Protein delivery in mechanically ventilated adults in Australia and New Zealand: current practice

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Critical illness is a hypercatabolic state which causes marked loss of lean muscle mass[1] and persistent poor functional recovery.[2] Higher protein doses may play a role in attenuating muscle loss. International guidelines for critically ill adults recommend protein delivery between 1.2 g/kg and 2.0 g/kg actual body weight (ABW) per day when body mass index (BMI) is ≤ 30 kg/m^2, and between 1.2 g/kg and 2.0 g/kg ideal body weight (IBW) per day when BMI is > 30 kg/m^2.[3,4] However, these recommendations are based on low quality evidence.[5-7] Such limited evidence highlights the need for larger, more definitive studies to inform international recommendations.

Observational studies enrolling critically ill mechanically ventilated patients have suggested that higher protein doses (> 1.3 g/kg IBW per day) are associated with reduced mortality.[8] Similarly, post hoc analyses of prospective data from an international multicentre nutrition survey reported that 60-day mortality was reduced in critically ill mechanically ventilated patients meeting ≥ 80% of protein goals compared with those not meeting goals.[9,10] Nevertheless, observational studies have a potential inherent risk of bias from unidentified confounders and do not imply causation. Conversely, there is also evidence for harm. Higher protein intakes have been associated with higher rates of muscle loss,[11] and a post hoc analysis of the EPaNIC trial (*n* = 4640) reported an association between early amino acid administration and prolonged time to discharge from the intensive care unit (ICU).[12] Further, a meta-analysis by Davies and colleagues[13] failed to show a mortality benefit from higher protein doses, although the higher protein group received just 0.67 ± 0.38 g/kg per day (body weight calculations were not stipulated), well below the international recommendations.

In order to inform the standard care arm of a definitive randomised controlled clinical trial, it is important that usual clinical practice is quantified.[14] In Australia and New Zealand, two multicentre observational analyses have reported protein delivery during critical illness. Bellomo et al[15] reported protein doses of 0.5 ± 0.4 g/kg ABW per day

ABSTRACT

Objective: To quantify current protein prescription and delivery in critically ill adults in Australia and New Zealand and compare it with international guidelines.

Design: Prospective, multicentre, observational study.

Setting: Five intensive care units (ICUs) across Australia and New Zealand.

Participants: Mechanically ventilated adults who were anticipated to receive enteral nutrition for ≥ 24 hours.

Main outcome measures: Baseline demographic and nutrition data in ICU, including assessment of requirements, prescription and delivery of enteral nutrition, parenteral nutrition and protein supplementation, were collected. The primary outcome was enteral nutrition protein delivery (g/kg ideal body weight [IBW] per day). Data are reported as mean ± standard deviation or *n* (%).

Results: 120 patients were studied (sex, 60% male; mean age, 59 ± 16 years; mean admission APACHE II score, 20 ± 8). Enteral nutrition was delivered on 88%, parenteral nutrition on 6.8%, and protein supplements on 0.3% of 1156 study days. For the 73% (88/120) of patients who had a nutritional assessment, the mean estimated protein requirements were 99 ± 22 g/day (1.46 ± 0.55 g/kg IBW per day). The mean daily protein delivery was 54 ± 23 g (0.85 ± 0.35 g/kg IBW per day) from enteral nutrition and 56 ± 23 g (0.88 ± 0.35 g/kg IBW per day) from all sources (enteral nutrition, parenteral nutrition, protein supplements). Protein delivery was ≥ 1.2 g/kg IBW per day on 29% of the total study days per patient.

Conclusions: Protein delivery as a part of current usual care to critically ill adults in Australia and New Zealand remains below that recommended in international guidelines.

Crit Care Resusc 2021; 23 (4): 386-93

delivered to critically ill patients on renal replacement therapy for severe acute kidney injury in 2005–2008.[15] Similarly, in a large cohort of critically ill mechanically ventilated patients (n = 2776), Ridley and colleagues[16] reported protein doses of 0.60 ± 0.35 g/kg per day (weight calculated using multiple methods) from 2007 to 2013. These data were collected before the most recent updates of international guidelines in which higher protein doses were recommended and, hence, may not be reflective of current usual practice. Therefore, the aim of this study was to quantify current protein prescription and delivery practices (in g/kg IBW per day) in Australian and New Zealand ICUs in order to inform the design of a phase 3 randomised controlled trial of augmented protein delivery in which the control arm is representative of current clinical practice.

