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Controversies Surrounding Critical Care Nutrition: An Appraisal of Permissive Underfeeding, Protein, and Outcomes

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Abstract

Over the past few years, numerous studies have called into question the optimal dose, timing, composition, and advancement rate of nutrition during the early acute phase of critical illness. These studies suggest permissive underfeeding with slow advancement may be more beneficial than aggressive full feeding. These counterintuitive results were possibly explained by enhanced autophagy, less hyperglycemia, or prevention of refeeding syndrome. This review underscores the controversies surrounding permissive underfeeding, aims to answer whether permissive underfeeding is appropriate for all critically ill patients, describes the impact of optimal protein delivery on critical care outcomes, discusses nutrition risk, and cogitates on the impact of nutrition on critical care outcomes. (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords

nutrition risk; permissive underfeeding; hypocaloric feeding; trophic feeding

The past 3 years have been difficult times for interpreting the literature and deriving an optimal strategy for providing nutrition therapy to the hospitalized, critically ill patient. Recent trials promoting starvation, trophic feeding, or avoidance of immunonutrition for patients in the intensive care unit (ICU) may be misinterpreted by healthcare providers that nutrition may not be as important as previously thought and provide the opportunity to revisit longstanding dogma. Now more than ever, nutritionists and clinicians need to understand the literature, appreciate the value of providing early enteral feeding in critical illness, and realize when it is appropriate to provide reduced energy and protein to the hospitalized patient.

One of the most contentious issues in understanding the literature is the argument over timing of initiation of nutrition therapy with a focus surrounding the first week of ICU admission. On one hand, an argument is made to avoid or reduce feeding that first week. The premise of this argument suggests that this time period represents the height of the disease process, inflammation, insulin resistance, and that intolerance to enteral feeding is likely. There is evidence full feeding may be harmful and that better outcomes may be achieved with underfeeding, although some of these data may have methodologic limitations. Some critical care experts have suggested outright starvation may be important to preserve autophagy.[1] And finally, age-old teleological concepts raise the argument that providing feeding early in critical illness disrupts the fight, fright, or flight response to injury.

An opposing argument is that the first week in the ICU is the most important time to provide feeding, as this is a window of opportunity by which early enteral nutrition (EN) can attenuate disease severity and hasten recovery from the systemic inflammatory syndrome (SIRS).[2] It is during this time that clinicians need to provide the nonnutrition benefits of nutrition therapy.

It remains unclear when the metabolic switch is turned off, and responses may vary from patient to patient. Arbitrarily, the second week of critical illness may be less contentious. There is a change in priorities during the second week; however, no randomized controlled trials (RCTs) have evaluated the effect of different energy or protein doses during the second week. An increasing caloric deficit implies a need for the nutrition benefits of feeding.[3] Efforts to convert from

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catabolism to anabolism implicate the need for full protein provision and optimal stimulation of protein synthesis and utilization. Tolerance of nutrition therapy, level of inflammation, and insulin resistance tend to improve with provision of modern critical care.

More recently, the issue over timing of nutrition has been extended beyond the first week to cover the entire "initial phase" of critical illness. These opposing arguments on whether to underfeed or fully feed may still be pertinent up to the point that the patient resolves the initial phase and turns the corner toward convalescence, at which time there seems to be greater consensus that complete energy and proteins requirements should be met.

Impact of Nutrition Therapy on Clinical Outcome

The impact of providing enteral feeding with regard to clinical outcome relates to 1 simple question. Does providing early enteral feeding compared with not providing that feeding improve patient outcomes? In studies asking this question, the treatment groups had EN initiated within 24–36 hours.[4] The control groups in these same trials did not receive early enteral feeding, either because they never received the enteral tube feeding (this is referred to as standard therapy, in which they were on their own to make it back to an oral diet), or there was intentional delay in initiation of tube feeding to the fourth day or beyond. The forest plots that were generated for the American Society for Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (SCCM) 2016 guidelines showed that providing early EN (rather than not providing that feeding) was associated with an absolute risk reduction in infection from 51.7% to 36.3% ($P = .03$) and an absolute reduction in mortality from 14.1% to 8.7% ($P = .05$).[4] The quality of evidence demonstrated by these forest plots has been criticized in that the studies represent smaller RCTs and that they were somewhat dated (being published from the late 1990s to 2012).[4]

What Is the Optimal Strategy of Feeding?

