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INVITED REVIEW

Nutrition dose in the early acute phase of critical illness: Finding the sweet spot and heeding the lessons from the NUTRIREA trials

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Abstract

The landmark NUTRIREA-2 and NUTRIREA-3 trials compared the route and dose of nutrition, respectively, in critically ill patients with circulatory shock. The results of both trials support a "less-is-more" paradigm shift in the early acute phase of critical illness. In this review, the authors outline and appraise the results of the NUTRIREA-2 and NUTRIREA-3 trials, introduce the concept of identifying the "sweet spot" for nutrition dose based on severity of illness/nutrition risk and nutrition dose, and identify the unintended consequences of delivering full-dose nutrition in sicker critically ill patients during the early acute phase of critical illness.

KEYWORDS
circulatory shock, critical illness, enteral nutrition, nutrition support, nutrition therapy, parenteral nutrition

INTRODUCTION

Circulatory shock represents one of the most common reasons for intensive care unit (ICU) admission and poses a conundrum for timing and dose of enteral nutrition (EN).[1] On one hand, early EN has been shown to preserve gut barrier functions, and on the other hand, introducing luminal nutrients into a hypoperfused gut may increase the risk of enteral feeding intolerance (EFI), including the gravest consequences of nonocclusive mesenteric ischemia and bowel necrosis.[2] The past two decades have provided the critical care nutrition community with well-designed multicenter randomized controlled trials testing EN dose in critically ill patients, including EDEN, PERMIT, and TARGET.[3–5] However, these trials did not exclusively test EN dose on critically ill patients with circulatory shock, which limits the generalizability of findings from these trials and constrains societal critical care nutrition guidelines' recommendations.[6] Here, we present an overview and appraisal of the NUTRIREA-2 and NUTRIREA-3 trials; discuss the concept of identifying the "sweet spot," based on severity of illness and nutrition dose, where nutrition may have a positive impact on outcomes; and identify the harms of full-dose nutrition during the early acute phase of critical illness in sicker critically ill patients with shock who are undergoing mechanical ventilation.

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AN OVERVIEW AND APPRAISAL OF THE NUTRIREA-2 AND NUTRIREA-3 TRIALS

In 2018, Reignier and colleagues reported the results of the NUTRIREA-2 trial, which was the first large multicenter trial to test early EN (relative to early parenteral nutrition [PN]) in patients with circulatory shock undergoing mechanical ventilation.[7] NUTRIREA-2 was a well-designed pragmatic trial with high internal and external validity. The robust trial enrolled >4000 patients with circulatory shock who were undergoing mechanical ventilation across 44 ICUs in France.[7] Approximately two-thirds of patients had septic shock with a mean norepinephrine dose of 0.5 mcg/kg/min, and patients received the assigned intervention within 24 h of ICU admission.[7] Overall, there were no between-group differences on the primary outcome of 28-day mortality. However, the early EN group, which was prescribed full-dose (received 17.6 kcal/kg/day) EN within 24 h of randomization, experienced significantly more gastrointestinal complications, including a higher rate of clinically relevant bowel ischemia, compared with the early-PN group (2% vs <1%; $P = 0007$).[7] NUTRIREA-2 informed the critical care nutrition community that introducing early full-dose EN in patients with circulatory shock undergoing mechanical ventilation and receiving high-dose norepinephrine during the acute phase of critical illness might be harmful.

In 2023, Reignier and colleagues reported the results of the NUTRIREA-3 trial, which compared low-dose (6 kcal/kg/day and 0.2–0.4 g/kg/day protein) with standard-dose (full-dose) nutrition (25 kcal/kg/day and 1.0–1.3 g/kg/day protein) during the first 7 days of ICU stay in critically ill patients with circulatory shock undergoing mechanical ventilation to test the hypothesis that early energy and protein restriction improved outcomes in these patients, compared with standard energy and protein targets.[8] NUTRIREA-3 was another robust pragmatic multicenter trial that included 3044 critically ill patients with circulatory shock undergoing mechanical ventilation across 61 French ICUs, including 34 university hospitals.[8] The patients were well matched at baseline and represented a sick population (mean Sequential Organ Failure Assessment [SOFA] score of 10) with a high burden of inflammation (more than half had septic shock, and the median C-reactive protein [CRP] level on days 0–2 was >100 mg/dl) and 90-day mortality of 42%.[8] Study protocol compliance was high, such that nutrition support was started early within 17 h of intubation and reached target nutrition goals within the next 24 h.[8] The route of feeding was similar in both groups. Nearly 60% in each group received exclusive EN, and 23% in each group received exclusive PN.[8] The low-dose group reached target nutrition dose within 24 h. More importantly, the standard-dose group reached 88% of energy and 90% of protein goals within 24 h, a key accomplishment that allowed for significant separation between the two groups.[8]

