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REVIEW ARTICLE

Protein First: Whey Protein Administration Strategy in Critically ill Patients

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ABSTRACT

Background: Critically ill patients in the intensive care unit (ICU) frequently develop hypercatabolic states associated with progressive muscle wasting and immune dysfunction. Meeting adequate protein targets remains a persistent challenge in standard ICU nutrition practice.

Methods: A narrative review of the literature was conducted by searching PubMed, MEDLINE, and Google Scholar using the keywords "whey protein," "critically ill," "ICU nutrition," "protein-first strategy," "enteral nutrition," and related terms. Articles published between 2015 and 2025 were prioritized, and foundational earlier studies were included where relevant. Randomized controlled trials, systematic reviews, meta-analyses, observational studies, consensus guidelines, and mechanistic studies were included. Articles without full-text availability or not relevant to critical care nutrition were excluded.

Results: Whey protein is biologically characterized by rapid absorption, a rich essential amino acid profile, and a high leucine content that may activate the mTORC1 pathway to stimulate muscle protein synthesis. Whey protein–based enteral formulas have been shown in selected studies to facilitate achievement of recommended protein targets (1.2–2.5 g/kg/day) with acceptable gastrointestinal tolerance. Some evidence suggests potential benefits in nitrogen balance and inflammatory markers; however, evidence for consistent improvement in hard clinical outcomes—including mortality, ventilator duration, and ICU length of stay—across the general critically ill population remains limited. Most supportive studies are small, single-center, or focused on specific subpopulations, and several are feasibility assessments rather than outcome trials.

Conclusion: Whey protein is a biologically plausible and practically useful component of individualized ICU nutrition. A "Protein First" approach using whey-based formulas may assist in meeting recommended protein targets; however, current evidence does not support claims of universal outcome benefit. Individualized dosing—with particular caution in patients with renal or hepatic impairment—remains essential.

Keywords: Critically ill; Intensive care unit; High-Protein Enteral Nutrition; Protein First; Whey protein.

INTRODUCTION

Nutritional support in critically ill patients admitted to the intensive care unit (ICU) is an important determinant of clinical outcomes, including morbidity, mortality, and recovery. Critical illness is commonly associated with a hypercatabolic state characterized by accelerated skeletal muscle protein breakdown and increased nitrogen loss, resulting in progressive loss of lean body mass and impaired immune function.[1,2] These processes create a substantial nutritional challenge, as conventional enteral formulas designed primarily to meet caloric targets frequently fail to deliver sufficient protein.[1,8]

The current paradigm in ICU nutrition has shifted toward prioritizing protein delivery, commonly referred to as the "Protein First" strategy. International guidelines generally recommend protein intake of 1.2–2.0 g/kg/day in critically ill patients, with higher targets of up to 2.5 g/kg/day in those with severe hypercatabolism or undergoing renal replacement therapy (RRT).[8,12] Whey protein, derived from bovine milk, has attracted interest as a potential protein source in this context due to its rich essential amino acid profile, rapid absorption kinetics, and high leucine content, which may activate muscle protein synthesis pathways.[3–5]

Despite this biological rationale, the clinical evidence for whey protein supplementation in the ICU setting remains heterogeneous, and robust data consistently demonstrating improvement in major clinical outcomes are limited. Therefore, this review aims to summarize current evidence regarding the "Protein First" strategy using whey protein in critically ill patients, with attention to mechanisms of action, clinical efficacy in specific populations, dosing considerations, safety, and special populations requiring individualized management.

Literature for this review was identified through searches of PubMed, MEDLINE, and Google Scholar databases using the terms "whey protein," "critically ill," "ICU nutrition," "protein-first strategy," "enteral nutrition," "muscle protein synthesis," and related terms. Articles published between 2015 and 2025 were prioritized; foundational studies of earlier date were included where relevant. Eligible study types included randomized controlled trials, systematic reviews and meta-analyses, prospective observational studies, and consensus guidelines. Narrative reviews and mechanistic studies were included for biological background. Studies without full-text availability in English were excluded. Article selection

was based on relevance to critical care nutrition and clinical applicability.

