REVIEW ARTICLE

Nutrition Therapy in Critically Ill Adults

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SUMMARY

In the acute phase of critical illness, adults have severe catabolism, inflammation, muscle loss, and gut dysfunction, all of which shape nutritional requirements. Early enteral nutrition supports gut integrity and microbiome health, but trials have shown that early short-term parenteral nutrition is a safe alternative when enteral feeding is not possible. Large trials have shown that early full-dose energy delivery offers no benefit over restrictive dosing and may increase gastrointestinal and metabolic complications, findings that support a restrictive nutrition strategy, especially in patients who have circulatory shock or are at risk for refeeding syndrome. Similarly, large trials have shown no advantage of high-dose over standard-dose protein and suggest harm in patients with acute kidney injury. Because adverse events are common with enteral nutrition, safe nutrition delivery requires gradual advancement, strategies for prevention of refeeding syndrome, glycemic control, and avoidance of routine gastric residual volume monitoring. Patient heterogeneity underscores the need for precise, biomarker-guided, phase-specific nutrition to preserve lean muscle mass and improve recovery.

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CME

Nutrition therapy, the provision and monitoring of enteral and parenteral nutrition, is essential for critically ill adults who are unable to maintain volitional intake during both the acute and late phases of illness. Contemporary randomized, controlled trials have challenged long-established practices, prompting a reevaluation of nutrition delivery methods, energy and protein dosing, and appropriate monitoring. This review focuses on the acute phase of critical illness and discusses the key physiological changes that affect nutritional needs. Contemporary evidence is interpreted to provide practical guidance on best practices for routes of nutrition delivery, target ranges for energy and protein doses, and monitoring of nutrition therapy.

THE ACUTE PHASE OF CRITICAL ILLNESS

The European Society for Parenteral and Enteral Nutrition partitions critical illness into acute and late phases.[1] The acute phase is further divided into the early acute and late acute phases, which together generally encompass the period of time from admission to the intensive care unit (ICU) through the first week of critical illness.

Understanding the pathophysiological mechanisms of the acute phase of critical illness provides a foundation for evidenced-based nutritional strategies. During this phase, physiological perturbations caused by insults such as sepsis, trauma, and acute respiratory distress syndrome initiate a complex metabolic stress response. This response involves activation of the sympathetic nervous system, the hypothalamic–pituitary axis, gastrointestinal and adipose hormones, and the inflammatory–immune system (Fig. 1).[2] These coordinated responses drive a state of accelerated

catabolism and resistance to anabolic signals to supply glucose to vital organs.[2]

Under the influence of stress hormones and inflammatory cytokines, the ubiquitin–proteasome pathway becomes overactivated, which leads to excessive proteolysis and a net negative nitrogen balance.[2] The circulating amino acid pool from the breakdown of muscle protein is directed toward gluconeogenesis and oxidation as an energy source.

The metabolic response to stress commonly manifests as hyperglycemia and muscle wasting. Insulin resistance and hyperglycemia correlate with disease severity, and poor glycemic control is associated with worse clinical outcomes.[3] A systematic review showed that critically ill adults lose 2% of their skeletal muscle mass per day during the first week of critical illness, and nearly 48% of critically ill patients have muscle weakness — a complication associated with a prolonged stay in the ICU.[4] Key histologic changes seen in muscle during this period include the loss of myosin filaments, an altered actin-to-myosin ratio, disruption in the sarcoplasmic reticulum, electrical inexcitability, bioenergetic failure (the inability of cells to generate and use sufficient ATP to meet metabolic demands because of mitochondrial dysfunction and impaired oxidative metabolism), and infiltration of muscle tissue by inflammatory cells.[5,6]

Inflammation and increasing oxidative stress cause gut dysfunction — a common occurrence characterized by a breakdown of epithelial barrier defenses and the development of gut dysbiosis. Intestinal cross-talk signaling, which normally maintains the dynamic interaction among epithelium, immune tissue, and gut microbiota to maintain barrier function, is disrupted in critical illness.[7]

Under normal physiological conditions, commensal gut bacteria play a critical role in preserving intestinal homeostasis. Their molecular signals interact with intestinal epithelial cells to enhance the release of tight-junction proteins, stimulate Paneth cells to secrete defensins, prompt goblet cells to produce mucus, and engage subepithelial dendritic cells to support antiinflammatory T-cell differentiation.

