate provision (e.g., ~1.2–1.3 g/kg/day) for selected patients without RRT	During evolving AKI	Worsening renal/ metabolic status	RCT subgroup evidence (e.g., EFFORT Protein trial, summarized in Ref. 1)	Avoid harm while supporting recovery
Recovery phase	Lean-mass loss or ICU-acquired weakness	Full nutrition plus rehabilitation	Energy expenditure, muscle mass/strength, physical function	Advance toward 80–100% energy needs; individualize protein + resistance exercise	After acute stabilization	Feeding or exercise intolerance, clinical instability	Emerging evidence	Restore lean mass, function, and quality of life

Table 1 provides a conceptual rather than prescriptive framework. Nutritional targets, including the ~1.2–1.3 g/kg/day protein target for selected AKI patients, are not universal prescriptions and must be individually tailored to clinical dynamics.

REFERENCES

1. Patel J.J. and McClave S.A. (2026). Nutrition therapy in critically ill adults. *N. Engl. J. Med.* **395**:162–174. DOI:10.1056/NEJMra2506111

2. Harvey S.E., Parrott F., Harrison D.A., et al. (2014). Trial of the route of early nutritional support in critically ill adults. *N. Engl. J. Med.* **371**:1673–1684. DOI:10.1056/NEJMoa1409860

3. Casaer M.P., Mesotten D., Hermans G., et al. (2011). Early versus late parenteral nutrition in critically ill adults. *N. Engl. J. Med.* **365**:506–517. DOI:10.1056/NEJMoa1102662

4. Huang L., Wang P., Liu S., et al. (2025). Gut microbiota-derived tryptophan metabolites improve total parenteral nutrition-associated infections by regulating group 3 innate lymphoid cells. *iMeta* **4**:e70007. DOI:10.1002/imt2.70007

5. Shi Y., Zhou D., Wang H., et al. (2025). Succinate regulates exercise-induced muscle remodelling by boosting satellite cell differentiation through succinate receptor 1. *J. Cachexia Sarcopenia Muscle* **16**:e13670. DOI:10.1002/jcsm.13670

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AUTHOR CONTRIBUTIONS

M.Z. drafted the initial manuscript and performed the revisions. X.W. conceptualized the core ideas, provided critical revision suggestions, and acquired funding. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.