DISCUSSION

Nutritional Requirements in Critically Ill Patients

Nutritional support in critically ill patients, particularly protein delivery, is an important component of ICU management with substantial impact on morbidity, mortality, and recovery.[1,2] Critically ill patients frequently experience hypercatabolic states characterized by accelerated muscle protein breakdown and nitrogen loss, necessitating targeted nutritional strategies to attenuate muscle mass loss and support immune function. Conventional enteral formulas designed around energy-based targets frequently fail to deliver adequate protein, contributing to protein deficits that have been associated with prolonged mechanical ventilation and extended ICU length of stay.[1,8,10]

Nutritional support should ideally be initiated early, within 24–48 hours of ICU admission, via the enteral route when clinically feasible.[1,2] Caloric requirements are generally recommended at 25–30 kcal/kg/day, adjusted for metabolic phase and clinical condition, but protein delivery has emerged as the primary nutritional priority. Most current guidelines recommend protein intake of 1.2–2.0 g/kg/day, with higher targets up to 2.5 g/kg/day in patients with severe hypercatabolism or those receiving RRT.[8,12] It should be noted that many patients do not consistently achieve these targets in routine clinical practice, reinforcing the importance of formulas specifically designed for high protein delivery.

Whey Protein Characteristics and Mechanisms

Whey protein is a high-quality protein derived from bovine milk during cheese production, characterized by a rich essential amino acid profile including branched-chain amino acids (BCAAs) such as leucine, isoleucine, and valine.[3,5] Essential amino acids constitute approximately 43% of whey protein content, and the rapid digestibility of whey results in a relatively swift rise in plasma amino acid concentrations following ingestion.[3]

Among BCAAs, leucine functions not only as a substrate for protein synthesis but also as a signaling molecule activating the mammalian target of rapamycin complex 1 (mTORC1), a central regulator of muscle protein synthesis and cell growth.[4,5] Whey protein contains approximately 10–12% leucine by protein weight, and a dose of approximately 2–3 g of leucine per serving is considered sufficient to optimally stimulate muscle

protein synthesis in skeletal muscle.[4] These mechanistic properties provide the biological rationale for whey protein as a preferred protein source in catabolic states; however, it must be acknowledged that most mechanistic evidence derives from studies in non-ICU populations, and the extent to which mTORC1 activation is effectively sustained in the setting of critical illness—where anabolic resistance is common—requires further investigation.[4,5]

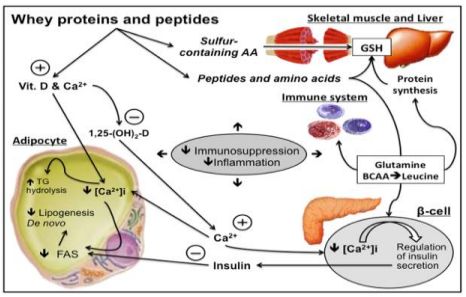

Figure .1 Mechanisms involving whey protein as a source of various immunonutrients, illustrating effects on lipid metabolism, muscle protein synthesis, and protein breakdown.

In addition to its anabolic properties, whey protein contains bioactive components including α-lactalbumin, β-lactoglobulin, lactoferrin, and immunoglobulins that may confer anti-inflammatory and immunomodulatory effects.[3] These characteristics have prompted interest in whey protein specifically within the ICU context, where systemic inflammation and immunosuppression are common and interrelated challenges.

Clinical Evidence

Clinical evidence supporting whey protein use in critically ill patients is available primarily from small, heterogeneous studies, and the overall evidence base must be interpreted with appropriate caution. The following subsections summarize and critically appraise the key available evidence, organized by study type and patient population.

Feasibility and tolerability data. Tedeschi-Jockers et al. (2022) conducted a prospective, single-center observational tolerability study evaluating a high protein-to-energy enteral formula containing whey protein hydrolysate in ICU patients.[1] The primary endpoint was achievement of protein targets and gastrointestinal tolerability. The study demonstrated that the formula facilitated attainment of higher protein targets without excessive caloric provision. Major limitations include the observational design with no control group, single-center setting, and the fact that tolerability rather than clinical outcome was the primary endpoint. Findings cannot be used to infer efficacy for hard clinical outcomes and generalizability remains uncertain. Reinhold et al. (2020) similarly conducted a trial evaluating protein delivery with intermittent versus continuous enteral feeding using a protein-rich formula in ICU patients, demonstrating that intermittent administration may produce higher peak amino acid concentrations.[13]

Generalizability is limited by small sample size and protocol-specific feeding parameters.

