A systematic review with meta-analysis of patient-centered outcomes, comparing international guideline recommended enteral protein delivery to usual care

Kate Fetterplace[1,2] APD BNutrDiet, Benjamin MT Gill[1] APD MDiet, Lee-anne S. Chapple[3,4] APD PhD, Jeffrey J. Presneill[2,5] MBBS PhD, Christopher MacIsaac[2,5] MBBS PhD, Adam M. Deane[2,5] MBBS PhD.

1. Allied Health (Clinical Nutrition), Royal Melbourne Hospital, Melbourne, Australia
2. The University of Melbourne, Department of Medicine, Royal Melbourne Hospital, Parkville, Australia
3. Discipline of Acute Care Medicine, School of Medicine, University of Adelaide, Australia
4. Intensive Care Research, Royal Adelaide Hospital, Adelaide, Australia
5. Intensive Care Unit, Royal Melbourne Hospital, Parkville, Australia

Corresponding author:

Ms Kate Fetterplace[1, 2] BNutDiet, APD

Senior Dietitian, Royal Melbourne Hospital

Allied Heath, Royal Melbourne Hospital

Grattan St Parkville, Victoria, Australia 3050

Phone: +61 3 9342 7440

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jpen.1725.

Fax +61 3 9342 8440

Email: Kate.Fetterplace@mh.org.au

Conflicts of interest

AMD or his institution have received honoraria, travel grants or project grant funding from Baxter, Cardinal Health, Fresenius Kabi, GSK, Medtronic and Nutricia. AMD has participated on advisory boards for Lyric Pharmaceuticals and Takeda. KF has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi, Nutricia and Nestle Health Science (not related to this study). LC has received project grant funding from Nutricia.

Funding

This review was conducted as part of the PhD program of Ms. Kate Fetterplace. No funding was received.

Abstract:

Background

International guidelines recommend that protein be administered enterally to critically ill patients at doses between 1.2-2.0 g/kg per day. Observational data indicate that patients frequently receive less protein. The aim of this systematic review was to evaluate patient-centered outcomes with guideline recommended enteral protein compared to usual care.

Methods

A systematic review was performed of randomized controlled trials including critically ill adult patients provided predominately enteral nutrition with mean protein at ≥ 1.2g/kg per day (intervention) and < 1.2g/kg per day (comparator). Random effects models were applied for outcomes reported in ≥ 3 trials.

Results

Of 1375 abstracts, 69 full-text articles were reviewed and six trials meet the inclusion criteria, including 511 patients. The intervention group received a mean (SD) of 1.3 (0.08) g/kg per day and the comparator group received 0.75 (0.15) g/kg per day protein. Insufficient data were available for meta-analyses on the primary outcome (muscle mass or strength). According to our meta-analyses mortality at 28 days (5 studies) [RR 0.92 (95% CI 0.63 to 1.35), p = 0.66] and the durations of ICU (6 studies) and hospital admission (4 studies) were similar between the intervention and comparator; with some uncertainty due to sample sizes and heterogeneity.

Conclusion: There are insufficient data to conclude if protein provision within the current international guideline recommendations improves outcomes. In a limited dataset, enteral protein intakes near the lower level of current recommendations, does not appear to reduce admission duration or mortality when compared to usual care in critically ill.

Introduction

Recommendations from international critical care guidelines suggest that critically ill patients should receive at least 1.2 g/kg body weight per day of protein via the enteral route (1-4). These guidelines were developed on the assumption that protein delivery > 1.2 g/kg body weight per day may reduce morbidity and mortality (3). However, observational data suggests that many patients do not meet these recommended protein targets, with several studies reporting that during usual critical care management patients only receive a mean of 0.6-0.8 g/kg per day protein, presumably due to interruptions to feeding, intolerance and limited availability of higher protein formulas (5-9).

During critical illness the frequent occurrence of muscle loss is associated with inferior patient-centered outcomes (3). Inflammatory mediators, coupled with inactivity, may drive an imbalance between protein breakdown and synthesis (10, 11), with rapid muscle loss of up to 1-2% of lean body mass per day (11, 12). It remains unclear whether increased delivery of protein may stimulate protein synthesis and attenuate this muscle loss (11), or otherwise favorably influence important patient-centered outcomes, including acute illness duration and mortality, or functional capacity and quality of life in survivors (3, 13, 14).

The aim of this systematic literature review was to evaluate data from all eligible randomized clinical trials to estimate the effect of enteral protein delivered according to international guideline recommendations (i.e. ≥ 1.2g/kg per day) when compared to the care usually administered (i.e. < 1.2g/kg per day). The outcomes of interest were muscle

mass and strength, duration of ICU and hospital admission, requirement for transfer to a rehabilitation facility, physical function, quality of life and mortality.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15) and methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (16) and the Centre for Research and Dissemination (CRD's) Guidance (17). The protocol was registered on PROSPERO (registration CRD42018109924).