Overall, there were no between-group differences in the two primary outcomes (90-day mortality and time to readiness for ICU discharge). The low-dose nutrition group, compared with a standard dose, had a trend toward improved ICU mortality (32.7% vs 29.5%; $P = 0.051$) and time to weaning from vasopressors (hazard ratio [HR], 1.07; 95% confidence interval [CI], 0.99–1.15; $P = 0.054$) and significantly improved time to wean from invasive mechanical ventilation (HR, 1.12; 95% CI, 1.03–1.22; $P = 0.007$).[8]

Importantly, and as observed in NUTRIREA-2, the standard-dose nutrition group, compared with the low-dose group, had a higher incidence of gastrointestinal complications, including vomiting (21.3% vs 14.2% during the first 7 days; $P < 0.001$) and overall bowel ischemia (1.8% vs 0.9%; $P = 0.030$), and more prokinetic drug therapy use (20.9% vs 13.1%; $P < 0.001$).[8] In addition, the standard-dose nutrition group, compared with the low-dose group, had worse daily glycemic control and more daily insulin use.

FINDING THE SWEET SPOT FOR NUTRITION DOSE

What explanations could account for the potentially harmful findings from the NUTRIREA-2 and NUTRIREA-3 trials? It must be acknowledged that a wide array of conditions can (sometimes unpredictably) induce critical illness in individuals with varying degrees of preexisting disease. Furthermore, the critical illness–defining conditions, such as sepsis, have varying phenotypes with different trajectories.[9] Therefore, no two ICU patients nor their critical illness trajectories are identical, and the "sweet spot" for benefit of nutrition therapy in critically ill patients may depend on the severity of illness, nutrition dose, nutrition route, and clinical outcome (Figures 1 and 2).

Figure 1 demonstrates the theoretical relationship between severity of illness and/or nutrition risk and potential for benefit from delivering early full-dose nutrition. For trials on the left side of the graph that enroll patients with only a mild to moderate degree of illness, full-dose nutrition therapy may show little benefit.[10,11] For example, the PYTHON trial showed no difference in outcomes between early EN by feeding tube within 24 h of admission and an oral "on-demand" diet within 5 days per patient wishes in patients with acute pancreatitis, 83% of whom were on the ward with mild to moderate disease.[10] In the EPANIC trial, nutrition therapy using EN and early supplemental PN showed no benefit (and actually showed net harm) compared with lower-dose nutrition therapy with delayed supplemental PN in a group mostly comprising patients undergoing elective cardiovascular surgery (who may have needed little nutrition support).[11] For trials on the right side of the graph that enrolled patients with much greater disease severity, the chances for benefit from higher-dose nutrition therapy may be diminished (and may even be harmful). Patients in the NUTRIREA-2 and NUTRIREA-3 trials had a mortality rate of 35%–42% and showed little benefit (and potential harm) from full nutrition support.[8,12] In between, there may be a "sweet spot" or a point of peak benefit for those trials that enrolled patients with a moderately severe degree of illness and/or nutrition risk. In the Swiss EFFORT trial, hospitalized malnourished inpatients (defined by Nutrition Risk Screening-2002 score ≥3) were randomized to a nutrition protocol with stepwise advancement of nutrition support, with oral nutrition, EN, and PN showing benefit compared

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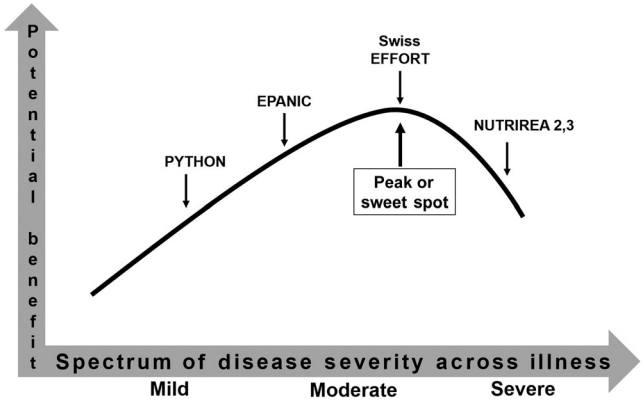

