


Meeting Calorie and Protein Needs in the Critical Care Unit: A Prospective Observational Pilot Study

Shinobu Yamamoto¹, Karen Allen^{2,3}, Kellie R Jones^{2,3}, Sarah S Cohen⁴, Kemuel Reyes¹ and Maureen B Huhmann¹ 

¹Clinical Sciences, Nestlé Health Science, Bridgewater Township, NJ, USA. ²Pulmonary, Critical Care & Sleep Medicine, University of Oklahoma Health Sciences Center, Oklahoma, OK, USA. ³Veterans Affairs Hospital, Oklahoma, OK, USA. ⁴Epidemiology Practice, EpidStat Institute, Ann Arbor, MI, USA.

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ABSTRACT

BACKGROUND: Inadequate calorie and protein intake during critical illness is associated with poor clinical outcomes. Unfortunately, most critically ill patients do not consume adequate levels of these nutrients. An enteral formula with appropriate macronutrient composition may assist patients in meeting nutritional goals.

DESIGN: This study was a single center, prospective, observational study of 29 adults in the medical intensive care unit who required enteral nutrition for at least 3 days. Subjects received a calorically dense, enzymatically hydrolyzed 100% whey peptide-based enteral formula for up to 5 days to assess the ability to achieve 50% of caloric goals within the first 3 days (primary outcome), the daily percentage of protein goals attained and gastrointestinal tolerance (secondary outcomes).

RESULT: A total of 29 subjects consented and began the study. Four subjects dropped out before first day and 25 subjects were included in analyses. Subjects were aged 55.5 ± 16.9 years with mean body mass index (BMI) of 27.9 ± 7.5 kg/m². Most (92%) subjects were on a mechanical ventilator and experienced organ failure. At least 50% of caloric and protein goals were achieved in 78.9% and 73.7% of the subjects, respectively, during the first 3 days. Overall, $75.0 \pm 26.3\%$ and $69.3 \pm 26.7\%$ of calorie and protein goals were achieved using the study formula.

CONCLUSIONS: Subjects fed enterally with a calorically dense, enzymatically hydrolyzed 100% whey peptide-based enteral formula exceeded 50% of caloric and protein goals in most critically ill subjects included in this study. Use of study formula did not lead to severe gastrointestinal intolerance.

KEYWORDS: Enteral nutrition, critically ill, calorie, protein, gastrointestinal tolerance

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CORRESPONDING AUTHOR: Maureen B Huhmann, Clinical Sciences, Nestlé Health Science, 1007 US Highway 202/206, Building JR2, Bridgewater, NJ 08807, USA. Email: maureen.huhmann@us.nestle.com

Introduction

Enteral nutrition (EN) plays an essential role in assisting patients in the medical intensive care unit (MICU) in satisfying daily nutrition goals.¹ In addition, EN is suggested to help maintain gut structure² and function including that of T-cell-associated lymphoid tissues³ and neutrophil activation.⁴ Preservation of mucosal barrier and immune function are, in turn, thought to prevent systemic infection as a result of translocation of intraluminal bacteria into circulation.⁵

Recent guidelines recommend nutrition intervention should be initiated in all ICU patients; however, to avoid overfeeding, EN and parenteral nutrition (PN) should be provided as hypocaloric nutrition, not exceeding 70% of estimated energy needs in the first 3 days. Energy provision should be increased to 70% to 100% of estimated needs on days 3 to 7.⁶ This recommendation is based, in part, on studies such as TARGET and PermiT, which indicated that higher calorie delivery initiated within the first 12 to 24 hours of admission to the ICU did not lead to improved outcomes, length of stay, or survival.^{7,8} For example, the lower calorie feeding group in the TARGET

study received 15.6 cal/kg ideal body weight (IBW) per day equating to approximately 1260 kcal and the higher calorie feeding group received 23.1 kcal/kg IBW/d equating to approximately 1860 kcal. This has led to debate in the field of nutrition support as to how to feed the critically ill patient early in their ICU stay.

