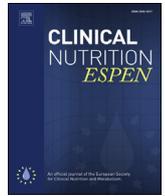




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Original article

## Critical care: Meeting protein requirements without overfeeding energy

Stephen Taylor<sup>\*</sup>, Natalie Dumont, Rowan Clemente, Kaylee Allan, Claire Downer, Alex Mitchell

Department of Nutrition & Dietetics, Southmead Hospital, Bristol, United Kingdom

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### SUMMARY

**Background and aims:** Relatively high protein input has been associated with improved clinical outcome in critical illness. However, until recently differences in clinical outcome have been examined in terms of the energy goal-versus under-feeding. Most studies failed to set the energy goal by an accurate measure or estimate of expenditure or independently set protein prescription. This leads to under-prescription of protein, possibly adversely affecting outcome. We determined whether an enteral nutrition prescription could meet local and international protein guidelines.

**Methods:** Protein prescriptions of consecutive patients admitted to Southmead Hospital ICU and requiring full enteral nutrition were audited against local and international guidelines. Prescriptions were designed to not exceed energy expenditure based on a validated estimation equation, minus non-nutritional energy, and protein requirements were based on local or international guidelines of between 1.2 and 2.5 g protein/kg/d or 2–2.5/kg ideal body weight (Hamwi ideal body weight)/d.

**Results:** From 15/1/15 to 12/4/15 139 ICU patients were prescribed full enteral nutrition. Protein prescriptions failed to meet local guidelines in 75% ( $p < 0.001$ ) and international guidelines in 45–100%. Prescriptions meeting at least 90% of protein guidelines and 130 g of carbohydrate could be increased from between 0 and 55%, depending on the guideline, to between 53 and 94% using a protein supplement and 82 and 100% using a protein plus glucose supplement. Non-nutritional energy (NNE) proportionately reduces feed protein prescription and contributed 19% of energy expenditure in 10% of patients.

**Conclusions:** We need feeds with a lower non-protein energy: nitrogen (NPE:gN) ratio and/or protein supplementation if prescriptions are to meet protein guidelines for critical illness. NNE must be adjusted for in prescriptions to ensure protein needs are met.

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### 1. Introduction

Relatively high protein input whilst not exceeding energy expenditure appears to be beneficial in terms of preserving lean body mass (LBM) during catabolism, reducing mortality and improving wound healing [1–3]. Conversely overfeeding energy is associated with hyperglycaemia, infection and increased protein catabolism [4]. Early in severe inflammatory states, optimal protein supply may help maintain vital LBM and supply amino acids to maintain acute-phase protein synthesis, wound healing and

immunity [2]. Prolonged negative nitrogen balance is associated with poor outcome [1,5].

Guidelines for critical illness suggest 1.2–2.5 g protein/kg/d [6,7] compared to 0.83 g/kg/d in health [8]. Amino acid toxicity is rare except where continuous renal replacement therapy (CRRT) is unavailable in renal failure or during unbalanced amino acids loads from GI haemorrhage in liver failure [9]. Conversely, in patients who are energy substrate intolerant, giving a high protein prescription but less than the energy expenditure may be optimal [10]. However, most enteral feeds and parenteral solutions have a non-protein energy: nitrogen (NPE:gN) ratio too high to provide adequate 'protein' without overfeeding energy in critically ill patients [11].

In a 'baseline' audit we determined whether protein prescription met the local and international guidelines for our critically ill

<sup>\*</sup> Corresponding author. Department of Nutrition & Dietetics, Level 6, Gate 10, Brunel Building, Southmead Hospital, Bristol BS10 5NB, United Kingdom. Tel.: +44 0117 4145428.

E-mail address: [stephen.taylor@nbt.nhs.uk](mailto:stephen.taylor@nbt.nhs.uk) (S. Taylor).