FIGURE 1 The potential benefit of high-dose nutrition based on the spectrum of disease severity and nutrition risk. In the PYTHON study, >80% of enrolled patients with acute pancreatitis were patients in the general ward with mild to moderate disease and did not actualize the benefit of aggressive nutrition. Similarly, in the EPANIC trial, >60% were patients undergoing elective cardiothoracic surgery who did not actualize the benefit of aggressive nutrition during the early acute phase of critical illness. In the Swiss EFFORT trial, that enrolled patients in the general ward who were at high nutrition risk, those randomized to aggressive nutrition support had an improved 30-day mortality, compared with those randomized to standard of care. In contrast, in the NUTRIREA-2 and NUTRIREA-3 trials, enrolled patients had severe critical illness, and pushing aggressive nutrition in patients with severe critical illness during the early acute phase of critical illness reduced the potential for benefit (and increased the risk of harm; see Figure 2).

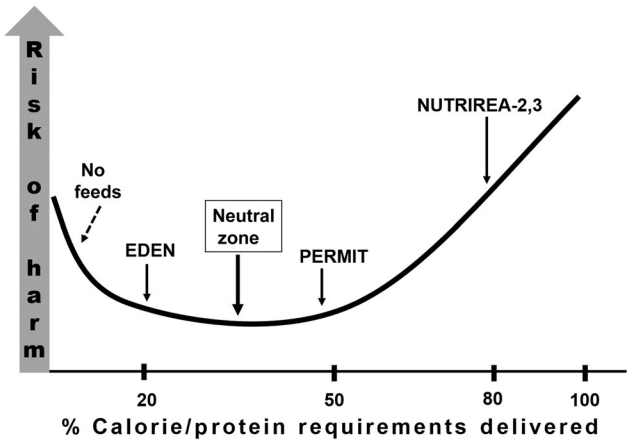

FIGURE 2 Risk of harm with percentage of energy and protein delivered in contemporary randomized controlled trials testing nutrition doses during the early acute phase of critical illness. In the EDEN study, trophic-dose enteral nutrition at a rate of 20 ml/h was delivered in the intervention arm. In the PERMIT trial, 40%–60% of goal energy was delivered in the intervention arm. In the NUTRIREA-2 and NUTRIREA-3 trials, full-dose nutrition resulted in significantly more harm, compared with early PN in NUTRIREA-2 and low-dose nutrition in NUTRIREA-3.

with hospital food only, translating to a 3% absolute risk reduction in 30-day mortality (adjusted odds ratio, 0.65; 95% CI, 0.47–0.91; $P = 0.011$).[13] Survivors of critical illness who have anabolic potential may represent a population in whom the "sweet spot" shifts and patients may benefit from an aggressive, goal-directed nutrition prescription.

RATIONALE FOR LACK OF BENEFIT WITH FULL-DOSE NUTRITION IN NUTRIREA-3

Why was early full-dose nutrition found not to be beneficial in NUTRIREA-3? The physiology of the early acute phase is characterized by high levels of inflammation, oxidative stress, and mitochondrial dysfunction, which may explain why standard-dose nutrition was not beneficial for patients in NUTRIREA-2 and NUTRIREA-3. Serum CRP level and SOFA score have been used to stratify inflammation and severity of illness, respectively.[14,15] In a recent secondary analysis of the Swiss EFFORT trial, Merker and colleagues stratified inflammatory status using CRP and found no benefit of full-dose nutrition support in those with CRP > 100 mg/L, with perhaps a trend toward harm.[13] In NUTRIREA-3, the mean CRP was >100 mg/L on days 0–2 in both groups. In NUTRIREA-2 and NUTRIREA-3, the mean SOFA scores were ≥10, corresponding to a predicted mortality of >40%. In the EFFORT protein trial, Heyland and colleagues found a higher protein dose was associated with worse outcomes in a subgroup of patients with a SOFA score of >9.[16] These data suggest early full-dose nutrition, irrespective of vasopressor dose, in sicker patients is not beneficial. The early acute phase of critical illness is also marred by anabolic resistance. Chapple and colleagues found protein delivered to critically ill patients during the acute phase of critical illness was digested and absorbed but failed to stimulate muscle protein synthesis.[17] Puthucheary and colleagues found pushing protein in severe illness increased the urea-to-creatinine ratio (a surrogate of dysfunctional mitochondria unable to metabolize ammonia) with associated muscle toxicity and demonstrated impaired post ICU recovery.[18,19] After EDEN, PERMIT, and TARGET, the results of the NUTRIREA-3 trial have shown little benefit from full-dose nutrition during the acute phase of critical illness. It is likely the patients in the NUTRIREA-3 trial were positioned toward the right side of the curve in Figure 1 (beyond the sweet spot) and were unlikely to benefit from full-dose nutrition therapy during the early acute phase of critical illness.