Despite recommendations to feed patients enterally and to feed early, nutritional support is not always a priority in the ICU. Frequently, inadequate amounts of nutrients are delivered to patients for protracted periods of time due to unnecessarily prolonged cessation of feeding for procedures⁹ or lack of advancement to goal. In the United States, the achievement of nutrition goals in ICU using EN were found to be, on average, 35% and 42% of estimated energy and protein needs, respectively.^{10–13} This is well below the recommendation of the most recent American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines.^{1,6} Inadequate nutritional provision in the ICU is associated with poorer short- and long-term outcomes, including prolonged ventilator-free days and



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Table 1. Nutrition profile of the study formula.

AMOUNT PER 250 ML		
Calories	kcal	375
Total fat	g	14
Medium chain triglycerides	g	10
Sodium	mg	220
Potassium	mg	520
Total carbohydrate	g	47
Dietary fiber	g	0
Protein	g	17

ICU stay and increased mortality.¹³⁻¹⁵ Malabsorption, as a result of the gastrointestinal (GI) intolerance that is frequently observed in the critical care settings, can also contribute to inadequate nutritional provision.^{13,16,17} The literature reports intolerance rates in the critically ill ranging from 30.5% to 75%.^{13,16,18-20} Enteral tube feeding intolerance is associated with reduced nutritional goal achievement.²⁰ Common GI intolerance symptoms include vomiting, large gastric residual volume, abdominal distention, and diarrhea.^{13,17,21} Reducing GI intolerance to EN is critical to be able to promote adequate nutritional intake.

Several components of enteral formulas can affect GI tolerance. The type of fat used in the formula can effect gastric emptying and incidence of diarrhea, especially in patients at risk of fat malabsorption. In contrast to long chain triglycerides, medium chain triglycerides (MCT) are directly absorbed into portal circulation and do not require bile salts.²² Data indicate that MCT intake is associated with decreases in GI symptoms.²³ A high MCT:LCT ratio helps enhance fat absorption and metabolism, thereby promoting tolerance.^{22,24,25} Protein source and form also influence tolerance. It has been observed that whey protein facilitates faster gastric emptying compared with casein²⁶ and may prevent cessation of enteral feeding as a result of large gastric residual volume due to delayed gastric emptying.^{9,13,21} In addition, protein that has been hydrolyzed to peptides requires less digestion thereby decreasing the risk of malabsorption. Whole protein can be hydrolyzed to peptides using enzymes from animal or microbial sources. As such, inclusion of MCT and whey in enteral formulas may promote formula delivery in patients with conditions such as malabsorption, diarrhea, elevated protein requirements, and impaired GI function.²⁷ The formula used in this study contains protein hydrolyzed using microbial enzymes with 70% of the fat content from MCT oil.

The purpose of this study was to demonstrate the ability to meet nutritional needs with a calorically dense, enzymatically hydrolyzed 100% whey peptide-based enteral formula. The hypothesis was that patients receiving the study formula would

be able to meet at least 50% of calorie requirements in the first 3 days of initiation of EN in the critical care unit.

Methods

Study design

This single center, prospective, observational study included 29 adults in an MICU who required EN for at least 3 days. Subjects received a 1.5-kcal/mL enteral formula that contained 18%, 50%, and 32% of calories from protein, carbohydrate, and fat, respectively (Peptamen 1.5; Nestlé Health Science, Bridgewater, NJ; Table 1) in a volume to meet estimated needs based on clinician assessment. The protein source in the formula is whey protein that is hydrolyzed using microbial enzymes and is provided at a level of 68 g/L. The lipid in the formula is provided as a combination of 30% long and 70% MCT. In general, caloric needs were estimated by the study dietitian at 25 to 30 kcal/kg actual body weight (ABW) in subjects with BMI \leq 25 and at 12 to 22 kcal/kg ABW in subjects with a BMI $>$ 25; however, clinical judgment was applied to adjust this according to the medical situation. Similarly, protein needs were calculated at 1.2 to 1.5 g/kg ABW with adjustments made based on clinical condition.