**Abbreviations**

ASPEN	American Society of Parenteral and Enteral Nutrition
BMI	body mass index
CRRT	continuous renal replacement therapy
EN	enteral nutrition
ESPEN	European Society of Parenteral and Enteral Nutrition
IBW	ideal body weight
IQR	inter-quartile range
LBM	lean body mass
NAP	nutrison advanced protison
NNE	non-nutritional energy
NPE:gN	non-protein energy: nitrogen
NPP	nutrison protein plus
PSUm	Penn-State University (mifflin) equation from Frankenfield et al., 2009; 2011.
REE	resting energy expenditure

population and, if not, whether protein supplementation could reduce the deficit. In a follow-on 'supplementation' audit we examined whether actual prescriptions of a protein supplement or very high protein feed would improve adequacy.

## 2. Methods

We prospectively compared protein prescription with local and international guidelines. We determined protein adequacy of current feed prescription in a 'baseline' audit and then the effect of added protein in a pilot 'supplementation' audit. The primary outcome was the difference between protein prescription and the local guidelines on days 1–3. Secondary outcomes compared this prescription with other guidelines and the effect of prescribing protein supplements in addition to feed. In addition to protein needs, there is an obligatory glucose requirement (130 g/d) [8]. While glucose can be derived via gluconeogenesis from glycerol or amino acids we made the assumption that to provide at least 130 g of glucose-equivalent carbohydrate would optimise protein utilisation. Because protein supplementation was rounded down to nearest pack, prescription could never equal 100% of the requirement. For this reason, 'prescription adequacy' was set at >90% of the estimated protein requirement and 130 g of carbohydrate.

### 2.1. Study population and setting

Consecutive patients admitted to Southmead Hospital ICU and requiring full enteral nutrition (EN) were assessed between days 1–3, 5–7, 8–10 and 18–20. Patients were excluded or data collection stopped if oral or parenteral nutrition commenced or EN or protein prescription was restricted, for example, in patients with liver dysfunction refractory to medical treatment, renal dysfunction requiring conservative (non-CRRT) treatment, short-bowel syndrome or severe refeeding risk. We calculated the protein deficit using feeds alone and feeds plus protein supplements.

### 2.2. Estimating requirements

Experienced nutrition support dietitians prescribed feed type and volume as closely as possible to estimated protein and energy requirements. Protein requirements were calculated according to the estimated level of catabolism [11].

- Mild: 1.25 g/kg/d (major surgery, no infection).
- Moderate: 1.875 g/kg/d (major trauma or systemic infection but not septic).
- Severe: 2.0 g/kg/d (sepsis).
- Very severe 2.5 g/kg/d (severe sepsis on CRRT) and
- ICU obese 1.9 g with 20Kcal/kg Hamwi ideal body weight (IBW)/d [12].

We compared these with the following international guidelines:

- ASPEN: 1.2–2.5 g/kg/d and 2.0 or 2.5 g/kg Hamwi IBW/d if BMI >30 or >40, respectively [6].
- ESPEN: 1.3–1.5 g/kg/d [7].
- Weijs et al., 2012 [13]: 1.2 g/kg or adjusted kg/d where 'Adjkg' is normalised to BMI 20 and 27.5 kg/m<sup>2</sup> when <20 and > 30, respectively.

We estimated energy requirements (EER) from equations that were either validated, used a physiological parameter or that were specific to condition and basal metabolic rate formula [11]. Calculations were done using FeedCalc v1.56 and v1.68 software (see [Supplementary file](#)). To avoid consequences of overfeeding, prescriptions did not exceed 105% of EER. In instances of substrate intolerance (blood glucose >10 mM, high insulin requirements or feed-related hypercapnia), hypocaloric feeding (about 75% EER) was considered. Feed prescription was proportionality reduced after deducting non-nutritional energy (NNE).

Sources of NNE included Propofol, IV glucose and CRRT fluid. For CRRT we made a conservative estimate that 200 Kcal per day was absorbed by patients receiving our pre-dilution method of regional citrate anti-coagulation [14].

### 2.3. Feed prescription

In the 'baseline' audit, we used feeds from the Nutrison range that had a non-protein energy (Kcal): nitrogen ratio (NPE:gN) of between 100 and 142:1. We also calculated the effect of substituting a higher protein feed, Nutrison Advanced Protison (NPE:gN ratio: 80:1), or, alternatively, supplementing with ProSource<sup>®</sup> TF (11 g protein, 1 g carbohydrate, 44 Kcal per 45 mL) or ProSource<sup>®</sup> Plus (15 g protein, 11 g carbohydrate, 100 kcal per 30 mL). In the 'supplementation' audit we prescribed ProSource<sup>®</sup> TF in gastric feeding or Nutrison Advanced Protison for intestinal feeding, when proteins needs were not met by standard feeds.