Methods

A prospective, multicentre, observational study was conducted in five metropolitan ICUs, four in Australia and one in New Zealand. All the ICUs were mixed level 3 adult quaternary or tertiary referral sites with 14–60 beds each. The study included 120 consecutive mechanically ventilated adult patients who were about to commence enteral nutrition or had commenced enteral nutrition within the preceding 12 hours and were expected to receive enteral nutrition for at least 24 hours. These inclusion criteria were informed by a recent protein delivery feasibility trial.[17] Patients were excluded if palliative treatment was being considered, death was deemed imminent by the treating intensivist, or higher than standard protein delivery (eg, burns) was deemed appropriate. No more than 30 patients were included at any individual site to ensure representative data. Ethics approval was obtained through the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/19/CALHN/452), with local governance obtained for each site. Informed consent was waived as there was no intervention and the data were collected in a de-identified manner.

Baseline data variables collected at ICU admission included demographic data (age, sex, ABW, height, BMI), Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and APACHE III diagnostic codes. The method used to obtain ABW was also documented (estimated, reported, or measured).

If a formal nutritional assessment was conducted by a health care professional as part of routine care during the ICU admission, the estimated calorie and protein requirements were recorded.

Nutritional data (nutrition prescription, delivery, and gastric residual volumes) were collected daily for the duration of the enteral nutrition delivery or until oral intake commenced, day 28 of ICU admission, ICU discharge or death. Nutrition prescription data included the type and volume of enteral nutrition, parenteral nutrition, and protein supplements (via any route) prescribed by the treating team at 12:00 pm on each study day. The 12:00 pm prescription was taken as indicative of the daily prescription. Nutrition delivery data included the type and total volume of enteral nutrition, parenteral nutrition, and protein supplements delivered on each calendar day. These data were used to calculate total calorie and protein delivery per day. Total gastric residual volumes aspirated and discarded on each study day were also recorded.

The primary outcome was mean enteral protein delivery in g/kg IBW per day. Clinical outcomes included ICU and hospital length of stay, and ICU and hospital mortality censored at day 28.

Statistical analysis

A pragmatic sample size of n = 120 was set to establish feasibility of recruitment at different sites and to complete the study within a suitable time frame to inform further studies on protein delivery.

Categorical data are reported as number (percentage, %) and continuous data are reported as mean ± standard deviation (SD) or median (interquartile range [IQR]). Protein data are described as g/kg per day, with weight reported in two ways: ABW, in keeping with international guidelines; and IBW, where IBW was calculated using these formulae: Men = (height (cm) – 152.4) × 0.9 + 50; Women = (height (cm) – 152.4) × 0.9 + 45.5).[18]

In addition, for patients who had a nutritional assessment, the daily protein deficit was calculated as the total protein received from enteral nutrition, parenteral nutrition, and protein supplements subtracted from the calculated daily protein requirements. Daily protein deficits were summed to determine the total protein deficit over the study period.

Results

Baseline characteristics

One-hundred and twenty patients were enrolled between 8 January and 15 April 2020 across five sites (12–30 patients per site) (Table 1). Mean age was 58.5 ± 15.7 years, and 60% of patients were male. Mean ABW was 86 ± 24 kg and IBW was 64 ± 10 kg, and the mean BMI was 30 ± 8 kg/m^2. Mean admission APACHE II score was 20 ± 8 and the most common APACHE III diagnostic category was neurological (23%).

Table 1. Patient baseline demographic and clinical characteristics

Characteristics	Values
Total number of patients	120
Age, years	58.5 ± 15.7
Sex, male	72 (60%)
Actual body weight, kg	86 ± 24
Method used to determine weight	
Measured	60 (50%)
Reported	33 (27.5%)
Estimated	27 (22.5%)
Body mass index, kg/m^2*	30 ± 8
Ideal body weight, kg†	64 ± 10
APACHE II score‡	20 ± 8
APACHE III diagnostic code	
Neurological	28 (23%)
Cardiovascular	20 (17%)
Respiratory	20 (17%)
Trauma	16 (13%)
Gastrointestinal	14 (12%)
Sepsis	9 (7.5%)
Cardiothoracic surgery	7 (5.8%)
Metabolic	3 (2.5%)
Other	3 (2.5%)
Post-operative	42 (35%)
Number of patients for whom a nutritional assessment was performed	88 (73%)
Length of stay (days), median (IQR)	
ICU	8.4 (5.7–13.7)
Hospital	20.5 (13.5–31.2)
Mortality	
ICU	22 (18%)
Hospital	27 (23%)

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; IQR = interquartile range. Data are presented as mean ± standard deviation unless otherwise stated. * Actual body weight in kg/height in m^2. † Ideal body weight calculated as Men = (height (cm) – 152.4) × 0.9 + 50; Women = (height (cm) – 152.4) × 0.9 + 45.5).[18] ‡ Calculated on admission to the ICU.