Formula consumption and adverse events were recorded daily. Day 0 was defined as the day nutrition support was initiated and day 1 was the first full day (24 hours) of enteral feeding. During the time on study, the study formula was the only enteral formula consumed by the subject. GI events including stooling, vomiting, distention, nausea, and elevated gastric residuals were assessed and evaluated by the medical team daily. The medical team performed a comprehensive assessment of the patient condition to evaluate the influence of the study formula on these events.

Compliance with the protocol was defined as exclusive feeding of the study formula in the first 3 days of EN initiation. The goal of 50% of needs was chosen based on previously published data reporting that critically ill patients received on average only 35% of estimated energy requirements using EN¹⁰ and the recent recommendations that nutrition support should be gradually increased in the first 3 days of critical illness. The time frame of 3 days was chosen based on the average length of stay in the ICU in the United States.²⁸

Study conduct

Families of subjects aged at least 18 years, admitted to the MICU with expected admission of at least 3 days, and had established enteral access were approached for informed consent. Subjects were excluded if there was presence of condition which contraindicates enteral feeding or study formula, lack of enteral access, receiving PN, pregnant or lactating, could not comply with the study protocol, or were participating in another trial.

The study recruitment and data collection took place between June 2016 and July 2017 at the University of Oklahoma Health Sciences Center, Oklahoma City, OK.

This trial was approved (IRB# 6866) by the institutional review board of The University of Oklahoma Health Sciences Center, Oklahoma City, OK, and fulfilled all requirements for human research including Declaration of Helsinki and Good Clinical Practice. This trial was registered at ClinicalTrials.gov (identifier: NCT02806427).

Statistical analysis

Patients were considered to have completed the study if they received study formula for at least days 1 through 3. Statistical analyses were performed using SAS/STAT software, version 9.4 (SAS Institute Inc., Cary, NC). All analyses were performed using descriptive statistics. Mean, SD, minimum and maximum values were presented for continuous data, and counts and percentages are presented for categorical data.

Results

In total, 29 adults were enrolled and 4 subjects dropped out of the study before day 1 due to change in clinical condition or change in formula needs. Therefore, demographics were determined based on 29 subjects and nutrition intake assessments were performed for 25 subjects. In addition, completed subjects were defined as those who received study formula for at least days 1 through 3, and their nutrition intake assessments are also reported.

Demographics

Subject demographics based on 29 subjects are summarized in Table 2. Subjects were 62% men with mean age and BMI of 55.5 ± 16.9 years and 27.9 ± 7.5 kg/m², respectively, and 24 (86%) subjects were fed through nasogastric (NG) tube. The mean prescribed calorie and protein levels at enrollment for the 29 subjects were 1646 ± 315 kcal/d (21 kcal/kg ABW/d) and 82.3 ± 21.9 g/d (1.1 g/kg ABW/d), respectively.

The primary and secondary diagnoses of the 29 subjects are summarized in Table 3. Twenty (68.9%) subjects were with respiratory failure, 5 (17.2%) with cardiac arrest, 9 (31%) with sepsis, and 9 (31%) with pneumonia. Other diagnoses include asthma, congestive heart failure, fractures, liver failure, seizures, hypotension, muscle weakness, and pleural effusion. Twenty-eight (97%) subjects were on ventilator and experienced organ failure on day 0. The breakdown of number of subjects who were on a ventilator or experienced each specific type of organ failure on that day is presented in Table 4. These values reflect the incidence of organ failure in subjects who were receiving study formula that day. Subjects who experienced organ failure on multiple days were counted for each day they experienced failure of that organ.

Daily caloric goals met

Percentages of subjects who remained in the trial and met at least 50% of caloric goal by enteral formula on days 1, 2, and 3 were 84%, 88%, and 79%, respectively (Figure 1). Among 19

Table 2. Demographics of enrolled subjects (N=29).

	NO. (%)
Gender: Male	18 (62.1)
Feeding tube type/location ^a	
Nasogastric (NG)	24 (85.7)
G-tube	2 (7.1)
Orogastric (OG)	1 (3.6)
NG/OG	1 (3.6)
	M (SD) [MIN, MAX]
Age, y	55.5 (16.9) [21.8, 77.5]
Height, cm	171.1 (13.2) [127.0, 190.0]
Weight, kg	82.2 (24.2) [42.1, 145.7]
BMI, kg/m ²	27.9 (7.5) [15.4, 43.0]
Prescribed calories, kcal/d	1646.0 (315.3) [900.0, 2160.0]
Prescribed protein, g/d	82.3 (21.9) [41.0, 135.0]

Abbreviations: BMI, body mass index; N and n, number of subjects.