However, during critical illness, proinflammatory pathways disrupt this balance. Multiple mechanisms, including reduced tight-junction protein expression, accelerated enterocyte apoptosis, and mucosal atrophy, contribute to the loss of barrier integrity.[8] The gut microbiota shifts from a commensal to a dysbiotic state owing to disruptions in the intestinal environment — such as reduced oral intake, hypoperfusion, and impaired mucosal immunity — and common ICU interventions including gastric acid suppression and broad-spectrum antibiotic administration.[9]

With increased permeability and breakdown of gut defenses, bacteria can exert a proinflammatory response and contribute to the development of multiple organ failure even if they don't physically translocate from the gut to distant sites. Instead, through cross-talk signaling, virulent bacteria can bypass normal clearance mechanisms and activate dendritic cell–mediated responses, which drives systemic inflammation. The lung microbiome in adults with sepsis and acute respiratory distress syndrome has been shown to be dominated by bacteria that are typically associated with the gut, such as enterococcus, bacteroides, and prevotella.[10] This phenomenon, called the gut–lung axis of inflammation, has challenged the long-standing paradigm of pulmonary sterility and has underscored the emerging role of gut microbiota in the pathogenesis of respiratory disease. Through this gut–lung axis of inflammation, systemic inflammation contributes to downstream injury and multiple organ failure.

ROUTE, TIMING, AND DOSE OF NUTRITION

ROUTE AND TIMING

Unlike parenteral nutrition and the receipt of nothing by mouth, which impair gut health by reducing epithelial-cell proliferation, increasing apoptosis, and disrupting mucosal integrity, enteral nutrition supports gut function by enhancing tight-junction protein expression, reducing enterocyte apoptosis, preserving villous and crypt architecture, maintaining Paneth-cell function, supporting gut-associated lymphoid tissue, and helping to sustain commensal microbiota (Fig. 2).[11,12] The collective evidence from 21 randomized, controlled trials has shown that early enteral nutrition, initiated within the first 24 to 36 hours after ICU admission, leads to better outcomes than delayed delivery or no provision of enteral nutrition.[13] For patients in whom the gastrointestinal tract is functional and no contraindications exist, major critical care nutrition