Nutrition assessment

A formal nutrition assessment was completed by a dietitian for 73% (88/120) of patients. The mean estimated protein requirements were 99 ± 22 g per day (1.1 ± 0.2 g/kg ABW per day) (Table 2).

Nutrition prescription

The final analysis included 119 patients due to incomplete data collection for one patient. Of these, 97.5% (116/119) were prescribed enteral nutrition on any day, 8.4% (10/119) were prescribed parenteral nutrition, and one patient was prescribed protein supplements (Table 2). Of the 1156 total study days, enteral nutrition was prescribed on 78.8% (799/1156), parenteral nutrition on 5.4% (63/1156), and protein supplements on 0.3% (4/1156) of the study days. No nutrition was prescribed on 27.9% (323/1156) of the study days.

The mean volume of enteral nutrition prescribed was 1357 ± 410 mL/day. Fifteen different types of enteral nutrition formulae were prescribed (Table 3); the most common being Nutrison Protein Plus Multi Fibre (Nutricia Australia). Parenteral nutrition formulae prescribed included Olimel N9 (Baxter) and SmofKabiven (Fresenius Kabi) and the protein supplement prescribed was Beneprotein (Nestlé).

Nutrition delivery

Of the 119 patients with data available, 100% received enteral nutrition, 8.4% (10/119) received parenteral nutrition, and one patient received protein supplements during their ICU admission. Enteral nutrition was delivered on 87.5% (1012/1156), parenteral nutrition on 6.8% (79/1156), and protein supplements on 0.3% (4/1156) of the study days. The mean volume of enteral nutrition delivered was 891 ± 336 mL/day.

The mean amount of protein delivered to patients per day from all sources was 56 ± 23 g/day (0.88 ± 0.35 g/kg IBW per day) (Table 2). On average per patient, mean daily protein delivery was ≥ 1.2 g/kg IBW per day on 29% of the study days. The mean daily protein delivered in g/kg IBW per day from day 1 to day 21 is presented in Figure 1. The mean calorie delivery from all sources was 1148 ± 451 kcal/day (18.0 ± 6.9 kcal/kg IBW per day) (Table 2).

Clinical outcomes

The median ICU length of stay was 8.4 days (IQR, 5.7–13.7 days), and the median hospital length of stay was 20.5 days (IQR, 13.5–31.2 days). ICU and hospital mortality were 18% and 23% respectively.

Discussion

This prospective, multicentre, observational study quantified protein doses delivered as part of current clinical practice in five ICUs in Australia and New Zealand and may provide fundamental insights into the changes in protein delivery that have occurred since the international guidelines were updated. The results suggest that current Australian and New Zealand clinical practice delivers more protein compared with previous observational studies.

Although the international guidelines recommend IBW to calculate protein requirements, there is no consistency

Table 2. Nutrition data*

Characteristic	Total	
	N	Mean ± SD
Estimated protein requirement (from nutritional assessment)†		
Protein, g/day	88	99 ± 22
Protein, g/kg ABW per day	88	1.11 ± 0.20
Protein, g/kg IBW per day	88	1.46 ± 0.55
Protein dose prescribed		
Protein, g/day	116	82 ± 27
Protein, g/kg ABW per day	115	1.03 ± 0.39
Protein, g/kg IBW per day	115	1.28 ± 0.42
Protein dose delivered by enteral nutrition		
Protein, g/day	119	54 ± 23
Protein, g/kg ABW per day	119	0.67 ± 0.29
Protein, g/kg IBW per day	119	0.85 ± 0.35
Protein dose delivered from other sources, g/day		
Parenteral nutrition	10	63 ± 22
Protein supplements	1	9.4 (-)
Total protein dose delivered from all sources		
Protein, g/day	119	56 ± 23
Protein, g/kg ABW per day	119	0.69 ± 0.29
Protein, g/kg IBW per day	119	0.88 ± 0.35
Percentage of study days when delivered protein was ≥ 1.2 g/kg IBW per day per patient	80	29 (26%)
Volume of enteral nutrition, mL/day†		
Prescribed	116	1357 ± 410
Delivered	119	891 ± 336
Calories delivered by enteral nutrition		
kcal/day	119	1106 ± 441
kcal/kg ABW per day	119	14 ± 6
kcal/kg IBW per day	119	18 ± 7
Calories delivered from other sources, kcal/day		
Parenteral nutrition	10	1200 ± 425
Protein supplements	1	297 (-)
Calories delivery from all sources		
kcal/day	119	1148 ± 451
kcal/kg ABW per day	119	14 ± 6
kcal/kg IBW per day	119	18 ± 7
Number of study days when products were delivered		
Enteral nutrition	1156	1012 (88%)
Parenteral nutrition	1156	79 (6.8%)
Protein supplements	1156	4 (0.3%)
Total daily gastric residual volume‡		
Measured, mL	117	210 ± 207
Discarded, mL	117	64 ± 132