A number of strategies for feeding the critically ill patient have been proposed in the literature recently. Experts such as Schetz et al[5] and Marik[1] suggest that a brief period of starvation is important to support autophagy. At the other end of the spectrum, investigators such as McClave et al[6] and Heyland et al[7] recommend full-dose aggressive therapy through a Protein-Energy Provision via the Enteral Route in Critically Ill Patients (PEP-uP) protocol, getting to protein and energy goals as soon as possible over the first week of ICU admission. In between is a variation of strategies. Trophic feeding, in which only 10–20 mL/h of formula is provided, is a strategy supported by the Surviving Sepsis Campaign and the Acute Respiratory Distress Syndrome Network (ARDSNet) trial group.[8,9] A potpourri of trials exist under a more general term of *permissive underfeeding*, which can range from trials comparing under delivery of energy and protein to full feeding, to other studies where all patients get full protein and then are randomized to reduced vs full energy.[10–13] Several key issues have emerged from this literature, such as the determination of which macronutrients should be underdelivered, to what degree patients should be underfed, how fast the rate of infusion should be increased, and whether protein goals are more important than total energy goals.

The Argument for Starvation

The argument to have a brief period of starvation following admission to the ICU in the initial phase of critical illness is based on the notion that preservation of autophagy is of primary importance. Autophagy is an important physiologic process that provides 2 important functions to a cell that is bound by oxidative stress (eg, skeletal muscle cells, hepatocytes, intestinal epithelial cells).[14,15] The first function provided by autophagy is a housekeeping system for removing unfolded proteins, viruses, bacteria, and/or large organelles (such as damaged mitochondria).[15] A double-layered envelope encircles the large proteins (which are too large to be removed by the ubiquitin proteasome system), and the envelope is fused to a lysosome with lytic enzymes, which then leads to degradation of the protein into individual amino acids. The second function of autophagy provides a survival mechanism in which amino acids are recycled to make adenosine triphosphate (ATP) for energy and for protein synthesis to maintain cell structure. Because feeding suppresses autophagy, experts such as Schetz et al[5] and Marik[1] suggest a brief period of starvation and that "forced mandatory feeding" be avoided.

While autophagy certainly has potential benefit, that benefit may be limited in severe critical illness and should not be used to direct therapy. One issue is a time-dependent factor to autophagy, which has been described as the "autophagic switch." Only 2 forms of autophagy occur in mammals: macrophagic autophagy, which peaks at 4–6 hours, and chaperone-mediated autophagy, which peaks at 24 hours. This time-dependent factor suggests that autophagy is operative very early in critical illness. The second issue is one of a severity-dependent factor. In mild critical illness, factors such as endotoxin, oxidative stress, ischemia, or mitochondrial dysfunction stimulate autophagy, which maintains ATP production, removes damaged proteins, and improves cell survival. However, with increasing severity of illness, the same stimulatory factors lead to excessive autophagy, greater degradation of cytosolic proteins and organelles, and increased cell death. Identifying the transition point where autophagy converts from a homeostatic mechanism to a pathologic one is unclear. Autophagy operates in the absence of exogenous nutrients. In actuality, autophagy is a poor source for generation for ATP and new protein synthesis. Providing exogenous substrate through nutrition therapy results in much greater energy production and protein synthesis. Therefore, the argument to withhold nutrition therapy for multiple days to preserve a physiologic process, which is inefficient for generating energy

and stimulating protein synthesis and appears to be operative only during the early phase of mild critical illness, seems counterintuitive.

