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. Rugeles (2014) compared a hypocaloric hyperprotein regimen to a standard regimen. Fetterplace (2018) compared the high protein formula Nutrison Protein Plus to the lower protein formula Nutrison in medical and surgical ICU patients. Scheinkestel (2003) was excluded from this review because the average protein goals of the two groups did not differ (the control group's protein goal was 2 g/kg/d vs the intervention group's protein goal was 1.5 g/kg/d x 2 days, 2.0 g/kg/d x 2 days and 2.5 g/kg/d x 2 days).

Mortality: All three studies reported on mortality, though at different time intervals. Overall, there was no effect on mortality (RR 0.89, 95% CI 0.50, 1.60, p=0.70, I^2 heterogeneity=0%; figure 1).

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 (RR 1.50, 95 % CI 0.32, 7.1).

LOS and Ventilator days: Two studies reported on these outcomes (Rugeles 2014, Fetterplace 2018) and there was no significant difference on ICU LOS (WMD -0.94, 95% CI -2.75, 0.87, p=0.31, I^2 heterogeneity=0%; figure 2), hospital LOS (WMD 3.05, 95% CI -6.24, 12.35, p=0.52, I^2 heterogeneity=81%; figure 3) or length of mechanical ventilation (WMD -0.02, 95% CI -2.81, 2.77, p=0.99, I^2 heterogeneity=54%; figure 4).

Physical Outcomes: Fetterplace 2018 was the only study that reported on physical outcomes. They found no difference between groups with regards to hand grip strength, muscle strength (Medical Research Council (MRC) scale), ICU acquired weakness (MRC < 48), and physical function (Physical Function in Intensive Care Unit Test (PFIT-s)).

Other: In the study by Clifton (1985), nitrogen balance was higher in the higher protein group but this was not statistically significant. 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). Fetterplace 2018 showed significantly higher calories and protein received in the high protein group (84% vs 73% caloric adequacy, p=0.01 and 90% vs 57% protein adequacy, p<0.001). Time to start EN was significantly shorter in the high protein group (13 vs 20 hours, p=0.01). In the high vs low protein groups, there were no differences in diarrhea occurrence (16/30 patients in both groups, p=1.0) and feeding intolerance (30% vs 27%, p=0.77). No difference was found in the physical outcomes tested, except in quadriceps muscle layer thickness (QMLT) assessed by ultrasound at baseline and ICU discharge. The intervention was associated with less QMLT loss at discharge, with an average attenuated loss of 0.22 cm (95% CI 0.06, 0.38, p=0.01; table 2).

Conclusions:

1) A higher protein formula has no effect on mortality in critically ill patients.
2) A higher protein formula has no effect on infectious complications in critically ill head injured patients.
3) A higher protein formula has no effect on ICU length of stay, hospital length of stay or duration of mechanical ventilation in critically ill patients.

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 # (%) High protein	Mortality # (%) Low Protein	RR (CI)**	Infections # (%) High protein	Infections # (%) Low Protein	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	3 Month 1/10 (10)	3 Month 1/10 (10)	1.00 (0.07-13.9)	3/10 (30)	2/10 (20)	1.50 (0.32, 7.1)
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).	28 day 11/40	28 day 12/40		NR	NR	NA
4) Fetterplace 2018	Medical and surgical ICU patients. Single centre. N=60	C.Random: yes ITT: yes Blinding: single (10)	1.5 g/kg/d x 15 days from high protein EN (Nutrison Protein Plus) vs 1.0 g/kg/d from standard EN (Nutrison)	28 day 4/30 60 day 4/30	28 day 5/30 60 day 5/30		NR	NR	NA

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

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

Study	Mechanical Ventilation High protein	Mechanical Ventilation Low Protein	LOS High protein	LOS Low Protein	Nutrition parameters High protein	Nutrition parameters Low Protein
1) Clifton 1985	NR		NR		Calories (kcal/kg/d) 51 Grams nitrogen/day 0.42	 48 0.24
2) Rugeles 2013	8.5 + 4.6 days (40)	9.7 + 4.9 days (40)	ICU 9.5 + 5.5 days Hospital 19.5 + 6.5 days	 10.4 + 5.0 days 20.5 + 5 days	Calories (kcal/kg/d) 12 Protein (g/kg/d) 1.4	 14 0.76
3) Fetterplace 2018	8.7 + 7.5 days (30)	7.0 + 5.0 days (30)	ICU 10.6 + 8.3 days Hospital 27.4 + 19.0 days	 9.1 + 5.5 days 18.8 + 10.9 days	Calories (kcal/kg/d) 21 + 5.2 Protein (g/kg/d) 1.2 + 0.3 Caloric adequacy, % 84 + 21 Protein adequacy, % 90 + 25 Time to start EN (h) 13 + 8 Diarrhea 16/30 (53%) Feeding intolerance 9/30 (30)	 18 + 2.7, p=0.01 0.75 + 0.11, p<0.001 73 +11, p=0.01 57 + 8, p<0.001 20 + 10, p=.01 16/30 (53%), p=1.0 8/30 (27), p=0.77