### 2.4. Study size

In a pilot study (n = 23), patients categorised as having mild, moderate and severe catabolism had protein prescribed that was 9%, 19% and 33% less than their estimated requirement, respectively. To show similar deficits, without exceeding 105% of the EER, required 133 patients (catabolism level: 100 mild, 11 moderate, 11 severe, 11 very severe) using a power of 0.99 and a significance level of p < 0.05 in a paired, two-tailed test. The sample was pooled if too few 'mildly' catabolic patients were recruited.

### 2.5. Statistics

Analysis was undertaken using 'R Studio' Version 0.98.977. We used the Shapiro–Wilk test to determine whether data variables were normally distributed. Differences between the protein guideline and prescription were determined using paired t-test or Wilcoxon's signed-rank test, as appropriate. We also determined the proportions of patients falling below thresholds of protein

adequacy, both with and without use of high protein feed or protein supplementation using Fisher's exact or proportion test.

## 2.6. Ethics

This study was accepted by North Bristol NHS Trust as an audit of standard practice. All interventions were for clinical reasons. The study therefore did not require Ethics approval.

## 3. Results

### 3.1. Population and estimation of requirements

Our 'baseline' audit included 139 patients receiving full EN, including 6 re-admissions, of 441 patients admitted to ICU between 15/1/15 and 12/4/15. The protein 'supplement' audit included 14 patients admitted between 13 and 24/4/15 (Table 1). Of the exclusions, six received PN with the remainder being partially or completely reliant on oral nutrition or expected to remain on ICU for less than 24 h. Neurosurgical and trauma sub-groups were relatively large reflecting Southmead Hospital's regional specialties. Because observations were done only on ICU up to death, commencement of oral or parenteral nutrition or discharge out of ICU, the number of patients observed declined from 139 (d1-3) to 99 (d5-7), 91 (d10-12) and 53 (d18-20). Those patients remaining longer in the study tended to have more severe and/or chronic disease and therefore they don't represent the average nutritional course for a patient admitted to ICU. Most variables were not normally distributed therefore results are presented as median [IQR] or %.

EER was predominantly resting energy expenditure (REE) because initially 73% of patients were mechanically ventilated, declining to 43% (d5-7), 24% (d10-12) and 10% (d18-20). Combined physical activity and dietary-induced thermogenesis remained at ~10% of BMR. The upward trend in EER (d1-3: 1883 [1554–2176]; d5-7: 1946 [1622–2176]; d10-12: 1966 [1609–2207]; d18-20: 2080 [1726–2298]) may therefore be explained by the remaining patients being those with higher REE, possibly secondary to infection. Hypocaloric feeding fell from 23% to 14%, d1 to d20, so most prescriptions were for 100% of EER.

Most patients in both the 'baseline' and 'supplementation' audits were classified as moderately catabolic when estimating protein requirements (Table 2). Estimated protein requirements were similar between local (FeedCalc) guidelines for 'mild' catabolism, 1.2 g protein per Kg (ASPEN lower limit) or adjusted weight (Fig. 1). Local estimates for 'moderate' or 'severe' catabolism, ESPEN and ASPEN upper estimates (2 g/kg/d) or for obese and morbidly obese patients (2 and 2.5 g/kg Hamwi IBW/d) were higher. Median estimated protein requirements for days 1–3, 5–7, 10–12 and 18–20 are 108, 103, 97 and 113 g per day, respectively; lack of decline may reflect that data collection continued in only the sickest survivors.