The research question was: "In critically ill adult patients (population), does protein delivery equal to or greater than 1.2 g/kg per day of ideal body weight (IBW) via enteral nutrition (intervention), when compared to less than 1.2 g/kg per day of IBW (comparator), influence patient-centered outcomes (outcome)?" All of the study procedures were undertaken by the lead author (KF), with a second reviewer (BG) independently completing title and abstract screening, full-text review, quality assessment and data extraction, with a third and fourth reviewer (AMD and LC) resolving any conflicts and discrepancies between the first and second reviewers. Endnote reference manager software program (version X7.8, USA: Thomas Reuters, 2014), Covidence 2018 (www.covidence.org) and Review Manager (version 5.3), were used to undertake the review and track processes.

Inclusion and exclusion criteria

Studies were included if they:

- Were randomized clinical trials;
- Included only adult patients (≥ 18 years);
- The participants were admitted to an intensive care unit with the majority receiving mechanical ventilation;
- One group received greater than or equal to 1.2 g/kg ideal body weight (IBW) per day of protein via predominately enteral nutrition (more protein cohort), whereas the other group received less than 1.2 g/kg IBW per day of protein (less protein cohort);
- The difference in protein delivery between the two groups was statistically different (significance set at the 0.05 level); and
- At least one of the pre-defined outcomes was reported as a primary or secondary outcome.

Studies were excluded if:

- Protein provided was exclusive parenteral nutrition;
- Protein provision was due to glutamine supplementation or other immune enhancing amino acids such as arginine; and
- The original article could not be located or it was not available in English.

'Predominately enteral' protein was a definition used for this systematic review to identify studies that clearly provided nutritional therapy via the enteral route in preference to parenteral nutrition. Whilst parenteral nutrition, either as total or supplemental nutritional support, was not an exclusion criterion, studies were only included if parenteral nutrition was administered when the enteral route was not possible or insufficient. This approach to use 'predominately enteral' was taken because it is in line with current international guidelines and local practice (1, 6). This is in contrast to the use of parenteral nutrition as part of initial therapy, which does not represent usual care and the route of protein administration (i.e. intravenous) may be a potential confounding variable (18). The threshold protein provision of ≥1.2g/kg was based on IBW, to try to account for studies which included participants with body mass indices (BMIs) greater than the healthy weight range. Ideal body weight was selected as there is uncertainty about what weight (actual or ideal) should be used to dose protein (19).

Search Strategy

A systematic search of the literature was conducted using four databases, MEDLINE (Ovid SP, from 1948 to current), EMBASE (OVID SP, from 1948 to current), the current issues of the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index of Nursing and Allied Health Literature (CINAHL, EBSCOhost, from 1948 to current), including studies published up until 9th November 2018. The search strategy was refined to exclude infant and pediatric patients and animals. No other restrictions or limits were placed on the search strategy. The search terms used included all variations of critical ill, intensive care,

critical care, nutritional support, enteral nutrition, nasogastric, nasojejunal, dietary protein, protein and amino acids. A full sample of the MEDLINE search strategy is included in supplemental appendix 1. Additionally, reference lists from relevant reviews and guidelines were checked and the Medline search was repeated on the 15th of March 2019 for any additional studies for inclusion (1, 2, 20-22).

Outcome measures

The major outcomes of interest were: muscle mass at ICU or hospital discharge, assessed using ultrasonography of any muscle, such as quadriceps muscle layer thickness as described by Tillquist and colleagues (23), or any other validated technique such as computed tomography and bioimpedance (24); or muscle strength at ICU or hospital discharge, assessed using handgrip dynamometry or any other validated technique (25). The secondary outcomes were physical function at ICU discharge, quality of life at any time point, the requirement for transfer to a rehabilitation facility, mortality at any time point, duration of ICU and hospital admission, and incidence of diarrhea. Following the systematic review and extraction of trials it became apparent that only the outcomes of mortality, duration of ICU and hospital admission and incidence of diarrhea provided sufficient data to be included in the meta-analysis.

Data extraction and risk of bias

Data extraction was completed independently by two reviewers (KF and BG). Data collection included study characteristics (author, year of publication, patient inclusion criteria, trial objectives, intervention and control methods, protein and energy targets, characteristics of participants, protein and energy provision, and all reported outcomes of interest). The corresponding authors of relevant publications were contacted to clarify missing data and protein provision if it was not documented in g/kg IBW per day and the mean BMI was above the healthy weight range. Each included study was assessed independently by the first and second reviewer for risk of bias in random sequencing generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting and other sources of bias using The Cochrane Risk of Bias Tool (16), with AMD providing assessment when required for consensus.