ABW = actual body weight; IBW = ideal body weight; SD = standard deviation. * Calculated protein requirements according to documented nutritional assessment when this study was performed. † Three patients had an intensive care unit length of stay < 48 h and thus received enteral nutrition, but prescription data were not recorded at 12:00 pm on day 0 and enteral nutrition was ceased by 12:00 pm on day 1. ‡ The gastric residual volume was recorded in 117 out of 119 patients.

Table 3. Enteral and parenteral formulae and non-oral protein supplements delivered

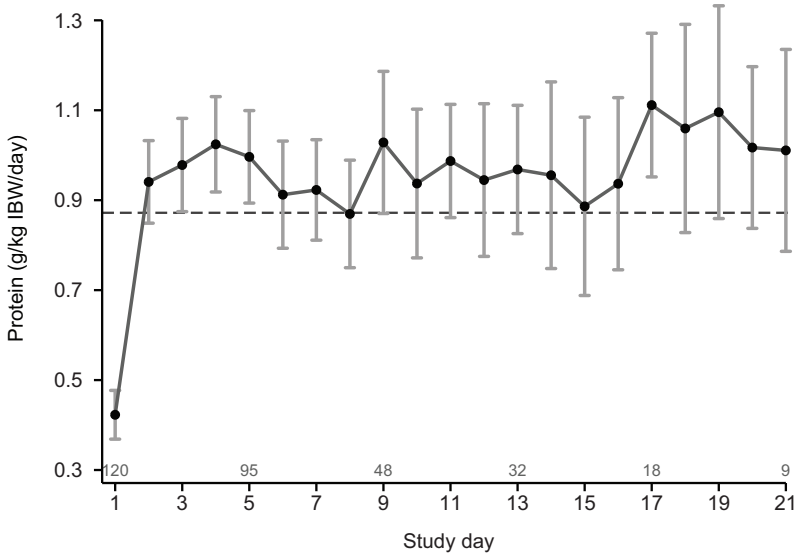
	Calorie content (kcal/L)	Protein content (g/L)	Protein delivered	
			Frequency*	Percentage of type†
Enteral nutrition formulae				
Nutrison Protein Plus Multi Fibre (Nutricia)	1280	63	419	41%
Jevity Promote (Abbott)	1000	55.5	264	26%
Nutrison 1.0 kcal/mL (Nutricia)	1000	40	89	8.8%
TwoCal HN (Abbott)	2000	84.8	48	4.7%
Nutrison Protein Plus (Nutricia)	1250	63	47	4.7%
Nutrison Energy Multi Fibre (Nutricia)	1530	60	40	4.0%
Nutrison Concentrated (Nutricia)	2000	75	29	2.9%
Novasource Renal (Nestlé)	2000	91	16	1.6%
Nutrison Energy (Nutricia)	1500	60	13	1.3%
Isosource Protein Fibre (Nestlé)	1330	67	12	1.2%
Nutrison Multi Fibre (Nutricia)	1030	40	7	0.7%
Nutrison Protein Intense (Nutricia)	1260	100	7	0.7%
Ensure Plus HN (Abbott)	1250	79	4	0.4%
Vital (Abbott)	1500	67.5	2	0.2%
Isosource 2.0 (Nestlé)	2000	84	1	0.1%
Other		-	15	1.5%
Parenteral nutrition formulae				
Olimel N9 (Baxter)	1070	47	44	70%
SmofKabiven (Fresenius Kabi)	1116	42	12	19%
Other	-	-	7	11%
Protein supplement				
Beneprotein powder (Nestlé)‡	-	857	4	100%

* Refers to the number of study days the formula was delivered. † Refers to the percentage of total study days the formula was delivered. ‡ Documentation on the preparation of Beneprotein was not recorded. A 7 g scoop of Beneprotein provides 6 g protein from whey protein isolate and needs to be administered with a minimum of 60 mL water per scoop.