Neurocritical care data. Tian et al. (2025) performed a post-hoc analysis of a pilot randomized controlled trial (RCT) evaluating the feasibility of whey protein powder supplementation in neurocritically ill patients.[6] Supplementation was associated with higher daily protein intake compared with standard care. Critical appraisal reveals several important limitations: the study was a post-hoc analysis of a pilot trial, which was not primarily powered to detect differences in clinical outcomes; the patient population was exclusively neurocritical care patients; sample size was small; and the primary endpoint was protein target achievement rather than mortality or functional outcomes. Findings are not directly generalizable to the broader heterogeneous ICU population.

Inflammatory markers in specific populations. Hashemilar et al. (2020) conducted a randomized, double-blind, placebo-controlled clinical trial evaluating whey protein supplementation over three weeks in patients with acute ischemic stroke.[7] Supplementation was associated with significant reductions in TNF-α, IL-6, and high-sensitivity CRP, as well as improved clinical outcomes. While the double-blind RCT design strengthens the quality of evidence, several limitations apply: the study population was neurologically specific (acute ischemic stroke) and not representative of general critically ill patients; inflammatory markers served as surrogate endpoints rather than hard clinical outcomes; and the intervention period of three weeks exceeds that of many ICU admissions. Results should therefore not be extrapolated to the general ICU population as evidence of whey protein's consistent anti-inflammatory efficacy.

Protein delivery and meta-analytic data. Lee et al. (2021) conducted a systematic review and meta-analysis of 16 RCTs comparing higher versus lower protein delivery in critically ill patients.[8] No statistically significant difference in mortality was identified between groups. However, higher protein delivery was associated with improved nitrogen balance and a lower incidence of gastrointestinal adverse events. Critically, this meta-analysis evaluated protein delivery in general, not whey protein specifically; protein sources were heterogeneous across included trials. These findings support adequate protein provision as a class effect but cannot be attributed specifically to whey-based formulas.

COVID-19 ICU patients. Scarcella et al. (2022) evaluated the effect of whey protein on malnutrition indices and extubation time in critically ill COVID-19

patients.[14] Results suggested potential benefits in nutritional status and shorter mechanical ventilation duration. However, the study was conducted in a disease-specific population during an extraordinary clinical context, used small sample sizes, and findings may not be generalizable to standard ICU practice.

Ongoing and planned trials. The TARGET protein study (Summers et al., 2023) is a large multicenter RCT designed to evaluate augmented enteral protein delivery in critically ill adults and is expected to provide higher-quality outcome data.[15] Until such trials report results, the current evidence base remains insufficient to support definitive conclusions regarding the impact of whey-based protein-first strategies on mortality or other hard outcomes in unselected ICU populations.

Timing and Route of Administration

Timing of protein delivery is an important consideration in critical care nutrition. Early protein administration—defined as more than 0.7 g/kg/day within the first three ICU days—has been associated with reduced 60-day mortality in large observational studies.[12] However, the causal nature of this association requires confirmation in prospective interventional trials, as observational data are susceptible to confounding by clinical trajectory.

The enteral route is preferred over parenteral nutrition in most critically ill patients, including those on mechanical ventilation, due to its role in preserving gut integrity, reducing infection risk, and supporting recovery.[1,2] Enteral formulas with high protein content, particularly those containing whey protein hydrolysate, have demonstrated improved protein target achievement with acceptable gastrointestinal tolerance.[1,13] Parenteral nutrition is reserved for cases where enteral delivery is contraindicated or insufficient.[1,2]

The optimal pattern of protein delivery—intermittent bolus versus continuous infusion—remains incompletely resolved. Mechanistically, intermittent or bolus protein administration may generate higher peak plasma amino acid concentrations, potentially producing a stronger anabolic stimulus.[13] However, clinical evidence comparing the two delivery patterns with respect to outcomes is limited, and individual factors including gastrointestinal tolerance and hemodynamic stability should guide practical decisions.