### 3.2. Protein adequacy of feeds

Protein prescription, our primary outcome, was significantly lower than local guidelines (median [IQR]: 82 g [65–94] vs 108 [85–127],  $p < 0.001$ ). The median percentage of the protein guidelines met increased from 75% d1-3 to 87–90% d5-20 as the decline in NNE permitted greater feed protein prescription. We then re-calculated prescriptions to account for NNE, thus optimising the percentage of protein guidelines met (Fig. 2). Deficits were 15–20% smaller using feed with an NPE:gN ratio of 80:1 than 100:1 and when using the adjusted weight (AdjKg\*1.2 g) guideline. The latter might suggest that ASPEN and ESPEN guidelines based on unadjusted weight may overestimate protein requirements in obese patients. However, deficits remain large using local (FeedCalc) guidelines calculating protein from IBW equivalent to a BMI of 22 or 'Hamwi IBW'. So, for most guidelines, feeds with an NPE:gN ratio of 100:1 would under-feed protein in more than half our patients. However, guidelines matched NPE:gN ratios of 45–123:1 so about a third of patients requiring 2.0 g protein/kg or/kg Hamwi IBW/d or hypocaloric feeding will be underfed protein even if feeds have an NPE:gN ratio  $\geq 80:1$ .

### 3.3. Protein adequacy of feeds + supplements

We then re-calculated whether we could have met  $\geq 90\%$  of protein requirements and the obligatory glucose requirement

**Table 1**  
Demography, disease and equation used to estimate energy expenditure.

Parameter	Group	'Baseline' N = 139		Protein 'supplementation' N = 14	
		Median	IQR	Median	IQR
Height_cm		170	165–179	175	164–188
Weight_kg		75.4	65–86.5	77.5	74–85.8
BMI		24.9	22.6–28.7	25.2	22.9–27.5
Apache II score		17	13–23	11	9–14
Age_years		62.3	48.7–71.6	43.1	38.3–69.3
		%		%	
Sex (male)		60		66	
Disease category (%)	Medical	38.1		7.1	
	Neurology	0.7		7.1	
	Neurosurgery (non-trauma)	20.9		28.6	
	Surgery	10.8		14.3	
	Trauma	29.5		42.9	
FeedCalc 'equation' when estimating energy expenditure d1-3 (%)	Infection	18.7		7.1	
	Liver	1.4		0	
	PSUm (Penn-State equation, 2009; 2011)	73.4		85.7	
	SAH	2.2		0	
	SAH + ICH	1.4		0	
	Surgery (major)	2.2		7.1	

**Table 2**  
Percentage of patients categorised by degree of catabolism or data completion.

Audit	Day	% by estimated catabolism					% completing
		ICU_obese	Mild	Moderate	Severe	Very severe	Data collection
1. Baseline (n = 139)	d1-3	0.7	38.1	55.4	5.8	0	0
	d5-7	0.7	30.9	35.3	3.6	0.7	28.8
	d10-12	0	21.6	21.6	2.9	0	54
	d18-20	0	7.9	7.2	1.4	0	83.5
2. Supplementation (n = 14)	d1-3	0	14.3	71.4	14.3	0	–

whilst not overfeeding (i.e.  $\leq 100\%$  EER) using feeds  $\pm$  liquid protein supplements (ProSource<sup>®</sup> TF or ProSource<sup>®</sup> Plus). Compared to clinical prescription, precise adjustment for NNE increased those meeting all criteria from 32% to 39% for Nutrison Protein Plus (NPP, ns) and 56% for Nutrison Advanced Protison (NAP,  $p < 0.001$ ) (Fig. 3). Complimenting NPP feed to the nearest protein supplement pack, without overfeeding energy, increased the number of prescriptions meeting their respective guidelines by 10–90%; for local guidelines (FeedCalc) it increased from 32% to 73% using ProSource<sup>®</sup> TF or 82% using ProSource<sup>®</sup> Plus (both  $p < 0.001$ ). Two findings were unexpected: a) In our ‘supplement’ audit, adding ProSource<sup>®</sup> TF only increased those meeting adequacy criteria from 7% to 57% because we failed to account for the effect of NNE; and b) Combined protein + glucose supplementation was more likely to meet both the estimated protein and obligatory glucose requirements than protein supplementation alone. Only one patient received the ‘very high’ protein feed, Nutrison Advanced Protison, precluding analysis.

### 3.4. ‘At risk’ groups

Patients with low body weight or high BMI and undergoing hypocaloric feeding had a relatively restricted feed prescription making them vulnerable to not meeting their obligatory glucose requirement. Post-hoc analysis of ‘baseline’ audit data confirms that patients with a weight of  $<60$  kg or a BMI  $>30$  had a lower carbohydrate prescription (171 [IQR: 153–176] vs 199 [170–227],  $p = 0.007$ ).