Are Clinical Outcomes Different for Underfeeding Compared With Full Feeding?

Nine published clinical studies have shown clinical outcomes are different when underfeeding is compared with full feeding.[12,16–23] Many of these studies were critically appraised in an earlier publication, but a brief summary is included here.[24] Unfortunately, these studies were methodologically limited and their results must be interpreted with caution. Is permissive underfeeding better than full feeding? This is an important question because, if true, it would mean that following ICU admission, patients should only receive underfeeding over the first week or throughout the initial phase of critical illness. Eight of these trials have shown improved outcome with underfeeding compared with full feedings, which would imply to the critical care practitioner that no patient should receive full feeding during the first week of critical illness.

Four observational trials by Krishnan et al,[17] Ash et al,[18] Arabi et al,[19] and Crosara et al[23] showed that when patients were divided into tertiles or quartiles based on delivery of energy and protein, the group that received the most nutrition had the worst outcome. In the study by Arabi et al,[19] the top tertile had twice the hospital mortality as the lowest tertile, a difference that reached statistical significance ($P = .02$). A subsequent study by Heyland et al[25] using the same methodology reproduced the same results. However, after adjusting for a single confounding factor (all oral feeding days), the data showed the opposite effect—greater delivery of nutrition was associated with lower hospital mortality. Two other single-center RCTs, one by Arabi et al[13] and the other by Braunschweig et al[26] (the Intensive Nutrition in Acute Lung Injury: Clinical Trial [INTACT]) showed that groups randomized to underfeeding had lower mortality than the group randomized to full or aggressive feeding. Both of these studies were at high risk for a type I α error. Indeed, the Arabi et al[13] trial was subsequently confirmed to have a type I error when a later larger multicenter trial by the same investigators using similar methodology showed no difference in mortality.[13] And finally, methodologic issues in 2 other trials, by Ibrahim et al[16] (bolus feeding into the stomach) and Casaer et al[21] (the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients [EPaNIC] trial with intravenous [IV] glucose loading and tight glucose control), reduced the applicability of these study results to clinical practice.[16,21]

Only 1 RCT showed worse outcome with underfeeding. Petros et al[22] compared permissive underfeeding (11.3 kcal/kg/d) with normocaloric feeding (mean, 19.7 kcal/kg/d) and demonstrated that permissive underfeeding was associated with a greater incidence of nosocomial infections (26.1% vs 11.1%, $P = .046$). The study was small (n = 100), and both groups received insufficient protein (0.4 vs 0.8 g/kg/d). The study was actually conducted nearly 10 years prior to publication, at a time when supplemental parenteral nutrition (PN) was readily added to EN, comprising ≥50% of energy/protein delivered beginning on day 1.[22] Applicability of these results to today's clinical practice is difficult.

Appropriateness of Various Methods of Underfeeding

Is it OK to start with trophic feeding? Four RCTs comparing underfeeding with full feeding have been published in the past few years and shown no difference in outcome between these 2 feeding strategies.[8,13,27,28] These trials have fewer methodologic limitations, and results would suggest that it is safe to provide trophic feeding the first week of critical illness and possibly through the entire initial phase of critical illness, with comparable results to full feeding.

A single-center RCT by Rice et al[27] in patients with acute respiratory distress syndrome (ARDS) receiving trophic EN compared with full EN demonstrated no difference in the primary outcome of ventilator-free days (VFDs) (median 23 days in both groups, $P = .90$), with a trend toward increased gastric intolerance in the full EN group (39.2% vs 26.5%, $P = .08$). In a multicenter RCT comparing trophic EN vs full feeding in patients with acute lung injury, the ARDSNet investigators showed no difference in the primary outcome of VFDs (14.9 vs 15.0 days, $P = .89$) or in 60-day mortality between groups (23.2% vs 22.2%, $P = .77$).[8]

In a smaller trial in trauma patients, Charles et al[28] randomized study patients to half energy provision (12.5–15 kcal/kg/d) vs controls, who were placed on full energy feeds (25–30 kcal/kg/d), with both groups receiving equal protein. There was no difference in outcomes between the 2 groups. The study was small (n = 86), with only half of the patients entered as determined by the power analysis, suggesting the potential for type II β error.