Data handling and statistical analysis

Binary data are presented as proportions or percentages. If original studies reported mortality at different time points, all were noted, however 28-day mortality was selected for analysis as the most complete outcome data. For continuous variables; mean and standard deviations (SD) were directly recorded, and median with interquartile range [IQR] data were converted prior to analysis to approximate mean (SD) data as described by Wan and colleagues (26). All included studies reported protein and energy provision in g/kg per day and kcal/kg per day; where actual weight was reported and the mean BMI was within the healthy weight range (BMI 18.5-25 kg/m^2 ≤ 65 years, 22 – 27kg/m^2 if >65 year) the reported mean (SD) protein dose was used in data analyses; if actual weight was reported and the

mean BMI was above the healthy weight range, then calculations were done to assess the protein provision based on IBW (defined as the upper end of the healthy weight range); if studies reported IBW or an adjusted IBW for the protein dose this was used in the data analyses. One author was contacted (27) to further assess their data to confirm that protein was provided at a level of 1.2g/kg IBW per day in the intervention.

Random effects meta-analyses were applied to the outcomes of mortality and length of admission using the package "metan" in Stata statistical software (version 15.1, College Station Texas, USA). Effect estimates for mortality are presented as risk ratios (RR) with 95% confidence intervals (CIs) and the effect estimates of length of stay are reported as standardized mean differences (SMD) with 95% Cl. Variation in RR and SMD attributable to heterogeneity was summarized for each of these outcomes using the I^2 statistic.

Results

There were 2215 records identified from the database searching and no additional papers from other sources. After duplicates and irrelevant papers were excluded based on titles and abstracts alone, 69 papers underwent full-text review. Six trials were eligible for inclusion, which included 511 patients (Figure 1: PRISMA diagram) (27-32).

Figure 1. PRISMA diagram

Study and patient characteristics

The included trials were conducted over a range of years and in various regions (three from Europe, and one each from the United States of America, South America and Australia) from 1993 to 2018. The study objectives and interventions varied, however all studies except that of Eyer and colleagues (29) aimed to deliver protein within the guidelines range from the outset in the intervention group and below the guidelines range in the comparator group. In order to meet the higher protein requirements, all studies incorporated the use of a higher protein enteral formula, with two studies also using supplemental protein powder (Rugeles 2013 and Fetterplace 2018). Three studies aimed to deliver standardized amounts of energy between groups (Jakob 2017, Fetterplace 2018 and Van Zanten 2018). Two studies used supplemental parenteral nutrition to meet energy and protein needs (Jakob 2017 and Allingstrup 2017). The full details of the included study methodologies are provided in Table 1. All studies, except Van Zanten and colleagues (32), were single centre and all studied relatively small cohorts, enrolling between 38 and 199 participants. The mean (SD) ages for the intervention and control groups were 57 (7.9) and 57 (8.3) years. The mean (SD) BMIs for the intervention and control group were 27 (3.7) and 27 (3.4) kg/m^2 and the mean (SD) Acute Physiology and Chronic Health Evaluation (APACHE) II scores were 22 (6.0) and 22 (5.4). Details of the participant characteristics in the included studies are provided in Table 2.

Table 1. Summary and methodology of included studies

Table 2. Participant characteristics of included studies

Protein and energy provision

The mean duration of the interventions ranged from 7 to 18 days, with an unweighted pooled mean of 11 (3.8) days. All studies included an intervention group that delivered a greater amount of protein (Table 3). The intervention group received a mean (SD) protein delivery of 1.3 (0.08) g/kg per day and the control group received a mean protein delivery of 0.75 (0.15) g/kg per day, with an unweighted pooled mean difference of 0.55 (95% CI 0.40 – 0.71) g/kg per day. Energy provision was variable within the two groups with two studies delivering substantially more energy in the intervention group (Table 3). The intervention group received an unweighted pooled mean of 21 (6.3) kcal/kg per day and the control group received a mean of 17 (3.8) kcal/kg per day, with the mean difference in energy delivery being 3.5 (95%CI -3.3 to 10.2) kcal/kg per day.

Table 3. Energy and protein provision of included studies

Assessment for Risk of Bias

The risk of bias assessment for each of the included studies can be visualized (Figure 2a and 2b). Four studies were considered of high quality (Allingstrup 2017, Jakob 2017, Fetterplace 2018 and Van Zanten 2018) and two studies were of low quality (Eyer 1993 and Rugeles 2013). Only one study had unequivocally adequate blinding (Van Zanten 2018) and while a second study reported using double blind methodology (Jakob 2017) it was unclear how this was achieved.

Figure 2A and B. Summary of risk of bias assessment

Outcomes

Functional outcomes

Muscle mass, muscle strength, quality of life and physical function outcomes were reported in only one study. Our group (Fetterplace and colleagues) reported that muscle mass loss, measured using quadriceps muscle layer thickness, was attenuated with greater protein delivery (30). There was no difference in muscle strength and physical function; however, inferences were limited by significant amounts of missing data (up to 80% of participants). Allingstrup and colleagues attempted to assess muscle strength but this was abandoned mid-study due to methodological difficulties (28). The latter study was the only one to assess quality of life; they found there was no difference between the high and low protein groups at six months post hospital discharge (28), however outcome data were missing in 18% of survivors. The requirement for transfer to a rehabilitation facility was only reported by a single study, where greater protein administration did not impact the proportion of patients who required rehabilitation (30).