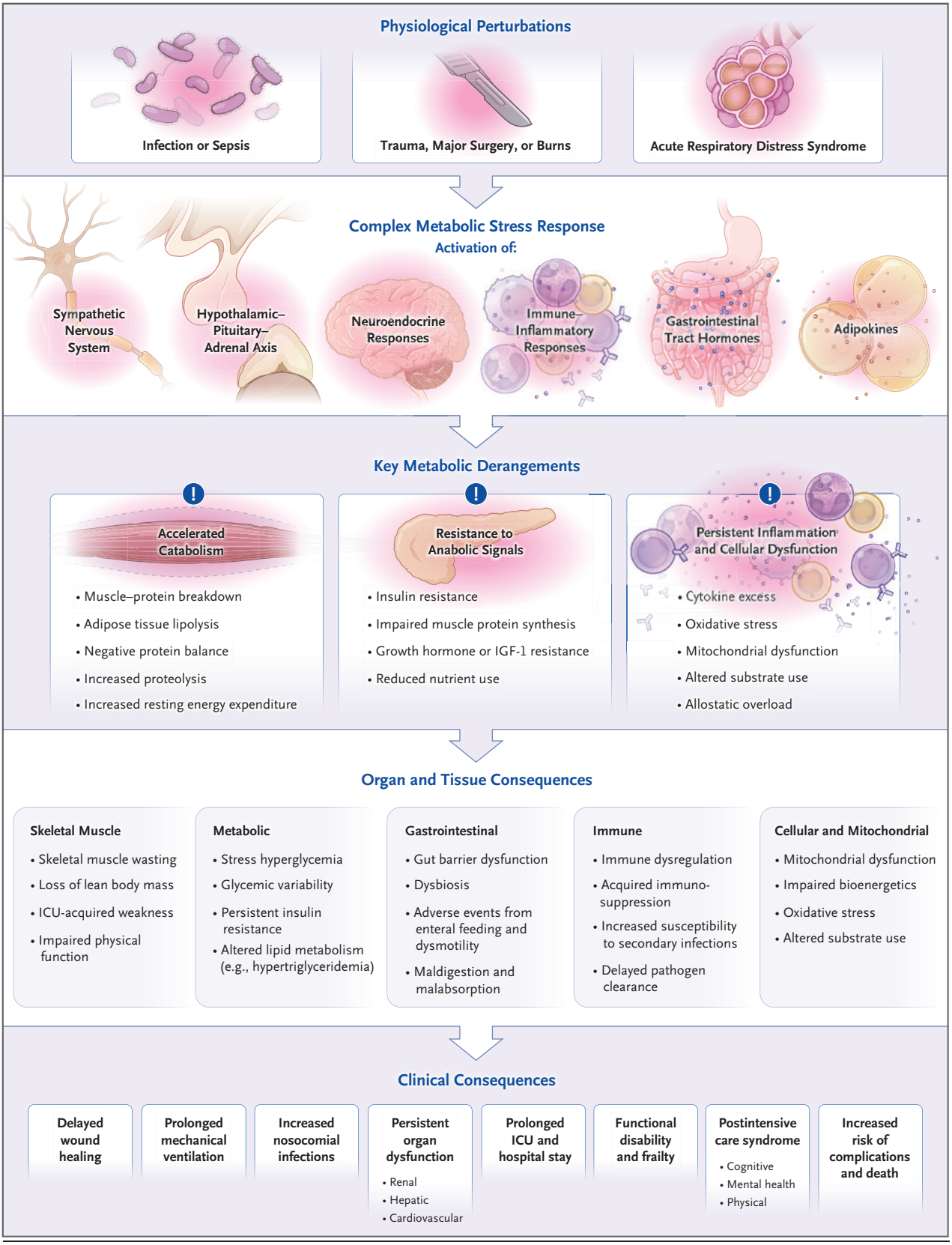

Figure 1 (facing page). Metabolic Stress Response and Downstream Consequences of Critical Illness.

Critical illness activates coordinated neuroendocrine, inflammatory, and hormonal responses that promote catabolism, anabolic resistance, and cellular dysfunction, leading to organ-specific complications and adverse clinical outcomes. ICU denotes intensive care unit, and IGF-1 insulin-like growth factor 1.

guidelines recommend early enteral nutrition over parenteral nutrition to preserve gut integrity and support the intestinal microbiome.[1,13,14] This recommendation has been challenged by large multicenter randomized, controlled trials evaluating the role of early short-term parenteral nutrition.[15-17] In a trial of critically ill adults determined to have a short-term contraindication to early enteral nutrition, receipt of early parenteral nutrition was found to be associated with 60-day mortality similar to that with standard care (delayed enteral nutrition).[15] The CALORIES and NUTRIREA-2 trials randomly assigned critically ill adults to receive early enteral nutrition or early short-term parenteral nutrition, and the results showed no between-group differences in 30-day and 28-day mortality, respectively (Table 1).[16,17] In these trials, early short-term parenteral nutrition was not associated with increased infectious complications.[15-17]

In the NUTRIREA-2 trial, specifically, patients who were randomly assigned to receive early enteral nutrition had more gastrointestinal complications, including a higher incidence of clinically relevant bowel ischemia than those who were assigned to receive early short-term parenteral nutrition (2% vs. <1%; P=0.007).[17,28] A 2024 meta-analysis of 14 trials comparing early enteral nutrition with parenteral nutrition, including the CALORIES and NUTRIREA-2 trials, showed that early enteral nutrition was associated with fewer bloodstream infections and shorter ICU and hospital stays but increased gastrointestinal complications, such as vomiting and diarrhea.[29] Together, these findings suggest that early parenteral nutrition is a reasonable alternative when early enteral nutrition is either contraindicated or unfeasible.

DOSE OF NUTRITION

Long-standing concepts of hyperalimentation, positive nitrogen balance, and calorie deficits led to the practice of providing early full-dose nutrition to critically ill adults, with the goal of meeting 80 to 100% of their estimated energy requirements.[30-33] These requirements may be measured with the use of indirect calorimetry, although this method is infrequently used in clinical practice worldwide; more commonly, energy requirements are estimated with the use of weight-based or predictive equations.[34] The EAT-ICU trial randomly assigned critically ill adults to receive early goal-directed nutrition, with energy needs measured by indirect calorimetry, or to receive standard nutritional care. There were no between-group differences in clinical outcomes, including quality of life at 6 months.[35]

Thirteen randomized, controlled trials questioned the practice of providing full-dose nutrition during the acute phase of critical illness and compared restrictive strategies — such as hypocaloric feeding, permissive underfeeding, and trophic feeding (Table 2) — with full-dose regimens.[18-22,36-43] Nine trials showed no significant between-group differences in mortality.[18,19,21,37-41,43] Four trials showed that restrictive-dose enteral nutrition led to better outcomes, including reductions in mortality and duration of mechanical ventilation and earlier time-to-readiness for ICU discharge, than full-dose nutrition.[20,22,36,42] Six trials showed a higher percentage of patients with adverse events from enteral feeding (often called enteral feeding intolerance) among those receiving full-dose enteral nutrition than among those receiving restrictive-dose enteral nutrition.[18,21,22,37,41,42] In addition, three trials showed that patients in the full-dose groups required greater amounts of insulin.[20,40,41] Of note, in four of the five largest multicenter trials,[18-22] more complications were observed among patients receiving full-dose nutrition (Table 1). These findings suggest that the potential benefits of full-dose enteral nutrition may be thwarted by iatrogenic stressors in the physiological context of inflammation, hemodynamic instability, impaired fuel use, and intestinal dysmotility. Early aggressive full-dose nutrition may cause net harm by increasing the risk of bowel ischemia, refeeding syndrome, overfeeding (exogenous nutrients combined with hepatic gluconeogenesis), suppression of autophagy, increased demand on dysfunctional mitochondria, delivery of excessive fluid volume, and gastrointestinal adverse effects.[28] A more cautious, restrictive approach to nutrition, such as a trophic dose delivered at a rate of 10 to 20 ml per hour to preserve gut integrity,[44,45] now appears to be more appro-