The largest study, the Permissive Underfeeding Versus Target Enteral Feeding in Adult Critically Ill Patients (PeRMIT) trial by Arabi et al,[13] was a multicenter RCT that compared enteral delivery of reduced (40%–60%) vs full (>70%) nonprotein energy, while providing full protein requirements to both groups in a mixed medical/surgical ICU setting.[13] PeRMIT was a robust well-designed multicenter RCT that randomized 894 patients across 7 centers in Saudi Arabia and Canada. The primary outcome, 90-day all-cause mortality, was no different between the 2 groups of patients, all of whom were followed for up to 6 months. There was no difference in secondary outcomes as well.

How Fast Should Feedings Be Advanced?

What is not clear and remains a matter of debate is how fast EN should be advanced following initiation. At what point should goal requirements be met? Two issues have been identified recently that would imply that a slower advancement toward

goal over the first week of ICU admission may be safer and more physiologic than rapid advancement to goal.

The first issue is that of endogenous glucose production, a physiologic process that is part of the response to critical illness and cannot be suppressed by providing nutrition therapy. During critical illness, oxidative stress is high and proteolysis and gluconeogenesis are the rules.[29] The amount of endogenous glucose production cannot be easily measured but probably decreases steadily over the first several days following admission. In the past, a focus on increasing caloric deficit led to aggressive delivery of nutrition therapy early in the first few days following ICU admission in an effort to minimize the caloric deficit.[3,30] Theoretically, the exogenous supply of energy via nutrition therapy is added to this endogenous glucose production. The combination of endogenous production and exogenous administration may result in inadvertent overfeeding early over the first week of critical illness. Thus, the strategy of providing hypocaloric feeding with slow advancement should avoid overfeeding, should be tolerated better, and should result in a more appropriate physiologic response.

A second issue related to the overly rapid advancement toward goal is evidence for refeeding syndrome. Refeeding syndrome may be more prevalent than previously thought in the ICU setting.[31] Patients at risk for refeeding syndrome are those who have been "nothing per os" for 7–10 days or longer, those with a low body mass index (BMI), or those who have experienced weight loss prior to admission.[32] Patients with congestive heart failure, those on mechanical ventilation, and those prone to hypercapnia may also be at increased risk. A wider spectrum of changes is now being appreciated with regard to the refeeding syndrome. Initiation of nutrition therapy is a stress to the patient, as Heymsfield et al[33] have shown, with increases in blood pressure, heart rate, minute ventilation, and maximal oxygen consumption seen in response to feeding. Such hemodynamic changes may unmask an underlying cardiomyopathy and precipitate congestive heart failure. Certainly with refeeding there are electrolyte shifts that can lead to gas exchange abnormalities. Low phosphorus levels causing a shift in the oxyhemoglobin disassociation curve can cause hemoglobin to reduce the release of oxygen to tissues. Insulin resistance and reduced white blood cell function are seen in refeeding syndrome, putting patients at increased risk for infection and respiratory failure. Evidence for these changes were seen in a study published by Doig et al[34] in which patients in an ICU setting on mechanical ventilation who demonstrated phosphorus levels <0.65 mmol/L were randomized to standard aggressive feeding vs a slow advancement by 20% increments to goal over a 4- to 5-day period. Results showed significantly greater difficulties in maintaining phosphate levels on the second and third days in the group receiving traditional aggressive feeding. Also, infection was twice as high in the standard traditional group at 16% vs 8% in the group randomized to slow advancement ($P = .01$).[32] While there was no difference in organ failure or duration of mechanical ventilation, there was an immediate separation in survival curves. Patients randomized to the traditional aggressive feeding strategy showed significantly lower survival compared with the study group with the slow advancement.[32] After the study, evidence of refeeding was seen by increasing difficulties with hypokalemia in 27% of patients, increasing hyperglycemia in 52%, increasing respiratory failure in 91%, and increased diuretic need in 30% of patients.[32] These issues of endogenous glucose production and the unmasking of refeeding syndrome would imply that slower advancement of EN is more appropriate over the first week of hospitalization in the ICU.