NNE contributed to protein deficits by limiting prescription of energy from feed. Propofol was the major source of (fat) NNE in most patients but IV glucose or citrate-based haemofiltration contributed up to 38% and 15% of goal energy in individuals, respectively. Propofol's contribution to NNE was highest days 1–3, paralleling mechanical ventilation; NNE from citrate or glucose was higher after d12 (Fig. 4). More importantly, the NNE contribution to goal energy days 1–3 was 12% in 25% of patients and 19% in 10%; after day 10 NNE was  $<10\%$  in even the top 25% of patients. Thus

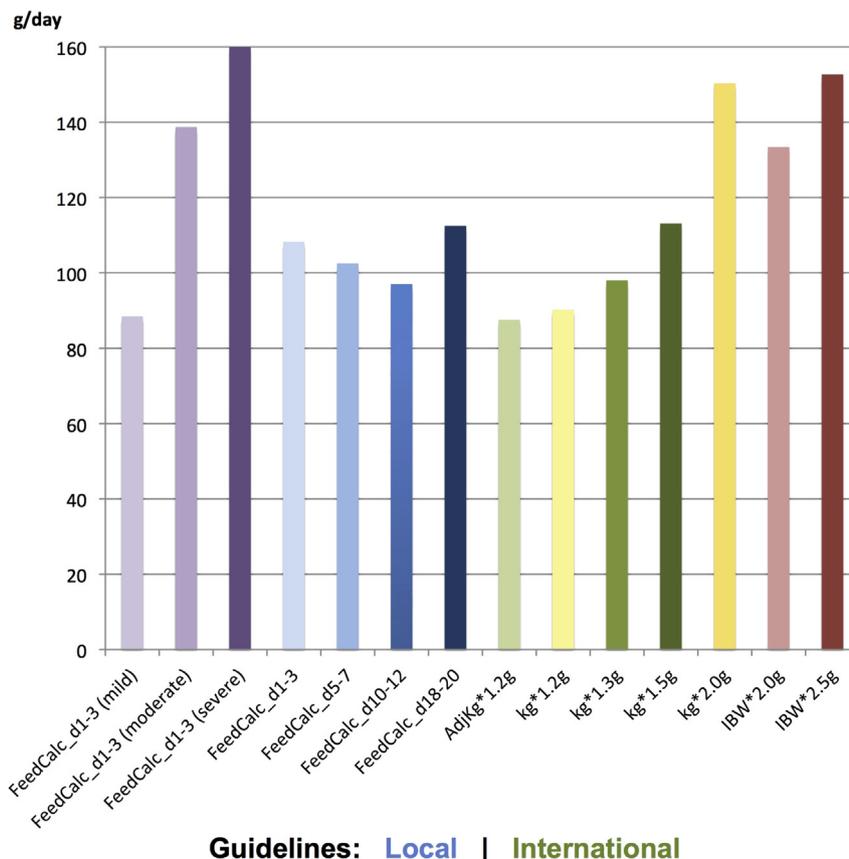


Fig. 1. Median estimated protein requirements.