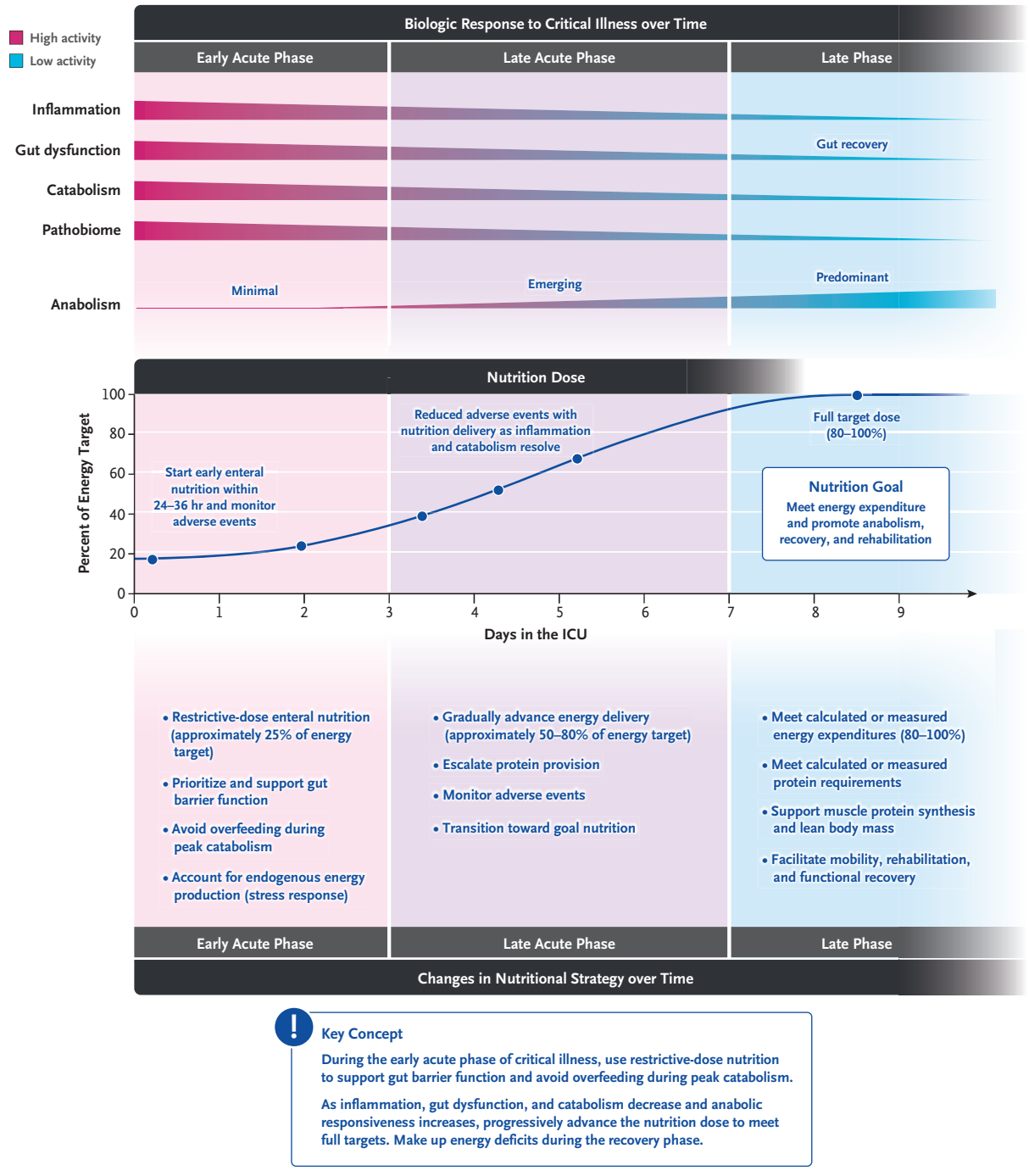

Figure 2. Evolution of Physiological Responses and Nutrition Strategy across Phases of Critical Illness.