Mortality

The provision of equal to or greater than 1.2 g/kg per day protein did not reduce 28-day mortality (Figure 3. 5 studies, 431 participants) (RR 0.92 95% CI (0.63 to 1.35), p = 0.66, I^2= 0.0% p = 0.99).

Figure 3. Random effects meta-analysis of mortality, sorted by ascending year of publication

Length of stay

Greater protein delivery did not reduce length of ICU or hospital admission. The standardized mean difference for length of ICU admission (Figure 4 (6 studies, 511 participants) was 0.01 days (95% CI -0.39 to 0.38, p = 0.98, I^2 = 76%, p = 0.001), and for hospital length of admission (4 studies, 393 participants) the standardized mean difference was 0.09 days (95%Cl -0.29 to 0.11, p = 0.38, I^2 = 76%, p = 0.01).

Figure 4. Random effect analysis of length of admission, sorted by ascending year of publication

Diarrhea

Three studies reported the incidence of diarrhea (Jakob 2017, Fetterplace 2018 and Van Zanten 2018). Diarrhea was not significantly different between the 2 groups (RR 0.90 (95%CI 0.71 to 1.1, p = 0.37, I^2 = 0%).

Discussion

This systematic literature review and meta-analysis did not detect any effect on mortality or length of admission with protein provision at the level of international guidelines (≥1.2 g/kg IBW per day) when compared to what the majority of patients receive as usual care (< 1.2 g/kg IBW per day). However, confidence in these results is low due to both the small

number of participants that have been included in trials (n=511) and heterogeneity of study methodology. Importantly, many of the outcomes of interest, including the major primary outcomes muscle mass and strength, as well as quality of life and the requirement for transfer to a rehabilitation facility, were not sufficiently reported in the original studies to enable meta-analyses. Accordingly, this review highlights the lack of trial data available to evaluate current guideline recommendations regarding optimal enteral protein administration to the critically ill.

Mean protein provision was consistent across the included studies with the intervention group receiving a mean of 1.3 (0.08) g/kg per day of protein; inferring that approximately two thirds of the patients in this group received the minimum recommended amount of protein (≥1.2g/kg per day). Protein delivery was less consistent in the comparator group, with the mean protein delivery ranging from 0.5-0.9 g/kg per day, (mean 0.75 (1.5) g/kg per day), this is reflective of variation in clinical practice (6). This review highlights that to date all studies aiming to achieve higher protein provision with predominately enteral nutrition have only managed to deliver mean protein at the lower end of the current international guidelines recommendations and, therefore, a proportion of patients in the intervention group of this systematic review received less than the recommendations. No randomized controlled trial has successfully delivered protein at the upper end of the international guidelines (i.e. 1.6 -2.0 g/kg per day) to all patients using predominately enteral nutrition and, therefore it is unknown if outcomes would be better or worse if this occurred. It is also uncertain as to whether it is the protein dose *per se* that is important, or whether the route of delivery or type of protein is relevant and what effect calorie intake has on protein

utilization or if protein should be delivered as a 'package' of care in combination with exercise (33-36). Furthermore, it remains unclear whether enteral protein digestion and absorption is impaired during critical illness, and how any abnormality impacts delivery of protein and outcome (37).

It should be recognized that energy delivery varied between trials. Energy provision across the high protein group and the comparator group was not standardized and in most of the studies the energy delivery was not in-line with the current guideline recommendations (1). Whilst the amount of energy delivered may confound the impact of protein delivery (7, 8, 38), a recent large blinded randomized controlled trial reported that augmented energy delivery (i.e. consistent with international guidelines) when compared to standard care had no impact on mortality or other patient-centered outcomes when similar amounts of protein were administered (39-41). However, functional outcomes for this trial are yet to be published.

The novelty of this systematic review is that only randomized clinical trials that provided predominately enteral protein; within the guidelines range in the intervention group, were included. Accordingly, the intervention group approached what current international guidelines recommend, and the comparator group represents 'usual' clinical care, as established in numerous observational trials in various regions. Three systematic reviews have previously evaluated the impact of protein provision in the critically ill (20, 22, 42). The most recent of these was by Davies and colleagues (20), who evaluated the effect of two

different protein doses on mortality, length of stay, incidence of pneumonia and length of mechanical ventilation. Similar to the current review, they reported that greater protein provision did not appear to influence mortality or any of the other secondary outcomes (20). However, this review included studies that administered enteral or parenteral nutrition, as well as including studies that administered specific amino acids such as glutamine. This is important as guidelines recommend that parenteral nutrition is reserved for specific cases and trial data suggests outcomes from exogenous glutamine supplementation are worse than with standard care (43). Hence, including studies using specific amino acids is unlikely to be representative of mixed protein administration. Davies and colleagues also included all studies that delivered two different amounts of protein, irrespective of whether this was within the current guideline recommendations. Of the eight studies included by Davies and colleagues that delivered predominately enteral nutrition (44-51), none of these achieved ≥1.2 g/kg per day protein in the intervention group (i.e. international guideline recommendations) and <1.2 g/kg per day in the comparator group. Furthermore, there have been trials recently published in this field, with four out of the six studies included in the current systematic review published after the review by Davies and colleagues (20). The two systematic reviews conducted prior to Davies and colleagues (22, 42) also incorporated both enteral and parenteral nutrition and multiple study methodologies. In addition, Ferrie and colleagues included studies that were not conducted in the ICU (22).