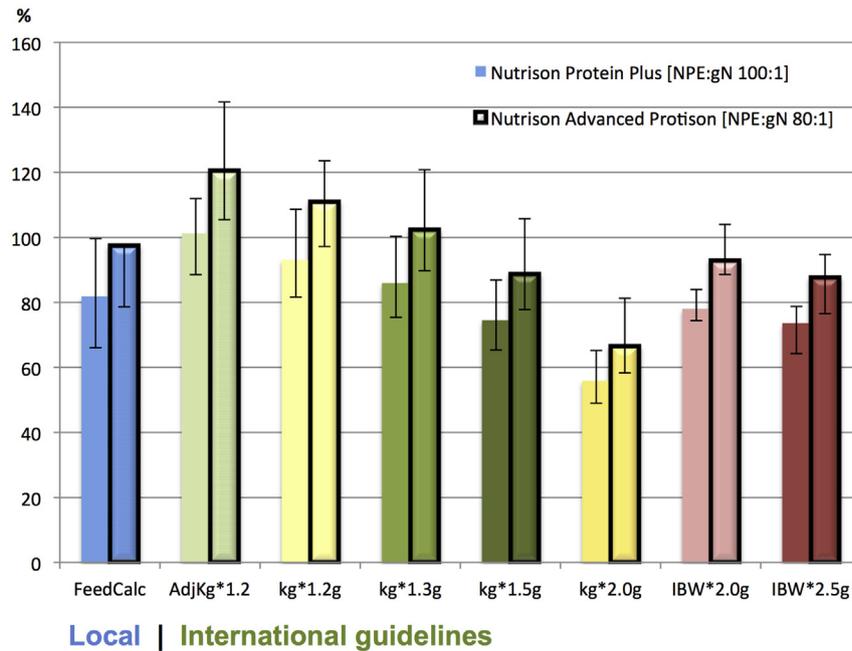


Fig. 2. Median percentage (±IQR) of protein standards that could be met.

days 1–3 is when NNE precipitates most protein deficit and 9% fail to meet obligatory carbohydrate requirements (130 g/d) [8].

#### 4. Discussion

##### 4.1. Main findings

Protein prescription failed to meet most guidelines in >50% of ICU patients receiving full EN, when constrained to not overfeed,

taking NNE into account and using feeds with NPE:gN ratios of ≥100:1. Substituting a feed with a NPE:gN ratio of 80:1 met prescriptions based on lower guidelines (1.2–1.3 g/kg/d) but deficits remained large for patients requiring ≥2.0 g protein per kg or kg Hamwi IBW/d or during hypocaloric feeding. We confirm that a pure protein supplement could significantly reduce this deficit [15]. However, when protein and carbohydrate requirements are relatively high, particularly in low body weight patients, a pure protein supplement compels reduced feed prescription below the

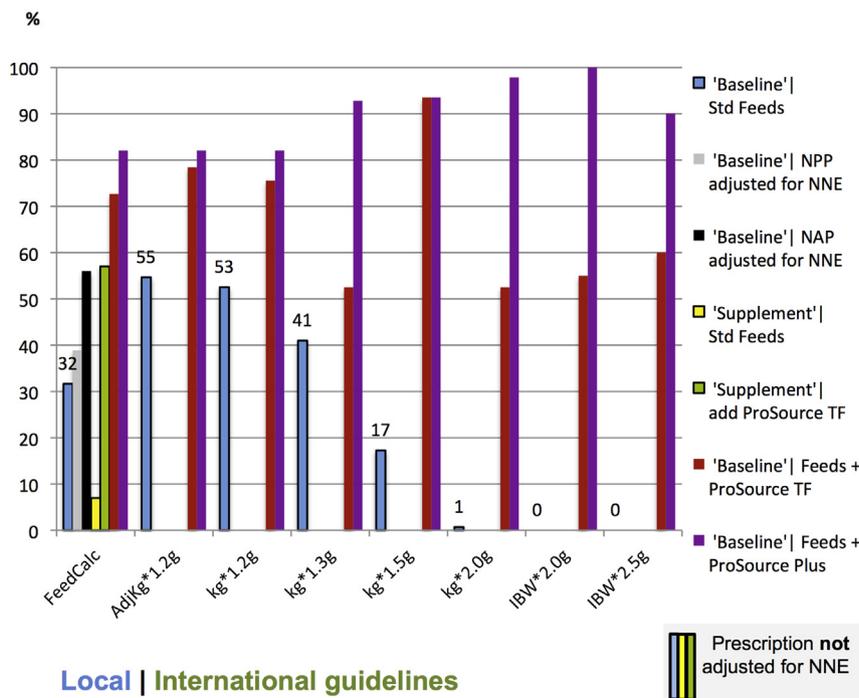


Fig. 3. Percentage of prescriptions meeting guidelines: Feed ± additional protein.