Shown is a conceptual model of the transition from early catabolism to recovery and anabolism during critical illness, with corresponding progression from restrictive-dose to full-dose nutrition as metabolic function improves.

priate during the early acute phase of critical illness and is a strategy recommended in recent critical care nutrition guidelines.[46,47] A recent meta-analysis showed that even among critically ill adults with or at risk for malnutrition — who have limited physiological reserve and are more vulnerable to the adverse effects of undernutrition — high energy delivery does not lengthen survival.[48]

The appropriate timing and dose of enteral nutrition in critically ill adults who have circulatory shock and are receiving vasopressor therapy remains uncertain.[1] Most randomized, controlled trials that compared early with delayed enteral nutrition excluded patients with circulatory shock. However, the NUTRIREA-2 and NUTRIREA-3 trials enrolled adults with circulatory shock who were receiving mechanical ventilation.[17,22] In both trials, the percentage of patients with adverse events with enteral feeding, including bowel ischemia, was higher with early full-dose nutrition than with either early parenteral nutrition (in the NUTRIREA-2 trial) or restrictive-dose enteral nutrition (in the NUTRIREA-3 trial). Of note, these patients were receiving norepinephrine at doses exceeding 0.5 μg per kilogram of body weight per minute, which suggests that initiating early full-dose enteral nutrition in patients receiving high-dose vasopressor therapy is harmful.[28]

The appropriate vasopressor threshold for starting or withholding enteral nutrition remains unclear, but emerging evidence suggests that early low-dose enteral nutrition may be safe in patients receiving moderate-dose vasopressors (norepinephrine equivalent, <0.3 μg per kilogram per minute). However, higher-quality efficacy data are needed.[49]

PROTEIN DOSE

The severe protein loss seen early in critical illness gave rise to the theory, supported by observational data and small trials, that high protein intake may improve nitrogen balance, reduce anabolic resistance, and promote muscle synthesis.[50] On the basis of these findings, the 2016 Critical Care Nutrition Guidelines from the American Society of Parenteral and Enteral Nutrition and the Society of Critical Care Medicine recommended a broad protein dose range of 1.2 to 2.0 g per kilogram per day.[13] A global survey of 187 ICUs showed that critically ill adults for whom the guideline-recommended protein dose of 1.3 g per kilogram per day was prescribed received only 55% of that amount, or 0.7 g per kilogram per day.[51] Beyond inadequate delivery, anabolic resistance — common both in older adults and in patients who are critically ill — further impairs effective use of protein for muscle building. In a study that used radiolabeled phenylalanine, Chapple et al. showed that whereas protein absorption and systemic availability were similar in healthy and critically ill adults, the latter incorporated only 60% of absorbed amino acids into muscle protein, which highlights a substantial metabolic limitation.[52]

The benefit from a higher protein dose observed in lower-quality studies could not be replicated in larger well-designed trials. The pragmatic EFFORT Protein trial randomly assigned 1301 critically ill adults who were undergoing mechanical ventilation to receive either a high dose of protein (≥2.2 g per kilogram per day) or the usual dose of protein (≤1.2 g per kilogram per day) within 96 hours after ICU admission.[23] Despite a similar energy intake and a mean between-group difference in protein intake of 0.7 g per kilogram per day, no between-group differences were observed in the time to discharge alive at 60 days or in secondary outcomes. Signals of harm emerged in patients with a greater severity of illness and in those with acute kidney injury who were not receiving renal replacement therapy and who received a high dose of protein.[23,53] These findings highlight the importance of patient subgroups in evaluating protein-dosing strategies. Preexisting malnutrition, present in more than 40% of the patients in the EFFORT Protein trial, was associated with a lower 60-day discharge rate and higher mortality than those in patients without preexisting malnutrition.[55] However, a secondary analysis showed that higher protein intake did not modify this association.[55] (For a description of the methods to assess for malnutrition in hospitalized patients, see the review in the Nutrition in Medicine series in the *Journal*.[54])

In the PRECISE trial, 935 patients in the ICU who were undergoing mechanical ventilation were randomly assigned to receive isocaloric enteral nutrition with either a standard dose of protein (1.3 g per kilogram per day) or a high dose of protein (2.0 g per kilogram per day). The high-protein group had more episodes of adverse events from enteral nutrition and had lower health-related quality-of-life scores 6 months after ICU discharge.[24]

In a large trial comparing protein dose in critically ill adults, the TARGET Protein trial (involving 3412 patients) showed that augmented enteral protein delivery did not result in a greater number of days alive and out of the index hospital at day 90 than usual protein delivery. No benefit was shown in secondary outcomes, and subgroup analyses suggested possible harm among patients receiving new kidney-replacement therapy, find-