^aFeeding tube type/location was missing from 1 subject.

Table 3. Diagnosis and ventilator and organ failure statuses at baseline (N=29).

CONDITION (N=29)	PRIMARY DIAGNOSIS NO. (%)	SECONDARY DIAGNOSIS NO. (%)
Respiratory failure	15 (51.7)	5 (17.2)
Cardiac arrest	4 (13.8)	1 (3.4)
Sepsis	4 (13.8)	5 (17.2)
Asthma	1 (3.4)	1 (3.4)
Congestive heart failure	1 (3.4)	0 (0.0)
Fractures	1 (3.4)	0 (0.0)
Liver failure	1 (3.4)	0 (0.0)
Pneumonia	1 (3.4)	8 (27.6)
Seizures	1 (3.4)	2 (6.9)
Hypotension	0 (0.0)	1 (3.4)
Muscle weakness	0 (0.0)	1 (3.4)
Pleural effusion	0 (0.0)	1 (3.4)
Ventilator and organ failure status on day 0 (N=29)		
Ventilator	28 (96.6)	
Organ failure	28 (96.6)	

Table 4. Organ failure occurrence over the course of the study.

	DAY 1 (N=25)	DAY 2 (N=24)	DAY 3 (N=19)	DAY 4 (N=14)	DAY 5 (N=7)
Ventilator, no. (%)	23 (92.0)	20 (83.3)	16 (84.2)	13 (92.9)	7 (100)
Organ failure, no. (%)	23 (92.0)	20 (83.3)	16 (84.2)	13 (92.9)	6 (85.7)
CNS/lung failure, no. (%)	1 (4.0)	1 (4.2)	1 (5.3)	0 (0.0)	0 (0.0)
Lung failure, no. (%)	21 (84.0)	18 (75.0)	13 (68.4)	11 (78.6)	5 (71.4)
Liver failure, no. (%)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)
Lung/renal failure, no. (%)	1 (4.0)	1 (4.2)	1 (5.3)	1 (7.1)	1 (14.3)

Abbreviation: CNS, central nervous system.