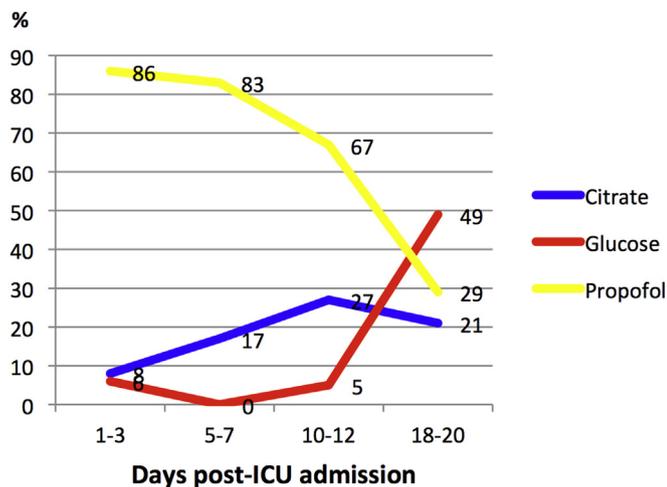


Fig. 4. Citrate, glucose and 'Propofol' as a percentage of NNE.

obligatory glucose requirement. A mixed protein + carbohydrate supplement largely overcomes the problem. A micronutrient supplement may often be required. In the 'supplement' audit we would have further reduced the deficit had we accounted for the reduction in feed protein caused by NNE; NNE contributed 19% of energy needs in 10% of patients.

#### 4.2. Protein and outcome

ASPEN offer ranges of protein intake per kg per day based on BMI (<30: 1.2–2.0, and using Hamwi IBW if 30–40: 2.0 g and >40: 2.5 g) but without guidance on individual requirement by disease severity [6]. FeedCalc recommends nitrogen (protein) input to minimise protein loss at different levels of loss either based on measurement or condition [11]. European data suggests a minimum of 1.2 g/kg or 'adjusted' kg/d [3,7,13]. Hypocaloric, high protein nutrition ( $\geq 1.2$  g protein, 80–90% EER) in the first 4 days of ICU admission may produce the lowest percentage mortality [16]. Thus inadequate protein may partially explain the failure to improve outcome regardless of whether energy input is below or above energy expenditure [17,18].

Restoration of amino acid levels may be central to the benefit of adequate protein. Inflammatory states increase amino acid utilization and the depression of the intracellular levels may trigger catabolism [19]. Acute-phase protein loss partly results from preferential utilisation of phenylalanine, tryptophan and tyrosine obligating oxidation of other unused amino acids [20,21]. In the future, supplementation of specific amino acid mixes may be most efficient, but high nitrogen input (0.4 g = 2.5 g protein/kg/d) of even mixed amino acids improved nitrogen balance and was associated with corrected amino acid levels [21] a driver of muscle protein synthesis [22].

Opposing this view, under- or late-feeding produced similar or better outcomes to 'adequate' or early feeding [18,23]. However, these studies provided  $\leq 50\%$  of current protein guidelines, inaccurately estimated energy requirements, risking under- and over-feeding, gave a higher proportion of protein to underfed patients [17], provided excess non-protein energy in the first 48 h [18] or included only well-nourished patients [23], the group shown not to benefit from nutrition support [24]. In contrast, each increment of 1000 kcal and 30 g protein given to nutritionally at risk patients (BMI <25 or >35) reduced mortality [24]. In those with pneumonia and sepsis, increased protein input was associated with reduced ventilator dependence [1]. Furthermore, compared to underfeeding

(measured energy expenditure: 58–77%, 0.58–0.8 g protein/kg/d), tailoring nutrition close to requirements (measured energy expenditure: 88–106%, 0.86–1.2 g protein/kg/d) was associated with a trend to reduced mortality [25], reduced infection [26] and reduced complication rate and hospital stay [27]. Improved survival was associated with higher protein intake (1.46 vs 1.01 vs 0.79 g/kg/d) but not nitrogen balance or energy intake [28]. This suggests that survival is not just dependent on preservation of LBM, but requires amino acid substrate for critical physiologic processes. Indeed, LBM size and protein supply may interact, with a small LBM being vulnerable to critical loss but a large LBM requiring greater protein supply for maintenance. For this reason, it is suggested that when calculating protein requirement for individuals with BMIs <20 or >30, they should have their weight normalised to BMI 20 and 27.5, respectively [13]. In contrast, mortality declines when providing  $\geq 1.2$  g protein/kg/d vs  $\leq 1.0$  g/kg/d in non-septic, non-overfed ( $\leq 110\%$ REE) patients; there is no relation between mortality and protein intake if septic or overfed. Lastly, hypocaloric feeding (<25 kcal and >2 g protein/kg Hamwi IBW/d) obese adult trauma patients produces similarly improved nitrogen balance and clinical outcomes regardless of age, but in older patients higher blood urea nitrogen warrants greater monitoring [29].