Table 1. Major Contemporary Nutrition Trials involving Critically Ill Adults.*

Topic and Trial (Year)	Population	Intervention	Comparator	Outcome	Complications
Route of nutrition delivery					
Early PN (2013)[15]	1372 Patients in multiple medical–surgical ICUs	Early PN	Standard care†	No significant between-group difference in 60-day mortality (22.8% vs. 21.5%; P=0.60)	No between-group difference in infectious complications
CALORIES (2015)[16]	2400 Patients in multiple medical–surgical ICUs	Early PN	Early EN	No significant between-group difference in 30-day mortality (33.1% vs. 34.2%; P=0.57)	No between-group difference in infectious complications, and more adverse events in the EN group
NUTRIREA-2 (2018)[17]	2410 Patients in multiple medical–surgical ICUs	Early PN	Early EN	No significant between-group difference in 28-day mortality (35% vs. 37%; P=0.33)	No between-group difference in infectious complications, and more GI complications in the EN group
Energy dose					
EDEN (2012)[18]	1000 Patients with acute lung injury at multiple medical ICUs	10 ml/hr (trophic)	25 kcal/kg/day (full dose)	No significant between-group difference in ventilator-free days or mortality	More GI complications in the 25 kcal/kg/day group
PERMIT (2015)[19]	894 Patients at multiple medical–surgical ICUs	40–60% of caloric requirements (hypocaloric)‡	70–100% of caloric requirements‡	No significant between-group difference in mortality	No significant between-group difference in GI complications
REFEEDING (2015)[20]	339 Patients in multiple medical–surgical ICUs	20 kcal/hr for 2 days and slow ramp-up based on serum phosphate level	Standard care§	More days alive at days 60 and 90 in the caloric-restriction group	More infections, hyperglycemic episodes, and insulin use in the standard-care group
TARGET (2019)[21]	3957 Patients in multiple medical–surgical ICUs	1 kcal/ml formula	1.5 kcal/ml formula	No significant between-group difference in mortality	More GI complications in the 1.5 kcal/ml group
NUTRIREA-3 (2023)[22]	3044 Patients in multiple medical–surgical ICUs¶	6 kcal/kg/day‖	25 kcal/kg/day (full dose)‖	Shorter time to readiness for ICU discharge in 6 kcal/kg/day group	More severe GI complications in the 25 kcal/kg/day group

Protein dose					
EFFORT Protein (2023)[23]	1301 Patients in multiple medical–surgical ICUs	High-dose protein (≥2.2 g/kg/day)	Low-dose protein (≤1.2 g/kg/day)	No significant between-group difference in time to discharge alive at 60 days	No between-group difference in GI complications from enteral feeding
PRECISE (2024)[24]	935 Patients in multiple medical–surgical ICUs	High-dose protein (2.0 g/kg/day)	Standard protein (1.3 g/kg/day)	Higher health utility score with high protein than with standard protein (430 vs. 419; P=0.031)	More GI complications from enteral feeding in the high-protein group
TARGET Protein (2025)[25]	3397 Patients in eight medical–surgical ICUs in Australia and New Zealand	Isocaloric, protein-intense formula (100 g/liter)	Isocaloric, standard-protein formula (63 g/liter)	No significant between-group difference in days of index hospitalization and alive at day 90 (median, 62 vs. 64)	No significant between-group difference in new renal replacement therapy
Gastric residual volume monitoring					
REGANE (2010)[26]	329 Patients in multiple medical–surgical ICUs	Gastric residual volume threshold of 500 ml	Gastric residual volume threshold of 200 ml	No significant between-group differences in GI complications	No between-group differences in pneumonia
NUTRIREA-1 (2013)[27]	452 Patients in multiple medical–surgical ICUs	No gastric residual volume monitoring	Gastric residual volume threshold of 250 ml	No significant between-group difference in ventilator-associated pneumonia	More GI complications from enteral feeding in the gastric residual volume monitoring group

* EN denotes enteral nutrition, GI gastrointestinal, ICU intensive care unit, and PN parenteral nutrition.
† The standard-care group received nutritional support defined pragmatically. The attending clinician selected the route, timing, metabolic targets, and composition of nutrition therapy according to local practice.
‡ ICU dietitians estimated patients' standard caloric requirements using the equation developed by investigators at Pennsylvania State University (the Penn State equation) for patients receiving mechanical ventilation who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of less than 30 and using the 1992 Ireton-Jones equation for patients receiving mechanical ventilation who had a BMI of 30 or higher and for spontaneously breathing patients.
§ The standard-care group received nutritional support defined pragmatically; nutrition support as planned before trial enrollment was continued.
¶ More than 80% of the patients were in a medical ICU.
‖ More than 70% of the patients received EN or a combination of EN and PN.

Table 2. Feeding Strategies in Critically Ill Adults.

Feeding Strategy	Definition
Trophic	10–20 ml/hr of continuous feeding to nourish the intestinal mucosa[44,45]
Hypocaloric	<70% of caloric requirements but full dose of protein
Permissive underfeeding	40–60% of caloric and protein requirements
Full dose	70–100% of caloric and protein requirements

ings consistent with those of the EFFORT Protein and PRECISE trials.[25]

These findings were supported by two meta-analyses that showed that a high dose of protein did not lead to better outcomes in critically ill adults than a lower dose.[56,57] Moreover, a high dose of protein may be harmful in patients with severe illness and acute kidney injury. The revised 2023 critical care nutrition guidelines from the European Society for Parenteral and Enteral Nutrition recommend gradually advancing protein intake to 1.3 g per kilogram per day during the first week of ICU stay.[46]