Strength and limitations

The main strength of this systematic review is that randomized clinical trials that provided predominately enteral nutrition, with mean protein provision within the current guidelines range in the intervention and similar to usual care in the comparator, were included. This removed potential confounders of parenteral nutrition and immune-modulating amino acids such as glutamine.

There are several limitations to this review. The most substantial limitation is the lack of data available to facilitate analyses for the primary outcomes. Likewise, many of the other secondary outcomes of interest were not able to be included in meta-analyses because of insufficient data; these outcomes included physical function, requirement for rehabilitation and quality of life. Even when there were sufficient data to conduct meta-analyses, such as with mortality, point estimates were limited by an inadequate number of patients, particularly for such a ubiquitous intervention as nutritional therapy (52), leading to wide confidence intervals. The duration of ICU and hospital admission point estimates were also limited by small sample sizes as well as significant heterogeneity, resulting in considerable uncertainty in these results. A limitation of meta-analyses includes clinical heterogeneity (53); clinical heterogeneity that may have affected the results of this study includes patient factors, pre-morbid nutritional state and duration of intervention. Lack of data and heterogeneity within existing data may explain why the current international guidelines acknowledge that there is some uncertainty regarding the optimal protein dose (1).

Conclusion

There are insufficient data to conclude if enteral protein provision within the current international guideline recommendations, improves patient-centered outcomes for critically ill patients. In a limited dataset of critically ill patients, mean enteral protein intake at approximately the lower end of the range recommended by international guidelines did not appear to reduce acute admission duration or mortality when compared to usual care. Large methodologically rigorous randomized clinical trials evaluating protein provision within the guideline recommendations, possibly combined with physical therapy interventions, are required to assess the impact on patient-centered outcomes such as functional capacity and muscle mass and strength and, thereby, inform clinical practice.

Acknowledgements

Thank you to Smaro Lazarakis, Senior Medical Librarian from the Royal Melbourne Hospital Library, and Lorena Romero, Senior Medical Librarian, Ian Potter Library, Alfred Health for their advice and assistance with developing the search strategies. Thank you to Stephan Jakob for providing data from the SPIRIT trial.

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Abbreviations: Kg: kilogram, EN: Enteral nutrition, PN: Parenteral nutrition, RCT: randomised controlled trial, LOS: Length of Stay

Table. 1 Summary of methods for Included studies

			Methods		Protein Target per day		Energy Target per day	
Author, year, country	**Number of centres**	**Study objective**	**Study intervention**	**Study control**	**Intervention**	**Control**	**Intervention**	**Control**
Allingstrup, 2017, Denmark	1	To assess the effects of individualized energy and protein nutrition optimised by indirect calorimetry and 24-h urinary urea excretion (nitrogen balance) on physical quality of life at 6 months in acutely admitted, adult ICU patients	Standard high protein formula (1.5kcal/ml, 75g protein per 1000ml), with addition of supplemental PN, if required to reach the goals, up to 90 days or discharge	Standard fromula (1.0kcal/ml, 38g protein per 1000ml), if calculated goal rate was not met by 7 days supplemental PN was commenced	At least 1.5g/kg actual weight, assessed with urinary nitrogen	Appoximately 0.95g/kg actual weight	Measured Energy expenditure	25kcal/kg
Eyer, 1993, USA	1	To assess if early enteral nutrition will attenuate the metabolic response after blunt trauma	Early Nutrition support (Day 0), Peptide based formula (1.33kcal/ml, 58g protein per 1000ml),	Late nutrition support (72hr, IV fluid), Peptide based formula (1.33kcal/ml, 58g protein per	1.5 g/kg actual weight	1.5g/kg actual weight (once feeds commenced)	Approximately 34kcal/kg	Apoximately 34kcal/kg (once feeds commenced)

			up to discharge	1000ml)				
Fetterplace, 2018, Australia	1	To determine whether a high protein volume-based enteral feeding protocol with additional protein supplementation delivered more protein and energy than a standard hourly-rate-based nutrition protocol critically ill patients without protein supplementation to mechanically ventilated	Stadard high protein formula (1.25kcal/ml, 63g protein per 1000ml), with a volume based feeding protocol, plus supplemental protein powder in 3 to 4 bolus per day, for up to 15 days or discharge	Standard formula (1.0kcal/ml, 40g protein per 1000ml)	1.5g/kg IBW Based on BMI for age For BMI> 32 Adjusted IBW was used = IBW + (25% actual – IBW)	Appoximately 1.0 g/kg IBW	25kcal/kg IBW Based on BMI for age, For BMI> 32 Adjusted IBW was used = IBW + (25% actual – IBW)	25kcal/kg IBW Based on BMI for age For BMI> 32 Adjusted IBW was used = IBW + (25% actual – IBW)
Jakob, 2017, Switzerland	1	To test the effect of a new enteral formula on the frequency of diarrhea and gastrointestinal tolerance, and on all diarrhea-related costs in ICU long-stayers	High protein enteral ICU specific formula (1.5kcal/ml, 94g protein per 1000ml), for up to 10 days or discharge	Standard formula (1.57kcal/ml, 61g protein per 1000ml)	Approximately 1.55g/kg actual weight	Approximately 0.97g/kg actual weight	25kcal/kg actual weight	25kcal/kg actual weight