UNINTENDED CONSEQUENCES FROM FULL-DOSE NUTRITION IN THE EARLY ACUTE PHASE OF CRITICAL ILLNESS

Figure 2 demonstrates the theoretical relationship between the dose of nutrition therapy and the potential for harm in contemporary trials enrolling patients with severe critical illness. The graph shows that failure to provide any EN, represented on the left side of the curve, may increase harm through loss of gut integrity, disordered immune

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responses, and the bloom of a virulent pathobiome.[20,21] A "neutral zone" may exist somewhere between the delivered nutrition in the low-dose group of patients in the EDEN (approximately 20% of energy requirements) and PERMIT trials (40%–60% of requirements), where risk of causing harm changes very little. In contrast, pushing the nutrition dose beyond 50% of energy/protein requirements in the early acute phase of severe critical illness, shown on the right side of the curve, may lead to net harm. In contrast to the EDEN and PERMIT trials, the NUTRIREA-2 and NUTRIREA-3 trials found pushing the nutrition dose beyond the "sweet spot" in sicker patients during the early acute phase of critical illness may generate unintended consequences (Table 1), contributing to worse outcomes in this group.

First, early full-dose EN in severely critically ill patients may increase the risk of "unwanted baggage" in the form of EFI.[22,23] In addition, sepsis represents the sine qua non of heightened and dysregulated host inflammatory response (to an infection), and delivering full-dose EN to septic patients may further increase the risk for EFI.[24] In NUTRIREA-2 and NUTRIREA-3, more than half of patients had shock secondary to sepsis.[8] Clinically, EFI manifests with nausea, vomiting, abdominal distention, constipation, reduced percentage of goal energy/protein delivered, and increased need for use of prokinetic agents. As mentioned earlier, patients in NUTRIREA-3 who received full-dose nutrition, compared with a low dose, had higher rates of vomiting (21.3% vs 13.2%; $P < 0.001$) and more prokinetic drug use (20.9% vs 13.1%; $P < 0.001$).[8]

Second, pushing full-dose nutrition in patients with risk factors for refeeding syndrome may be harmful. In a 2015 trial, Doig and colleagues compared rapid advancement of EN dose to a slower ramp-up in critically ill patients who showed a reduction in serum phosphate out of the reference range following initiation of nutrition therapy.[25] The trial found a higher 60-day mortality in the rapid advancement group group.[25] In NUTRIREA-3, the standard-dose group, compared with the low-dose group, had a higher rate of hypophosphatemia (61.3% vs 53.6%; $P < 0.001$), which was not explained by the low incidence of malnutrition in both groups, but the risk factors may have been concealed within the 70% of patients who had preexisting illness at ICU admission.[8]

Third, delivering full-dose EN in critically ill patients with circulatory shock (receiving vasopressor support) may increase the risk of bowel ischemia.[2] In NUTRIREA-2, all patients randomized to early EN achieved the full dose within 24 h and had a higher rate of bowel ischemia, compared with those randomized to early PN (2% vs <1%, $P = 0007$).[7] In NUTRIREA-3, approximately 60% of patients received early EN, and those who received full-dose nutrition, compared with a low dose, had a higher rate of bowel ischemia (1.8% vs 0.9%, $P = 0.03$).[8] Furthermore, bowel ischemia may also be a function of vasopressor dose. In a secondary analysis of the EFFORT protein trial of 621 patients in circulatory shock receiving a median of 13 kcal/kg/day (0.4–31.1 kcal/kg/day) and a median norepinephrine-equivalent dose of 0.2 mcg/kg/min (0–9.3 mcg/kg/min), those patients who received early EN (within 48 h of ICU admission), compared with delayed (>48 h), had improved clinical outcomes and no difference in gastrointestinal complications.[26] In NUTRIREA-2, the median norepinephrine dose in the EN group was 0.56 mcg/kg/min (0.3–1.20 mcg/kg/min), and in NUTRIREA-3, it was 0.50 mcg/kg/min (0.25–0.99 mcg/kg/min), suggesting a higher vasopressor dose coupled with full-dose EN may be the impetus for the observed gastrointestinal complications.[7,8]

Fourth, early in the acute phases of critical illness, endogenous glucose production (EGP) by the liver pours glucose into the circulation, and akin to catabolism of muscle, the degree of EGP is

TABLE 1 Unintended consequences of introducing high-dose nutrition in patients with severe critical illness during the early acute phase of critical illness.