Protein Delivery

A large prospective international study of nutrition practices demonstrated that ICU patients achieve approximately 60% of recommended protein intake.[34] Falling short on delivering protein is important to acknowledge because emerging data suggest protein may be the energy component that matters. ICU patients represent a heterogeneous group, yet 1 feature they share in common is the presence of metabolic stress. Stress invariably induces proteolysis and loss of lean muscle mass, which extends beyond ICU discharge.[35–37] Using ultrasonographic, histologic, and biochemical assessments, Puthucheary et al[38] showed that the cross-sectional area of the rectus femoris muscle was reduced by 12.5% over the first week of hospitalization in the ICU and by 17.7% at day 10. Although 1.2 g/kg/d of protein should be provided to offset this loss, it is not clear if it (or higher doses) improves clinical outcome.[4,36]

Prospective observational data suggest that achieving the prescribed protein target during critical illness is more likely to improve ICU outcomes than meeting energy goals.[39–44] Weijs et al[39] studied 886 patients in a mixed medical/surgical ICU at a single center between 2004 and 2010 to determine the effects of a nutrition-targeted approach on clinical outcomes. EN was started within 24 hours and protein was provided at 1.2–1.5 g/kg/d. Those who reached both their protein and energy target had reduced 28-day mortality, whereas those who reached energy target only did not.[39] In a second observational study by Allingstrup et al,[40] results showed that increasing delivery of protein was associated with improved survival in a stepwise dose-dependent manner. In a third observational trial, Nicolo et al[42] analyzed 2824 critically ill patients who remained in the ICU for at least 4 days to evaluate the impact of actual protein delivery on mortality. Only when critically ill patients received ≥80% protein target was a reduction in mortality observed.[42] In a fourth retrospective observational single-center study, Zusman et al[45] demonstrated increasing protein (as a percentage of requirement) was associated with reduced 60-day mortality. More recently, Compher et al[43] demonstrated the odds of death decreased significantly by 6.6% with each 10% increase in protein intake relative to goal for high-risk patients who remained in the ICU for at least 4 days ($P = .003$) and 10.1% with each 10% increase in protein intake relative to goal in

high-risk patients who remained in the ICU for at least 12 days (P = .003). High risk was defined by a Nutritional Risk in Critically ill (NUTRIC) score of >5 (see discussion of risk below). These observational studies draw inferences about the effect of protein on outcomes and may be limited by unmeasured confounders.

These results from observational trials have led some clinicians to suggest that IV amino acids or protein provided in the form of supplemental PN should be added to insufficient EN to optimize outcome. However, results from RCTs would suggest little added benefit is seen from such strategies. In the NephroProtect study by Doig et al,[46] patients were randomized to receive supplemental IV amino acids plus EN therapy vs controls receiving only EN. At the end of the trial, the only significant outcome was an improvement in creatinine clearance on day 4 in the group receiving IV amino acids. No other outcome parameters were different between groups.[46] In the Trial of Supplemental Parenteral Nutrition in Underweight and Overweight Critically Ill Patients (TOP-UP; presented at Clinical Nutrition Week 2016), patients started on early EN were randomized to supplemental PN with a focus on achieving protein goals vs controls receiving EN alone. No differences in outcomes were seen between the 2 groups.[47] Similar findings were observed in the Heidegger et al[48] Supplemental Parenteral Nutrition (SPN) trial in which patients receiving insufficient nutrition therapy were randomized to receive supplemental PN added to EN vs EN alone. Results showed no difference in clinically important outcomes between the 2 groups (only a significant reduction in "other infections" was seen in the intervention arm).[48]