Rugeles, 2013, Colombia	1	To compare two enteral nutritional regimens in the critically ill patient, and their impact in the development of severe organic failure, as measured with the SOFA	Standard enteral feed (1.3kcal/ml, 66.6g protein per 1000ml), plus supplemental soy protein powder in 2 bolus per day, for up to 7 days or discharge	Standard enteral feed (1.3kcal/ml, 66.6g protein per 1000ml),	1.5g/kg actual weight	Approximately 1.0g/kg actual weight	15kcal/kg actual weight	25kcal/kg actual weight
Van Zanten, 2018, Netherlands	4	To investigate protein and energy intake, gastrointestinal tolerance, and safety of this new polymeric very high protein formula	Very high protein formula (1.25kcal/ml enteral, 100g protein per 1000ml), up to 28 days or discharge	Standard high protein formula (1.25kcal/ml, 63g protein per 1000ml)	Appoximately 2.0g/kg IBW	Approximately 1.25g/kg IBW	25kcal/kg IBW For BMI > 30 IBW = 30x(Ht m^2)	25kcal/kg IBW For BMI > 30 IBW = 30x(ht m^2)

Abbreviations: PN, Parenteral Nutrition; IV, Intravenous fluid; IBW, Ideal body weight; BMI, Body mass index; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; Ht, height.

Table 2. Participant characteristics of included studies

Author, year	No. randomized		Age, year, Mean (SD)		Sex, n % males		BMI, kg/m2, Mean (SD)		Proportion of Medical admission, n (%)		APACHE II Score, mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Allingstrup, 2017	100	99	62 (15.8)	65 (17)	65 (65)	59 (60)	22.7(4.5)	22 (3.8)	52(52)	43 (43)	N/A	N/A
Eyer, 1993	19	19	44 (22)	41 (18)	14 (73)	8 (42)	N/A	N/A	0 (0)	0 (0)	N/A	N/A
Fetterplace, 2018	30	30	55 (13)	57 (16)	23 (77)	21 (70)	30 (7.1)	29 (5.3)	21 (70)	16 (53)	22 (6.2)	20 (5.9)
Jakob, 2017	46	44	64 (17)	61 (17)	33 (72)	28 (64)	29 (7.0)	28 (6.1)	N/A	N/A	28 (8.0)	28 (8.7)
Rugeles, 2013	40	40	53 (20)	56 (20)	22 (55)	24 (60)	24 (3.3)	24 (4.4)	40 (100)	40 (100)	14 (4.8)	15 (6.2)
Van Zanten, 2018	22	22	64 (13)	61 (15)	9 (41)	13 (59)	30 (4.1)	31 (8.4)	8 (36)	9 (41)	25 (5.6)	23 (7.1)

Abbreviations: BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation.

Table 3. Energy and protein provision of included studies

Author, year	Duration of Intervention mean (SD), days	Delivered protein, mean (SD), g/kg/day		Delivered energy, mean (SD), kcal/kg/day	
		Intervention	Control	Intervention	Control
Allingstrup, 2017	11.3 (12.8)	1.4 (0.42)	0.49 (0.30)	24 (6.6)	14 (6.8)
Eyer, 1993	11.8 (7.9)	1.3 (0.30)	0.9 (0.2)	30 (6)	19 (5)
Fetterplace, 2018	10.6 (8.3)	1.2 (0.30)	0.75 (0.11)	23 (5.7)	21 (3.3)
Jakob, 2017	7 (2.6)	1.2 (0.47)	0.90 (0.20)	20 (7.4)	22 (4.9)
Rugeles, 2013[a]	9.5 (5.5)	1.4	0.76	12	14
Van Zanten, 2018	18.4 (13.4)	1.3 (0.95)	0.70 (0.32)	16 (11)	15 (6.3)

[a]Only mean figures for protein and energy delivery were reported in the original paper, the author was contacted for clarification of the variance, however this was not provided.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jpen.1725.