Unintended consequence	Clinical manifestation(s)	NUTRIREA-3 findings (low- vs high-dose nutrition)
Enteral feeding intolerance	Vomiting	−13.2% vs 21.3% ($P < 0.001$)
	Prokinetic drug use	−13.1% vs 20.9% ($P < 0.001$)
Imbalance between gut oxygen supply and demand	Bowel ischemia	−0.9% vs 1.8% ($P = 0.03$)
Refeeding syndrome	Hypophosphatemia	−61.3% vs 53.5% ($P < 0.001$)
	Prolonged MV	Time to wean MV: 5 vs 6 days ($P = 0.007$)
Insulin resistance	Hyperglycemia	Daily glucose: 11.6 vs 13.6 mmol/L ($P < 0.001$)
	Insulin utilization	Cumulative insulin use: 63.1% vs 77.7% ($P < 0.001$)
Mitochondrial dysfunction	Lactic acid normalization	−86.5% vs 84.1% ($P = 0.01$)
	Persistent organ failure	−ΔSOFA: −0.08 (95% CI, −0.13 to −0.02; $P = 0.008$)
Inhibition of autophagy	Muscle function/quality	Not reported
Fluid overload	Impaired weaning from MV	Time to wean MV: 5 vs 6 days ($P = 0.007$)

Note: All clinical manifestations in the NUTRIREA-3 trial were worse in the high-dose nutrition group, compared with the low-dose group.
Abbreviations: CI, confidence interval; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment.

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a function of oxidative stress and cannot be mediated or diminished by nutrition strategies. Full-dose exogenous feeding added to the EGP may result in overfeeding, worsening control of hyperglycemia, and a deleterious effect on clinical outcomes.[27–29] In NUTRIREA-3, patients receiving early full-dose nutrition, compared with a low dose, had a higher median glucose value (daily glucose, 13.7 [11.2–17.1] vs 11.6 mmol/L [9.2–14.5]; $P < 0.001$) and more cumulative insulin use (77.7% vs 63.1%; $P < 0.001$).[8]

Fifth, there is a linear relationship between the severity of illness and mitochondrial dysfunction.[30] Unable to meet the demands for adenosine triphosphate (ATP) with increasing degrees of oxidative stress, mitochondria "hibernate" and reduce the percentage of respiration linked to the production of ATP, a self-preserving cellular process that occurs at the expense of an adverse effect on organ systems seen clinically as worsening multiple organ failure.[31–33] With disruption of the electron transport chain, the dysfunctional mitochondria become more dependent on the Cori cycle to meet energy needs, and as a result, serum lactate levels rise. In this situation, early full-dose exogenous nutrition increases the demand for ATP and reduces the chance for benefit on clinical outcomes. In NUTRIREA-3, patients receiving early full-dose nutrition, compared with a low dose, had a lower cumulative incidence of lactate normalization (84.1% vs 86.5%; $P = 0.01$), and slower decrease in the SOFA score (mean difference, −0.08; 95% CI, −0.13 to −0.02, $P = 0.008$), suggesting delayed return of mitochondrial function and resolution of multiple organ failure.[8]

