4.2c Composition of Enteral Nutrition: High Protein vs. Low Protein May 2015

Recommendation 2015: *There are insufficient data to make a recommendation regarding the use of high protein diets or escalating doses of protein in critically ill patients.*

Discussion 2015: The committee noted the addition on one new study (Rugeles 2014) that only reported on mechanical ventilation, ICU length of stay and showed no difference between the groups in these outcomes. There was also a lack of effect on mortality seen in all the studies that reported on this outcome. Although the signals from prior large-scale observational studies of critically ill patients suggest that optimal amounts and timely provision of protein intake is associated with reduced infectious complications, duration of mechanical ventilation, and mortality (1, 2, 3), along with perceptions of faster physical recovery (4), the committee acknowledged that there was limited data from randomized trials that prevents making strong conclusions about the dose of protein in critically ill patients. The committee decided not to make a recommendation on the use of high protein diets until more evidence from randomized trials is available.

1. Alberda C, Gramlich L, Jones NE, Jeejeebhoy K, Day A, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: Results of an international multicenter observation study. Intensive Care Med. 2009 Oct;35(10):1728-37.
2. Heyland DK, Stephens KE, Day AG, McClave SA. The success of enteral nutrition and ICU-acquired infections: A multicenter observational study. Clin Nutr. 2011 Apr;30(2):148-55.
3. Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients: Depends on how you slice the cake! Crit Care Med. 2011 Dec;39(12):2619-26.
4. Wei S, Day A, Oulette-Kunz H, Heyland DK. Nutritional Adequacy and Health-related Quality of Life in Critically Ill Patients Requiring Prolonged Mechanical Ventilation. Crit Care Med. 2015 (in press)

Recommendation 2013: *There are insufficient data to make a recommendation regarding the use of high protein diets or escalating doses of protein in critically ill patients.*

Discussion 2013: The committee noted the addition of one new study (Scheinkestel et al 2003) in continuous renal replacement therapy (CRRT) patients of an escalating dose of protein over a short duration which had no treatment effect with respect to mortality. The lack of an effect of a higher vs. lower protein formula on clinical outcomes in head injured patients from an older study was also noted (Clifton 1985). Despite the signals from observational studies showing improved outcomes with higher protein intakes in critically ill patients (1, 2) and no safety concerns, there is limited data from randomized trials that prevents making strong conclusions about the dose of protein in critically ill patients (3). Given this, the committee decided against making a recommendation.

1. Allingstrup MJ et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr. 2012 Aug;31(4):462-8.
2. Heyland D et al. Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol in Critically Ill Patients (The PEP uP Protocol): Results of a cluster randomized trial. Critical Care Medicine 2013 (in press).
3. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr. 2012 Sep;96(3):591-600.

Semi Quantitative Scoring

Values	Definition	2013 Score 0, 1, 2, 3	2015 Score 0,1,2,3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0	0
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	1	1
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1	1
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogeneous patients, diverse practice settings =3.	1	1
Cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2	2
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	3	3

4.2c Composition of Enteral Nutrition: High Protein vs. Low Protein

Question: Compared to a lower enteral protein intake does a higher protein intake enteral formula result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 3 level 2 studies that compared the effect of a higher protein regimen to a lower protein regimen. Clifton (1985) compared the high-protein formula Traumacal to the lower protein formula Magnacal in head injured patients. Scheinkestel et al (2003) compared a higher escalating protein feeding schedule (starting at 1.5 gm/kg/day to 2.5 gm/kg/day over 6 days) to a constant level of protein (1.5 gm/kg/day) in patients on with renal failure on continuous renal replacement therapy (CRRT) in a 4:1 trial. Rugeles 2014 compared a hypocaloric hyperprotein regimen to a standard regimen.