Figure 1. PRISMA diagram

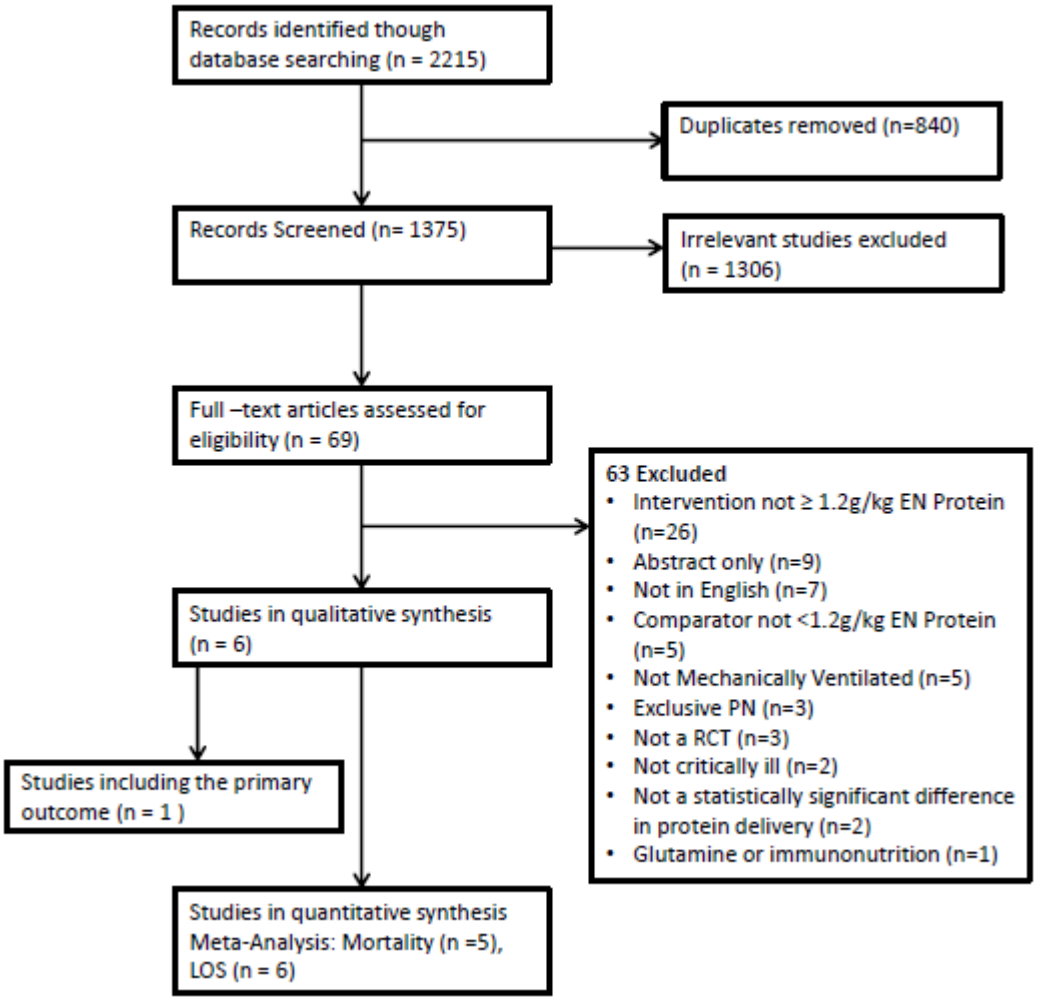
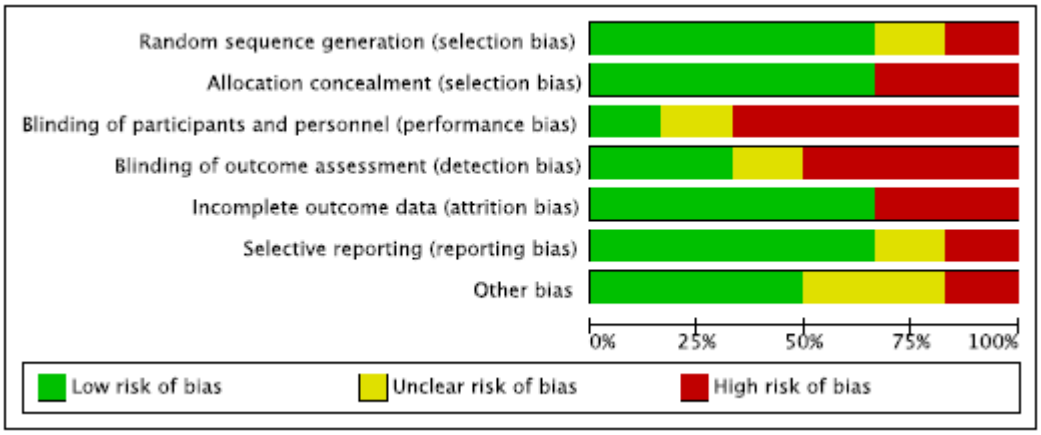