Sixth, early full-dose nutrition may impair liberation from mechanical ventilation via two mechanisms: volume overload and increased carbon dioxide (CO_2) production. In the 2006 Fluids and Catheter Treatment Trial (FACTT), 1000 adults with acute lung injury receiving mechanical ventilation were randomized to a conservative ($n = 503$) or liberal ($n = 497$) fluid management strategy.[34] Patients randomized to a liberal fluid strategy had a cumulative +6992-ml fluid balance at 7 days, compared with −136 ml in the conservative group.[34] The conservative-strategy group, compared with the liberal strategy, had more days alive and both off the ventilator and out of the ICU.[34] In NUTRIREA-3, the early full-dose nutrition group had a median daily 17.2 L of fluids (9.7–23.4 L), compared with 11.1 L (6.1–16.4 L) in the low-dose group.[8] It is unclear if the volume provided in the nutrition therapy accounted for the greater daily fluid intake in the early full-dose group. In addition, excess energy may increase CO_2 production and thus minute ventilation, but this may not be clinically significant unless energy provision exceeds requirements and lipogenesis occurs.[35] Nonetheless, the early full-dose group, compared with the low-dose group, had delayed time to weaning from mechanical ventilation (HR, 1.12; 95% CI, 1.03–1.22; $P = 0.007$), albeit it an environment without standardized weaning protocols at the enrolling sites.[8] Because weaning from mechanical ventilation was the primary determinant of time to readiness for discharge, the higher daily fluid balance (and perhaps an increased ventilatory requirement) in the full-dose group, compared with the low-dose group, might explain the 1-day difference between groups in the time to readiness for discharge (HR, 1.12; 95% CI, 1.02–1.22; $P = 0.015$).[8]

Seventh, autophagy is a host housekeeping and recycling process that clears cellular damage and is thought to provide an important benefit in maintaining muscle health and improving post-ICU recovery.[36] Delivery of exogenous nutrients, especially parenteral amino acids, inhibits autophagy.[30] Theoretically, higher-dose nutrition therapy would lead to greater inhibition of this protective process and possibly contribute to reduced post-ICU rehabilitation.

CONCLUSION

To date, the NUTRIREA trials represent two robust critical care nutrition trials conducted by a premier critical care nutrition research group. The lessons learned from the NUTRIREA trials include the following: (1) Introducing full-dose EN in critically ill patients with circulatory shock undergoing mechanical ventilation and receiving high-dose vasopressor in the early acute phase of critical illness is potentially harmful. (2) Low-dose nutrition is not superior to full-dose nutrition during the early acute phase of critical illness but represents a more appropriate and potentially less harmful approach. (3) Reducing the EN dose and supplementing it with PN or delivering full-dose exclusive PN may not be the answer, as patients with severe critical illness would still be at risk for many of the harms previously mentioned. (4) The results should not be misinterpreted that any early EN is dangerous. In a secondary analysis of the NUTRIREA-2 trial, Piton and colleagues found patients randomized to early EN, compared with PN, had higher plasma citrulline concentration and intestinal fatty acid binding protein, the former suggesting early EN preserves enterocyte mass and function and the latter reflecting enterocyte damage.[37] However, the optimal timing and dose of EN remain unclear, and it may be possible that even lower doses in very sick patients during the early acute phase of critical illness may be as efficacious (and less harmful). (5) Early EN likely has a heterogeneity of treatment effect in patients with circulatory shock, and further trials are needed to establish safe and efficacious dose (including consideration of nonnutrition energy intake) in subgroups, including those with varying severities of septic shock, in which the gut-protective effects of early EN would need to be balanced by the potential harm. Following in the footsteps of EDEN, PERMIT, and TARGET, the NUTRIREA-2 and NUTRIREA-3 trials weave valuable threads into the fabric of the evidence base for critical care nutrition by challenging existing practices and contributing to an emerging "less-is-more" paradigm during the early acute phase of critical illness.

AUTHOR CONTRIBUTIONS

Jayshil J. Patel: Conceptualization (lead); writing—original draft (lead); writing—review and editing (equal). **Todd W. Rice**: Conceptualization; writing—reviewing and editing (equal). **Manpreet S. Mundi**: Conceptualization; writing—reviewing and editing (equal). **Christian Stoppe**: Conceptualization; writing—reviewing and editing (equal). **Stephen A. McClave**: Conceptualization (supporting); writing—original draft (supporting); writing—reviewing and editing (equal).

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CONFLICT OF INTEREST STATEMENT

Jayshil J. Patel has served as a consultant for Baxter and on the advisory board for Fresenius Kabi. Todd W. Rice is a consultant for Baxter, Nestlé, and Cumberland Pharmaceuticals, Inc, and is a data safety monitoring board member for Sanofi, Inc. Manpreet S. Mundi has received research grants from Nestlé, Fresenius Kabi, Realfood blends, and Rockfield and has consulted for NorthSea. Christian Stoppe has consulted for Baxter, Fresenius Kabi, and Braun. Stephen A. McClave has consulted for Nestlé and Abbott and has served on the advisory board at Fresenius Kabi and Avanos.

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