#### 4.3. NNE and carbohydrate

Input of NNE is high days 1–3 when the requirement for protein and hypocaloric feeding are highest; NNE therefore risks the consequences of energy overload or protein and micronutrient deficits. In addition, because non-CNS tissues continue to oxidise glucose in critical illness, when NNE from Propofol restricts carbohydrate supplied from feed it may increase gluconeogenesis from amino acids and reduce insulin secretion for anabolism. Thus, optimal nutrition may require combined protein and carbohydrate supplementation, exogenous insulin to control hyperglycaemia and prevent down-regulation of muscle protein synthesis [30] and, during recovery, early mobilisation [31].

#### 4.4. NPE:gN ratio

Current feeds failed to meet protein requirement because their NPE:gN ratios (80–140:1) were often higher than those calculated from local and international guidelines (45–123:1). This highlights that protein requirements must be independently estimated because they are only weakly related to energy expenditure [32,33]. Indeed, excess energy (>30 kcal non-protein/kg/d) must not accompany high protein input (1.5–2 g protein/kg/d) because it increases net protein catabolism [4]. Lastly, the need for low NPE:gN ratio feeds or protein supplementation extends beyond critical care. The elderly, without acute disease, often have low energy expenditure. However, to prevent or treat sarcopenia, maximal muscle protein synthesis requires 1.5 g protein/kg/day or up to 2 g if protein quality or distribution is sub-optimal [34].

#### 4.5. Strengths of weaknesses of the study

A weakness of this study is that protein guidelines are not definitive and the 'supplementation' audit was small. In addition, problems achieving adequate nutrient delivery and testing the efficacy of different amino acid patterns need to be addressed in future studies. However, we describe large deficits between feed protein prescribed and the lowest guidelines. We also identify that feed  $\pm$  supplement prescription must meet the requirements of all nutrients and not be simply adjusted to energy requirements.

## 5. Conclusion

Optimal nutrition can only be attained if nutritional prescription meets individualised requirements. These cannot be met by a single feed or solution because the required NPE:gN ratio is wide (45–123:1). In addition, requirements for carbohydrate and certain micronutrients are absolute and independent of energy requirements. Patients most at risk from protein  $\pm$  glucose  $\pm$  micronutrients deficits or energy overload are those with relatively low energy requirements due to small body size or being hypocalorically fed or receiving NNE, especially where Propofol displaces protein and carbohydrate. Complete feeds and protein supplements are complimentary. In practice a complete feed that supplies the protein and micronutrient requirements within energy expenditure would be most convenient. However, at present, enteral feeds (or PN solutions) don't adequately account for protein needs and NNE load. In these cases a protein supplement is necessary; protein  $\pm$  glucose  $\pm$  micronutrient supplementation may be needed when feed prescription is very limited.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.clnesp.2015.12.003>.

## Conflict of interest and funding source

The time for this study was paid for by Nutrinovo to North Bristol NHS Trust. Nutrinovo played no part in study design, execution, analysis, reporting of results or choice of journal. There is no other conflict of interest.

## Submission declaration and verification

This paper has not been published previously and is not under consideration for publication elsewhere, its publication is approved by all authors and by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copy-right-holder.

## Authorship roles

	ST	ND	RC	KA	CD	AM
Study conception and design	✓					
Data acquisition	✓	✓	✓	✓	✓	✓
Data collation	✓	✓	✓			
Data analysis	✓					
Data interpretation	✓	✓	✓	✓	✓	✓
Manuscript drafting	✓					
Manuscript revision for important intellectual content	✓	✓	✓	✓	✓	✓
Approval of final manuscript	✓	✓	✓	✓	✓	✓

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