Figure 2. Summary of risk of bias assessment

2A. Risk of bias summary for each included study



2B. Summary of domains for risk of bias for included studies

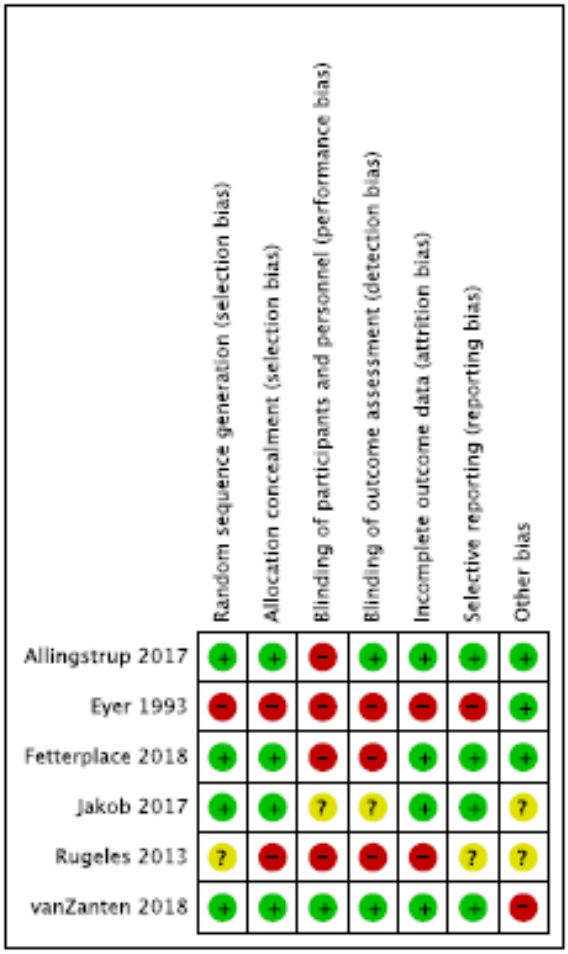


Figure 3. Random effects meta-analysis of mortality, sorted by ascending year of publication

Abbreviations: High; Higher protein (intervention group), Standard; Usual protein group (Comparator). Random effects model using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Analysis using Stata command *metan* in Stata version 15.1, College Station Texas, USA.

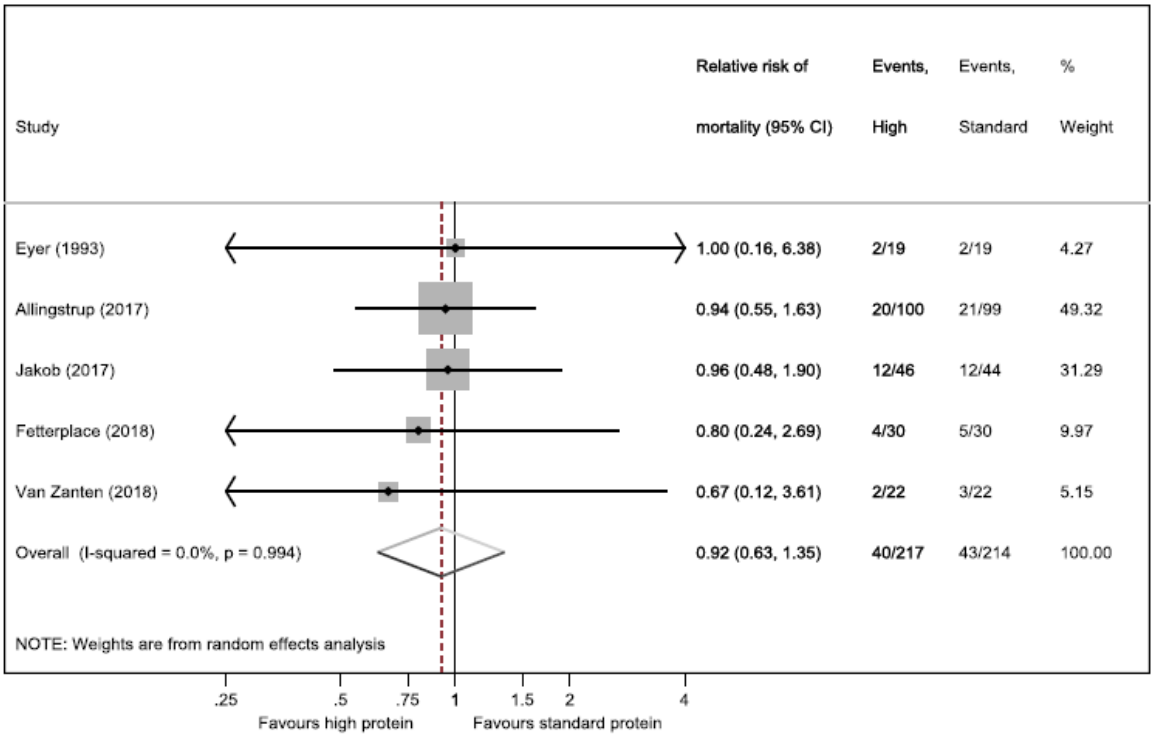


Figure 4. Random effect analysis of length of admission, sorted by ascending year of publication

Abbreviations: High; Higher protein (intervention group), Standard; Usual protein group (Comparator). Random effects model returned by using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the from the Mantel-Haenszel model. Analysis using Stata command *metan* in Stata version 15.1, College Station Texas, USA