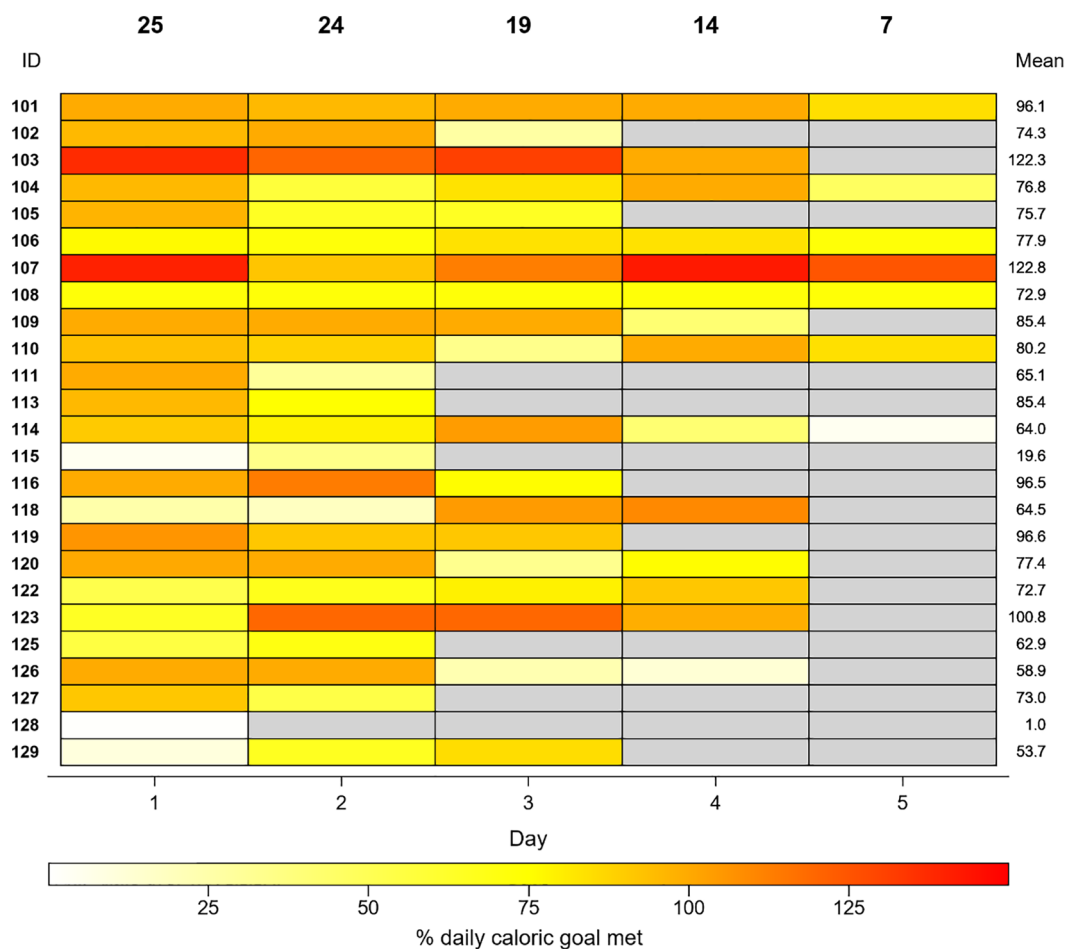


Figure 1. Percentages of caloric goal met by the study formula (N=25) for each subject for each day are shown in the heatmap. The rows and columns represent subjects (ID) and days on the study formula, respectively. The color changes from white-yellow-red based on lower to higher percentages of caloric goals met, as shown in the color key at the bottom. Means of percentages of caloric goal met over days on the formula for each subject are shown on the right. The days in which subjects did not receive the study formula is shown in gray, and the number of subjects remained in the trial each day are shown on the top.

subjects who had complete data for days 1 to 3, 100% of subjects met at least 50% of caloric goal with 84% of estimated calorie needs met, on average over days 1 through 3. In addition, of those 7 subjects who remained in the trial on day 5, 100% of the subjects met 50% of their calorie goals on day 5

(Figure 1). The mean caloric intake from formula over 5 days in ICU was 1237.0 ± 489.2 kcal/d (Table 5), and $75.0 \pm 26.3\%$ of daily caloric goal was met overall.

On days 1 to 5, 12 subjects received propofol. The mean caloric intake from propofol over 5 days in ICU was 110

Table 5. Calorie and protein intake from enteral formula (N=25), and calorie from propofol, total calorie from enteral formula + propofol (N= 13) by day.

	N	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	MEAN DAYS 1-5
		M (SD) [MIN, MAX]					
Calorie from enteral formula	25	1300.0 (596.7) [15.0, 2070.0]	1305.6 (564.1) [330.0, 2587.5]	1362.6 (566.7) [292.5, 2587.5]	1417.5 (583.0) [157.5, 2137.5]	1187.1 (586.5) [60.0, 1672.5]	1237.0 (489.2) [15.0, 2176.9]
Calorie from propofol	12	110.0 (0) [110.0, 110.0]	110.0 (0) [110.0, 110.0]	110.0 (0) [110.0, 110.0]	110.0 (0) [110.0, 110.0]	110.0 (n/a) [110.0, 110.0]	110 (0) [110.0, 110.0]
Calories from enteral formula + propofol	25	1339.6 (609.2) [15.0, 2090.0]	1337.7 (591.1) [330.0, 2697.5]	1408.9 (575.1) [402.5, 2697.5]	1472.5 (558.8) [267.5, 2247.5]	1202.9 (600.0) [60.0, 1685.0]	1275.7 (505.8) [15.0, 2286.9]
Protein from enteral formula	25	58.9 (27.1) [0.7, 93.8]	59.2 (25.6) [15.0, 117.3]	61.8 (25.7) [13.3, 117.3]	64.3 (26.4) [7.1, 96.9]	53.8 (26.6) [2.7, 75.8]	56.1 (22.2) [0.7, 98.7]

Table 6. Gastrointestinal tolerance.