MONITORING CRITICAL CARE NUTRITION

Adverse events with enteral feeding are common and closely associated with gastrointestinal dysmotility that often arises early in critical illness. Having appropriate monitors in place might help to promote safety with the delivery of enteral nutrition.[58] Common signs of adverse effects that can be observed at the bedside include hypoactive bowel sounds, abdominal distention, nausea, vomiting, and obstipation or constipation. The European Society of Intensive Care Medicine Working Group on Gastrointestinal Function further classifies the severity of adverse events with enteral feeding by adding diarrhea, gastrointestinal bleeding, intraabdominal hypertension, abdominal compartment syndrome, and bowel ischemia or infarction in a graded continuum.[59]

In practice, these findings can be grouped as low-risk (i.e., typical signs and symptoms) or high-risk (e.g., intraabdominal hypertension, abdominal compartment syndrome, and bowel ischemia).[49] Low-risk features may warrant pausing or maintaining the current rate of enteral nutrition delivery until adverse effects abate. In contrast, high-risk features require immediate cessation of enteral nutrition and clinical reassessment. It is important to note, however, that in severely ill patients, low-risk signs may indicate evolving high-risk complications.[49] Diarrhea and gastrointestinal bleeding should be evaluated independently, because enteral nutrition rarely needs to be discontinued for these issues. The causes of diarrhea are multifactorial and may be related to medications, infections, and malabsorption.[49] Overt clinically significant bleeding (characterized by melena, hypotension, and a reduction in hemoglobin), which occurs in 1.3% of medical ICU patients, warrants cessation of enteral nutrition and full investigation.[60] In the Reevaluating the Inhibition of Stress Erosions (REVISE) trial, which compared proton-pump inhibitors with placebo in adults who were receiving mechanical ventilation, enteral nutrition was shown to be protective against upper gastrointestinal bleeding (the primary outcome).[61]

The metabolic instability during the acute phase of critical illness, characterized by endogenous hepatic gluconeogenesis,[62] can lead to relative overfeeding when combined with exogenous calories from nutritional therapy, especially at the full dose, and can exacerbate hyperglycemia and increase insulin requirements.[17,20,22,40] On the basis of the results of several randomized, controlled trials, the 2024 Guidelines on Glycemic Control for Critically Ill Children and Adults from the Society of Critical Care Medicine recommend managing hyperglycemia by keeping the blood glucose level below 180 mg per deciliter (10 mmol per liter).[63]

Critically ill adults should be monitored for deterioration of prehospitalization nutritional status and for malnutrition, as indicated by decreased nutrient intake, weight loss, or a body-mass index (the weight in kilograms divided by the square of the height in meters) below 18.5.[54] Such patients are at risk for refeeding syndrome. The optimal nutrition advancement strategy in critically ill adults remains uncertain; however, rapid progression in patients who are at risk for refeeding syndrome has been shown to be harmful. The multicenter REFEEDING trial randomly assigned critically ill adults in whom hypophosphatemia had developed on initiation of feeding to either a slow ramp-up with caloric restriction or a rapid ramp-up with standard caloric intake. Patients who were assigned to caloric restriction had better outcomes than those receiving standard caloric intake, including higher 60-day survival (91% vs. 78%; P=0.002), shorter length of hospital stay

(21.7 days vs. 27.9 days; P=0.003), and fewer infections (21% vs. 32%; P=0.03).[20] In critically ill adults with risk factors for refeeding syndrome, the provision of empirical thiamine supplementation and cautious advancement of the nutrition regimen is recommended, along with close monitoring of serum phosphate, magnesium, and potassium levels.[64]

Despite the paucity of evidence to support the use of gastric residual volume as an accurate marker or predictor of gastric emptying or the risk of aspiration and pneumonia, monitoring of gastric residual volume continues to be included in the assessment of adverse events with enteral feeding in ICU patients.[65] However, the value of monitoring gastric residual volume has been questioned by several trials over the past two decades. In a trial involving critically ill adults who were receiving mechanical ventilation, no association between gastric residual volume and aspiration, as assessed by colorimetric microscopy and mass spectrometry, was shown.[66] The incidence of aspiration was similar regardless of whether gastric residual volumes were below 50 ml or above 400 ml. The multicenter REGANE trial randomly assigned critically ill adults to high (500 ml) or low (200 ml) thresholds for gastric residual volume and showed a lower incidence of gastrointestinal complications and better feeding delivery in the high-threshold group.[26] Similarly, the multicenter NUTRIREA-1 trial showed no differences in ventilator-associated pneumonia, mortality, or length of ICU stay between patients with routine gastric residual volume monitoring and those without such monitoring.[27] A meta-analysis of seven trials (involving 1240 patients) indicated that not monitoring gastric residual volume reduced unnecessary feeding interruptions and showed no between-group differences in the incidence of ventilator-associated pneumonia, the length of ICU stay, or mortality.[67] Current evidence does not support the use of gastric residual volume monitoring to reduce the risk of aspiration or pneumonia in ICU patients. Gastric residual volume monitoring may hinder enteral nutrition delivery, and no added benefit has been shown in surgical ICU populations as compared with medical ICU populations. Routine monitoring of gastric residual volume — as a marker of adverse events with enteral feeding — should be strongly discouraged.