Mortality: A meta-analyses could not be done on as one study reported on 3 month mortality (Clifton 1985), one reported on ICU mortality Scheinkestel (2003) and the other did not report on mortality. There were no statistically significant differences in mortality between the groups in either study (Clifton 1985 RR 1.00, 95 % CI 0.07-13.9; Scheinkestel et al 2003 RR 0.56, 95 % CI 0.22-1.46).

Infections: In the study that reported on infections (Clifton, 1985), there were more bacterial infections in the group receiving the higher protein formula but this was not statistically significant (Relative Risk 1.50, 95 % CI 0.32, 7.1).

LOS and Ventilator days: One study reported on these outcomes (Rugeles 2014) and there was no significant difference on ICU LOS (p=0.42) or length of mechanical ventilation (p=0.26).

Other: In the study by Clifton (1985), nitrogen balance was higher in the higher protein group but this was not statistically significant. Nitrogen balance became positive in patients in the escalating protein group compared to the control group over time (p =0.0001) in the Scheinkestel (2003) study. Rugeles 2014 showed no difference in calories received but a significant difference in protein received (1.4 g/kg/d vs 0.76 g/kg/d, p $\leq$0.0001).

Conclusions:

1) An escalating protein feeding schedule (1.5 to 2.5 gm/kg/day) vs 2 gm/kg/day has no effect on mortality in critically ill patients on CRRT.
2) A higher protein formula has no effect on mortality and infectious complications in head injured patients.
3) A higher protein formula has no effect on ICU length of stay or duration of mechanical ventilation

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study*: If any one of the above characteristics are unfulfilled.*

Table 1. Randomized Studies Evaluating Higher Protein vs. Low Protein Enteral Formula in Critically ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		RR (CI)**	Infections # (%)		RR (CI)**
1) Clifton 1985	Head injured patients Comatose for 24 hrs N=20	C.Random: not sure ITT: yes Blinding: no (8)	22% pro, 38 % CHO, 41 % fat, 1.5 Kcal/ml (Traumacal vs. 14 % pro, 50 % CHO, 36 % fat, 2.0 Kcal/ml (Magnacal) Isocaloric, 29 gm Nitrogen vs.17.6 gms Nitrogen	High protein 1/10 (10)	Low protein 1/10 (10)	1.00 (0.07-13.9)	High protein 3/10 (30)	Low protein 2/10 (20)	1.50 (0.32, 7.1)
2) Scheinkestel 2003	Critically ill ventilated pts on 6 days CRRT for renal failure N=50	C.Random: yes ITT: yes Blinding: no (9)	1.5 g/kg/d protein x2 days, 2.0 g/kg/d protein x2 days and 2.5 g/kg/d protein x2 days while receiving CRRT vs 2.0 g/kg/d protein x6 days while receiving CRRT	High protein ICU: 9/40 (23)	Low protein ICU: 4/10 (40)	0.56 (0.22-1.46)	NA	NA	NA
3) Rugeles 2013	Medical adult ICU patients N=80	C.Random: yes ITT: no Blinding: double (7)	hypocaloric hyperproteic (15 kcal/kg, 1.7 g/kg/d) x 7 days vs standard (25 kcal/kg, 20% calories from protein).	NR	NA	NA	NR	NR	NA

C.Random: concealed randomization ± : mean ± standard deviation

Study	Mechanical Ventilation	ICU LOS	Nutrition parameters
1) Clifton 1985	NR	NR	High protein Low Protein Calories (kcal/kg/d) 51 48 Grams nitrogen/day 0.42 0.24
2) Scheinkestel 2003	NR	NR	High protein Low Protein Calories per day 2063 2095 N balance -0.56 -4,5
3) Rugeles 2013	High protein Low Protein 8.5 ± 4.6 days 9.7 ± 4.9 days	High protein Low Protein 9.5 ± 5.5 days 10.4 ± 5.0 days	High protein Low Protein Calories (kcal/kg/d) 12 14 Protein (g/kg/d) 1.4 7.6

ITT: intent to treat
NR: Not reported

** RR= relative risk, CI= Confidence intervals