Dosing Strategy and Safety Considerations

Current guidelines recommend protein intake of 1.2–2.5 g/kg/day in critically ill patients, with higher requirements in those with burns, major trauma, or undergoing RRT.[8,12] A protein-first strategy typically begins at 1.2–1.5 g/kg/day and is titrated

according to gastrointestinal tolerance, nitrogen balance, and organ function assessment.[1,8] It is essential to emphasize that these targets are not universally appropriate and require individualized adjustment based on clinical context.

Acute kidney injury (AKI). The appropriate protein dose in ICU patients with AKI is a particularly contested area. Al-Dorzi and Arabi (2023) reviewed the evidence for early high-protein delivery in critically ill patients with AKI.[12] Current evidence does not clearly support high-dose protein as beneficial in this subgroup, and excessive protein delivery may exacerbate uremia, particularly in patients not receiving RRT. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend protein intake of 1.3 g/kg/day in critically ill AKI patients not on RRT, with higher targets of up to 1.7 g/kg/day for those on continuous RRT. These recommendations reflect the need to balance protein adequacy against metabolic burden. In patients with AKI receiving whey protein supplementation, close monitoring of blood urea nitrogen, serum creatinine, and metabolic tolerance is mandatory.

Hepatic dysfunction. In patients with significant liver dysfunction, impaired protein metabolism and the risk of hepatic encephalopathy must be considered. Although older dogma recommended protein restriction in cirrhotic patients, current evidence—particularly from non-ICU studies—suggests that adequate protein intake is important for preserving muscle mass and should not be routinely restricted. However, the evidence base in critically ill patients with hepatic failure is sparse, and individualized assessment with monitoring for encephalopathy exacerbation is warranted. Whey protein's BCAA content may theoretically be advantageous in this setting by providing an anabolic stimulus with potentially less hepatic metabolic burden compared with aromatic amino acid–rich proteins; however, clinical evidence for this is limited.

Allergic considerations. Whey protein contains potential allergens including α-lactalbumin and β-lactoglobulin.[3] Administration should be approached with caution in patients with known milk protein allergy. Partially or extensively hydrolyzed whey protein formulas may reduce allergenic potential and improve gastrointestinal tolerance in sensitive patients.[1y3] Ongoing monitoring of gastric residual volume and gastrointestinal symptoms remains essential during enteral nutrition in all critically ill patients.[1]

Protocol Development and Implementation

Implementation of a structured whey protein–based nutrition protocol in the

ICU should account for patient-specific metabolic demands, organ function, and nutritional risk. Education and training of nursing and dietitian staff responsible for enteral feed administration and documentation are important components of successful implementation. Quality improvement data suggest that structured protocols and targeted staff education may improve compliance with protein supplementation targets and documentation accuracy.[14] Institutional adoption of standardized nutritional assessment tools, including screening for malnutrition, regular monitoring of protein delivery achievement, and systematic reassessment of nutritional goals throughout the ICU stay, is recommended.

CONCLUSION

Critically ill patients in the ICU have substantial protein requirements that conventional enteral formulas frequently fail to meet. Whey protein–based enteral formulas represent a biologically plausible and practically useful option to facilitate achievement of recommended protein targets as part of an individualized "Protein First" strategy. Available evidence from selected studies suggests potential benefits in nitrogen balance and inflammatory markers in specific patient populations. However, current evidence does not consistently demonstrate improvement in hard clinical outcomes—including mortality, mechanical ventilation duration, or ICU length of stay—across the general critically ill population. The majority of supporting studies are small, single-center, focused on specific subpopulations such as neurocritical care or stroke patients, or primarily designed as feasibility assessments rather than outcome trials.

Therefore, whey protein should be regarded as a reasonable and potentially useful component of individualized ICU nutritional management, rather than a universally proven intervention with consistent outcome benefit. Protein dosing must be individualized, with particular caution warranted in patients with acute kidney injury or hepatic dysfunction, where excessive protein delivery may increase metabolic burden. Future large, multicenter randomized controlled trials—such as the ongoing TARGET protein study—are needed to more definitively establish whether whey protein–based protein-first strategies improve hard clinical outcomes across the diverse and heterogeneous critically ill population.

Conflict of Interest

The author declares no conflicts of interest in this review article.

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