	DAY 1 (N=25)	DAY 2 (N=24)	DAY 3 (N= 19)	DAY 4 (N= 14)	DAY 5 (N=7)	SUMMARY OVER ALL DAYS
Stool frequency, per day per subject						
M (SD) [min, max]	0.6 (0.9) [0, 3.0]	0.7 (1.1) [0, 4.0]	1.1 (1.7) [0, 6.0]	1.3 (2.7) [0, 10.0]	0.7 (0.8) [0, 2.0]	0.9 (1.5) [0, 10.0]
Consistency, no. of stools (%) ^a						
None	16 (64.0)	16 (66.7)	11 (57.9)	9 (64.3)	3 (42.9)	55 (61.8)
Vomiting, no. of subjects (%) ^a						
No	25 (100.0)	23 (95.8)	19 (100.0)	13 (92.3)	7 (100.0)	87 (97.8)
Abdominal distention, no. of subjects (%) ^a						
No	14 (56.0)	11 (45.8)	8 (42.1)	5 (35.7)	6 (85.7)	44 (49.4)
Nausea, no. of subjects (%) ^a						
No	25 (100.0)	24 (100.0)	19 (100.0)	14 (100.0)	6 (85.7)	88 (98.9)
Residuals, no. of subjects (%) ^a						
No	24 (96.0)	23 (95.8)	19 (100.0)	13 (92.9)	7 (100.0)	86 (96.6)
Volume if residuals were present	150 mL	130 mL	–	325 mL	–	

Tabulations based on 25 subjects as 4 subjects dropped out of study before day 1 (subjects 112, 117, 121, and 124).

^aMissing value treated as number for all days. Three subjects experienced elevated gastric residuals over the course of the study.

calories/d (Table 5). The combination of the study formula and propofol provided $1275.7.0 \pm 505.8$ kcal/d on average for these subjects, which was $77.5 \pm 27.3\%$ of estimated needs.

Daily protein goals met

The percentages of subjects who remained in the trial and met at least 50% of protein goal were 76%, 79%, and 74% for days 1, 2, and 3, respectively. Among 19 subjects who had complete data for days 1 to 3, 18 (95%) of them met equal or greater than 50% of protein goal. In addition, of those 7 subjects who remained in the trial on day 5, the percentage of subjects who

met at least 50% of their protein goals was 100%. Overall, the mean amount of protein a subject received in ICU was 56.1 ± 22.2 g/d (0.7 ± 0.3 g/kg ABW/d) (Table 5), and $69.3 \pm 26.7\%$ of daily protein goal was met over 5 days.

Tolerance and adverse events

The results of tolerance measures are summarized in Table 6. The subjects had mean stool frequency of 0.9 ± 1.5 per day per subject (range: 0–10.0). Liquid stool was reported on 19 of 89 study days; however, this was not reported as related to study product. Most subjects did not experience vomiting (98%; 87

of 89 days), nausea (99%; 88 of 89 days), or high gastric residuals (97%; 86 of 89 days) over the course of the study. Nine subjects experienced adverse events during the course of the study. Adverse events for 8 of the subjects were determined to be unlikely or unrelated to the study formula. Data for relationship to study product were missing for the remaining subject; however, study formula was not discontinued. No serious adverse events occurred during the course of the study.

Discussion

This prospective observational study examined an ability to meet nutritional needs and incidence of GI events in critically ill adult patients in the MICU who were fed a calorically dense EN formula. Most subjects were mechanically ventilated and over half of them had respiratory failure. The study formula was administered to the subjects largely through NG tube and most subjects achieved at least 50% of both caloric and protein goals within the first 3 days of EN initiation.