Getting to the protein goal may be more important than achieving the energy goal, although the time to get to either goal is not clear. With full protein delivery, varying the percentage of goal energy provided may not make much difference in outcome. Rugeles et al[49,50] conducted 2 trials to support this concept. In 1 trial, both groups of critically ill patients were given equal doses of protein at 1.4 g/kg/d and then randomized to low vs high caloric delivery (12.0 vs 19.2 kcal/kg/d).[49] There was no difference in outcome between the 2 groups. In the other trial, critically ill patients were randomized to high vs low protein (1.5 vs <1.0 g/kg/d).[50] The group that received more protein actually received less energy than controls (15 vs 25 kcal/kg/d).[50] The group getting more protein showed a significant reduction in severity of illness (measured by Sequential Organ Failure Assessment [SOFA] score) at 48 hours despite receiving less energy.[50] These findings would suggest that provision of high-protein hypocaloric feeding with a slower ramp-up over the first week may be the optimal strategy. The point at which caloric goal should be attained is not clear.

Discussion of Risk

The question that seems to linger is the following: should *all* critically ill patients be underfed during the first week of critical illness? The intuitive answer is "no" since critical illness represents a heterogeneous patient population. In fact, some ICU patients may have nothing to gain from early nutrition interventions, while other patients may only derive outcome benefit from early aggressive nutrition therapy that meets target goal feeding.

Including some form of nutrition risk calculation in the clinician's nutrition assessment may help differentiate these patients. Calculating nutrition risk does several things: (a) it forces clinicians to address the dual nature of nutrition risk, that both disease severity and nutrition status drive risk; (b) it may predict which patient will have worse tolerance issues to the delivered EN; (c) it may direct which patient needs to get to goal earlier; and (d) it may identify those patients whose outcomes are more likely to improve in response to early aggressive nutrition therapy.

With the wide spectrum of nutrition risk seen in medical and surgical ICUs, intuitively the value derived and clinical benefits seen in response to nutrition therapy are highly variable. Nonnutrition benefits from early enteral feeding include gastrointestinal, immune, and metabolic responses to EN.[2] These benefits are experienced by most, if not, all ICU patients and are probably achieved by trophic doses of enteral feeding. Nutrition benefits of feeding are different and are probably seen in only a subset of patients admitted to the ICU, who may already be compromised with regard to nutrition status when they experience the insult that necessitates ICU admission. These patients may have reduced lean body mass or sarcopenia or may have micronutrient deficiencies from a poor diet because of preexisting illness or chronic substance abuse. Ironically, this latter subset of patients may have greater oxidative stress and be at increased risk for refeeding syndrome, such that the benefits of providing full energy and protein requirements need to be weighed against potential harm.

Heyland et al[51] proposed and validated the NUTRIC score. Worldwide, critically ill patients who were identified as being nutritionally "at risk" by the NUTRIC score and possibly in most need of full feeding failed to receive optimal energy and protein targets.[51,52] Rahman et al[53] demonstrated a strong positive association between nutrition adequacy and 28-day survival in patients with a NUTRIC score of ≥6.[53] Arabi et al,[54] however, called into question the ability of the NUTRIC score to identify nutrition risk. They conducted a post hoc analysis of the PeRMIT study to examine the effect of permissive caloric underfeeding compared with standard feeding on 90-day mortality in critically ill adults stratified by the NUTRIC score and other common measures of nutrition risk.[54] The authors concluded that the NUTRIC score could not predict which patients would have a negative or positive response in clinical outcome from permissive underfeeding.