in published trials or in clinical practice about what weight to use. This makes it difficult to interpret and compare with previous data. Importantly, protein dose calculated and reported according to IBW will appear higher but will be less variable than when using ABW. In 2014, the RENAL trial reported protein delivery from all sources of 0.5 g/kg ABW per day during the ICU stay.[15] That study recruited patients with acute kidney injury requiring renal replacement therapy in whom higher protein delivery is recommended[19] and, thus, may not have represented standard care for a general ICU population. Conversely, Ridley and colleagues[16] extracted data on Australia and New Zealand practice from the International Nutrition Surveys from 2007 to 2013 and reported protein delivery from all sources of 0.6 g/kg per day; body weight was calculated using a mix of methods that were not provided.[16] This study included a heterogeneous critically ill mechanically ventilated population similar to our patient population, and suggests a likely true but small increase in protein delivery (from 0.6 g/kg ABW per day to 0.69 g/kg ABW per day; Table 2) between 2013 and 2020.

In pragmatic clinical trials, the aim is frequently to determine the effect of an intervention or change compared with usual care.[14] Two recent randomised controlled trials have explored augmented protein delivery compared with standard care. Both of these trials reported delivery of higher protein doses in their standard care arm than reported in previous observational studies. In a European study conducted in ICU patients with obesity, 0.76 g protein per kg IBW per day was delivered to the standard care arm at day 5;[20] and in an Australian study conducted in a mixed group of mechanically ventilated ICU patients, the standard care arm received 0.99 ± 0.27 g protein per kg IBW per

Figure 1. Mean daily protein delivered in g/kg ideal body weight per day, with 95% CI adjusted for within patient correlation, for days 1–21



Dashed line = population-averaged mean value over the displayed period.

day.[17] Our current study confirms that protein delivery is higher in the five ICUs studied than reported previously and similar to the standard care arms in recent European and Australian studies. This is an important consideration for future trial design to ensure the protein dose targeted as part of usual care achieves a dose representative of current clinical practice.

The higher protein dose received in our study likely reflects a shift towards prescription of enteral formulae with higher protein content, with Nutrison Protein Plus Multi Fibre (63 g protein/L and 1.25 kcal/mL) being the predominant formula delivered in the five centres studied. It was noted in the point prevalence study from Australia and New Zealand in 2012[21] that the most common enteral formula prescribed and delivered was a 1 kcal/mL standard formula with 40 g protein per L. This was similar to the formula most commonly prescribed in the International Nutrition Survey between 2007 and 2013 across Australia and New Zealand.[16] Hence, this signifies a likely change in practice in the centres studied. Another mechanism whereby additional protein could be delivered would be by providing more nutrition overall; however, the overall calorie delivery was similar to that reported in the International Nutrition Survey (1133 ± 572 kcal/day).[16]

Despite an increase in protein delivery over the past two decades, our results demonstrate that protein delivery remains below that recommended in international guidelines. In addition, there was minimal use of protein supplements or parenteral nutrition to increase protein delivery to achieve recommended doses. Although the feasibility of using protein supplements has been demonstrated to increase protein delivery[22] and attenuate muscle loss,[23] its widespread implementation into current clinical practice and effect on clinical outcomes remains to be explored.

The strengths of our study are that it was investigator-led, supported by independent funding, and sponsored by a university-affiliated hospital. A heterogeneous critically ill mechanically ventilated population was studied, excluding specific cohorts of patients believed to require higher protein doses (ie, burns), which improves generalisability across Australia and New Zealand. Illness severity and clinical outcome data were similar to that previously reported in ICU nutrition studies,[17] suggesting a cohort of patients representative of the general Australian and New Zealand ICU population. Limitations include that data were collected from only five metropolitan ICUs in Australia and New Zealand, which may limit generalisability. Prescription data were collected at a single time point and extrapolated to a calendar day to reduce data collection burden; hence, changes in prescriptions over a 24-hour period were not accounted for. A lack of consistency in the measurement of body weight is a limiting factor in the comparison of nutrition studies. To avoid this, we and others have recently been using IBW.[24,25] Although this provides some level of reproducibility and consistency, it remains uncertain whether nutrition prescription according to IBW is optimal. Finally, partial days of data on the day of enrolment, commencement of oral nutrition, and the day of discharge or death were not adjusted for in the analysis of the total delivery over the study period.

Conclusions

This prospective, multicentre, observational study demonstrated that current protein delivery to critically ill adults in patients from five ICUs in Australia and New Zealand is higher than previously reported in observational studies but below international recommendations. These findings can inform the usual care group of future investigations.

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Competing interests

No relevant disclosures.

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