Although there is consensus that early EN is beneficial in critically ill patients, there is some controversy over the appropriate level of calorie provision in the first 3 days of critical illness. For patients with high nutrition risk or malnutrition, the ASPEN and Society of Critical Care Medicine (SCCM) recommend that at least 80% of caloric goal be attained within 48 to 72 hours for short- and long-term clinical benefit.¹ However, more recent ESPEN Critical Care guidelines recommend, to avoid overfeeding, EN and PN should be provided as hypocaloric nutrition, not exceeding 70% of estimated energy needs in the first 3 days.⁶ In actual clinical practice, a previous study revealed only 1% to 48% of caloric goals were met using EN in the first 5 days in ICUs in the United States.¹⁰ This raises significant concern and is motivation to improve current feeding practice in the ICU. The current study supports the view that better nutrition delivery is possible as evidenced by the ability of the study formula to meet approximately 75% of prescribed caloric goal within the first 5 days of ICU admission. The average calories delivered from the enteral formula in the first 3 days of feeding in this study was 1322 kcal/d was similar to that of the lower calorie feeding group in the TARGET study that received approximately 1260 kcal.⁷

Data suggest that during critical illness, increased protein must be delivered to support protein synthesis and to maintain protein homeostasis in cells as protein catabolism exceeds anabolism.²⁹ Indeed, ASPEN/SCCM guidelines recommend protein provision of at least 1.2 g/kg/d and the ESPEN guidelines recommend 1.3 g protein/kg/d for patients with critical illnesses,^{1,6} while recommended dietary allowance for healthy adults is 0.8 g protein/kg/d.³⁰ Increased protein intake is associated with reduced mortality,³¹ in particular, Elke et al¹² observed 39% reduction in 60-day mortality among patients with protein intake of ≥ 58.9 g/d relative to patients with ≤ 39.5 g/d protein intake. In the current study, patients received 57.3 ± 26.3 g/d of protein on average. Protein provision in the

TARGET study was approximately 69 g/d and in the PermiT trial was 57 to 59 g/d.^{7,8} This study formula was able to provide approximately 69% of prescribed protein in most subjects, which was far above the observed 1% to 48% of protein goals achieved in a previous study.¹⁰

GI intolerance is a major concern as it is a contributor to malnutrition among the critically ill patients in ICU. In the current study, the study formula was well tolerated as measured by lack of common GI intolerance symptoms such as vomiting, nausea, and large gastric residual volume, in most subjects. Approximately 40% of the stools were liquid/loose. Loose stool has many causes in the ICU. Common causes include underlying illness, medications such as antibiotics or those containing sorbitol, and infections such as with *Clostridium difficile*.³²⁻³⁵ Although abdominal distention was observed in approximately half of the subjects (45 of 89 days), this was subjectively assessed by the nursing staff. In addition, all observed adverse events were unlikely or unrelated to the study formula (except for 1 subject, missing the relation to the product) and no serious adverse events occurred.

This study used a calorically dense formula in a mechanically ventilated population. This formula type may not be appropriate for patients with other conditions such as burns or severe trauma which likely require higher provision of protein, and patients with obesity which require high-protein hypocaloric formulas.¹ Therefore, these results may not be applicable to other critically ill populations. In addition, subjects were examined up to 5 days in the current study, and the long-term effect, therefore, remains to be elucidated.

Future studies with this formula should assess the impact of use of this formula in long-staying critically ill patients when fed according to the most recent guidelines recommending a slow ramp up to meet 70% to 100% energy needs. As this formula does not provide the very high levels of protein to meet the guidelines for protein provision in the critically ill obese, these patients should be excluded from a future study with this formula.

In summary, a calorie-dense enteral formula containing whey-derived peptides hydrolyzed by microbial enzymes and MCT was safe, well tolerated, and achieved higher nutrition goals in the first 5 days in ICU than those observed in a previous study.

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Author Contributions

SY wrote the manuscript with oversight and input from MBH. MBH and KA authored the protocol. KA and KRJ consented patients, executed the study and provided site oversight. KR reviewed and confirmed patient data and SSC conducted all statistical analyses. All authors reviewed the final manuscript.

ORCID iD

Maureen B Huhmann  <https://orcid.org/0000-0003-0282-7549>

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