Clearly, evaluating malnutrition in critically ill patients requires nutrition parameters, not only physiologic parameters. For example, a decrease in weight or oral intake before ICU admission, prolonged hospitalization before ICU admission,

and BMI <18.5 kg/m^2 may be important risk factors for poor ICU related outcomes. In addition, phase angle reflecting fat-free mass, as measured by bioelectrical impedance analysis, is associated with increased 28-day mortality.[55] Nutrition risk is an emerging concept, and a simple tool that precisely and accurately identifies preexisting malnutrition and disease severity is lacking. Whether it helps direct nutrition therapy or identify those patients likely to improve outcomes from feeding closer to goal remains to be seen.

Conclusion and Future Insights

What makes interpretation of the literature difficult is that as medical care improves in the ICU, the mortality drops. Such a trend makes it harder to tease out the treatment effect of any single aspect of therapy. Over the past 30 years of trials by the ARDSNet group, mortality in the control group has steadily decreased from close to 70% approximately 30 years ago to now around 20%.[56] The drop in mortality hopefully reflects improvements in critical care, such as low tidal volume mechanical ventilation, conservative fluid management, early goal-directed therapy, and sedation vacations. Improvements in nutrition therapy hopefully have contributed to this reduced mortality, as an emphasis on PN initially was replaced by a focus on delivery of early enteral feeding and, more recently, appropriate delivery of reduced energy and adequate protein. The problem is, as the mortality drops, it is more difficult to show a treatment effect from nutrition therapy. Larger and larger trials are required, which are costly and difficult to conduct.

Even the large, well-designed, multicenter PeRMIT trial may have been underpowered. The event rate for 90-day mortality predicted in the power analysis was accurate at 25% in the full feeding group, as the actual mortality demonstrated in the study was 29% (indicating that there was no event rate inflation).[13] However, the response to treatment from underfeeding (the δ rate) predicted in the power analysis was overestimated at 8%, as the reduction in mortality seen in the actual study was only 1.7%, indicating δ rate inflation.[13] The implications of δ rate inflation on interpretation can be huge. Since a power analysis determines the sample size, observed δ rate inflation would indicate the sample size was underestimated and an ostensibly "large" study is actually underpowered.[57] Consequentially, clinicians may misinterpret results of permissive underfeeding studies, concluding that nutrition therapy must have little effect on outcome.

What commonalities of agreement have emerged from the recent push for underfeeding during the first week or initial phase of critical illness? Not all ICU patients are equivalent. There is value in identifying the dual nature of nutrition risk to help predict which patients may benefit from achieving prescribed energy and protein goals sooner. Studies of underfeeding provide the clinician with a reasonable starting point for all patients, irrespective of nutrition risk. The nonnutrition benefits of EN on modulation of metabolic responses to stress, maintenance of intestinal defense, and promotion of commensal behavior of the microbiome may be achieved by underfeeding or even trophic feeding. Nutrition therapy can be started at a lower dose (permissive underfeeding), which avoids the deleterious consequences of overfeeding, hyperglycemia, gastrointestinal intolerance, and refeeding syndrome. If protein goals are met, advancing to caloric goal may be less important.

A number of questions remain unanswered. How quickly and in which patient to achieve the full energy target early in critical illness remain points of contention. Do the implications of permissive underfeeding apply only to the first week or to the entire initial phase of critical illness? How is resolution of the initial phase identified? Is there overreliance on large but still underpowered RCTs?

Certainly, large RCTs are needed to determine the impact of optimizing protein, energy, or both in critically ill patients. While outcomes such as change in severity of illness, VFDs, and mortality serve as important end points for the researcher, the critically ill patients are left wondering what "optimizing nutrition" really means for their acquired disability. Core domains such as physical functioning and quality of life should be considered to evaluate nutrition interventions in the ICU setting. A modified framework to organize and evaluate core domains (with core outcomes) has been developed for nutrition research.[58] For example, protein balance and histological muscle changes can be used to assess pathology and impairment during critical illness while the 6-minute walk test can be measured to identify participation restriction.[58] As survival after critical illness continues to improve, these core domains and outcomes may be more valuable (for the patient, researcher, and clinician).

Statement of Authorship

J. J. Patel drafted the manuscript. All authors contributed to the conception and outline of the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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