AREAS OF UNCERTAINTY AND OPPORTUNITIES

Critically ill adults comprise a highly heterogeneous population, with substantial variability in physiological, metabolic, and clinical profiles, as well as unique metabolic treatment responses.[68] Although contemporary randomized, controlled trials support a "less is more" approach during the acute phase of critical illness, the effects of nutrition therapy beyond the ICU — particularly after hospital discharge — remain unclear. Moreover, it is plausible that distinct subgroups of patients within these trials may have derived benefit from more-aggressive nutritional strategies. Patients with preexisting malnutrition are often excluded from critical care nutrition trials, which limits our understanding of how best to support this high-risk group. However, recent guidance highlights the importance of identifying malnutrition at ICU admission and monitoring its progression throughout the ICU stay. Including malnourished patients in future trials is essential, because such patients may be among those most likely to benefit from targeted or more-aggressive nutritional interventions.[69] A precision nutrition approach that tailors nutritional interventions to individual patient characteristics and biologic responses is needed to improve outcomes and minimize harm in critically ill patient populations.

Such a therapeutic intervention may require the integration of individualized approaches, such as predictive modeling with the use of machine learning to tailor therapies[70] and biomarker-guided[71] and phase-specific nutritional strategies.[72] These approaches should be implemented within a multidisciplinary framework and validated across diverse ICU populations. Their effectiveness should be assessed according to meaningful clinical outcomes, including functional recovery, quality of life, and long-term survival.[73]

Over the past four decades, survival from critical illness has improved but is marred by substantial loss of lean body mass, which is a major long-term consequence for survivors.[4] Loss of lean body mass contributes to acquired muscle weakness and functional disability, which can persist for up to 5 years after the initial ICU admission.[74] In healthy persons, resistance exercise combined with protein supplementation has been shown to elicit a greater anabolic response than

KEY POINTS

NUTRITION THERAPY IN CRITICALLY ILL ADULTS

- The acute phase of critical illness is marked by intense catabolism, inflammation, rapid skeletal muscle loss, and gut dysfunction.
- Early enteral nutrition preserves gut integrity and supports the microbiome, so it is the preferred approach, although contemporary randomized, controlled trials show that early short-term parenteral nutrition is safe when enteral nutrition is contraindicated.
- Providing full-dose nutrition early may lead to more metabolic and gastrointestinal complications than restrictive or trophic feeding.
- High-dose protein (>2.0 g per kilogram of body weight per day) offers no outcome benefit over standard dosing (≤1.2 g per kilogram per day) and may be harmful in patients with acute kidney injury.
- Adverse events with enteral feeding (often called enteral feeding intolerance) are common during critical illness, and the safe delivery of nutrition requires gradual advancement, strategies for prevention of refeeding syndrome, glycemic control (glucose level, <180 mg per deciliter), and avoidance of routine gastric residual volume monitoring.
- Patient heterogeneity highlights the need for precision, appropriate use of biomarkers, and phase-specific nutrition strategies, particularly for malnourished patients and patients who survived after a stay in the intensive care unit, to preserve lean mass and improve recovery.

protein supplementation alone.[75] The effect of protein supplementation and resistance exercise on patient-centered outcomes represents a key research gap in critical care nutrition.[76] A small randomized, controlled trial involving critically ill adults showed that the combination of high protein intake and resistance exercise was associated with better physical functioning, shortened length of ICU or hospital stay, and lower 6-month mortality than standard nutrition and routine physiotherapy.[77] Larger, well-powered trials are needed to confirm these findings. The role of medical nutrition therapy, including individualized nutrition counseling,[58] during the post-ICU recovery phase remains poorly defined, and future trials are needed to evaluate the effects of tailored nutrition prescriptions on long-term, patient-centered outcomes.

CONCLUSIONS

Nutrition therapy remains a cornerstone of supportive care for critically ill adults, particularly during the acute phase, when patients are unable to meet their nutritional needs through volitional intake. To support gut function, early enteral nutrition is recommended over early parenteral nutrition, but contemporary randomized, controlled trials suggest that early short-term parenteral nutrition is a safe option for critically ill adults who have contraindications to early enteral nutrition. Contemporary randomized, controlled trials suggest that early full-dose nutrition during the acute phase of critical illness increases the risk of adverse events and metabolic complications from enteral feeding, findings that support a cautious, restrictive approach to energy and protein delivery. Integration of precision nutrition — guided by biomarkers, monitoring of physiological signs, and multidisciplinary expertise — holds promise for improving outcomes and minimizing harm across the continuum of critical illness.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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