ITT: intent to treat
NR: Not reported
** RR= relative risk, CI= Confidence intervals

Table 2. Physical Outcomes

Study	Physical outcomes High protein Low Protein
3) Fetterplace 2018	Handgrip strength, kg 20 (6.1), n=6 21 (9.3), n=16, p=0.94 Muscle strength (MRC score) 55 (5.9), n=7 52 (9.6), n=14, p=0.53 ICU acquired weakness (MRC<48) 1 (14), n=7 4 (28), n=14, p=0.47 Physical function in ICU test 6.8 (3.8), n=8 7.9 (3.4), n=14, p=0.49 Quadricep Muscle Layer Thickness (ultrasound) Intervention: effect 0.22, 95% CI 0.06-0.038, p=0.01n=24 (intervention), n=23 (control)

Figure 1. Mortality

Study or Subgroup	High Dose Events	High Dose Total	Low Dose Events	Low Dose Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Clifton 1985	1	10	1	10	5.0%	1.00 [0.07, 13.87]	1985
Rugeles 2013	11	40	12	40	71.8%	0.92 [0.46, 1.83]	2013
Fetterplace 2018	4	30	5	30	23.3%	0.80 [0.24, 2.69]	2018
Total (95% CI)		**80**		**80**	**100.0%**	**0.89 [0.50, 1.60]**	
Total events	16		18				

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)

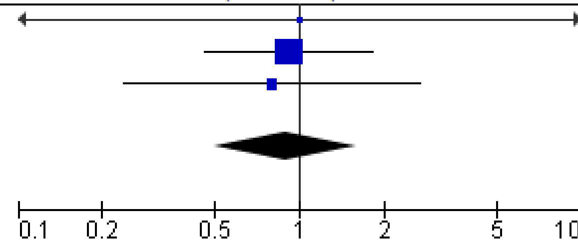

Figure 2. ICU LOS

Study or Subgroup	High Dose Mean	High Dose SD	High Dose Total	Low Dose Mean	Low Dose SD	Low Dose Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rugeles 2013	9.5	5.5	40	10.4	5	40	61.9%	-0.90 [-3.20, 1.40]	2013
Fetterplace 2018	19.5	6.5	30	20.5	5	30	38.1%	-1.00 [-3.93, 1.93]	2018
Total (95% CI)			**70**			**70**	**100.0%**	**-0.94 [-2.75, 0.87]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)

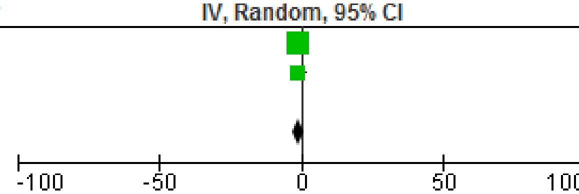

Figure 3. Hospital LOS

Study or Subgroup	High Dose Mean	High Dose SD	High Dose Total	Low Dose Mean	Low Dose SD	Low Dose Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rugeles 2013	19.5	6.5	40	20.5	5	40	57.8%	-1.00 [-3.54, 1.54]	2013
Fetterplace 2018	27.4	19	30	18.8	10.9	30	42.2%	8.60 [0.76, 16.44]	2018
Total (95% CI)			**70**			**70**	**100.0%**	**3.05 [-6.24, 12.35]**	

Heterogeneity: Tau² = 37.24; Chi² = 5.21, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.64 (P = 0.52)

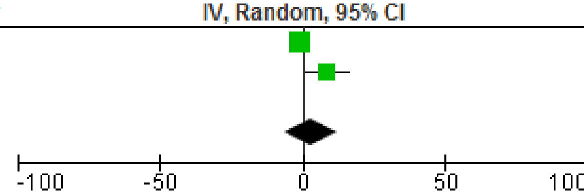

Figure 4. Duration of Ventilation

	High Dose			Low Dose				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Rugeles 2013	8.5	4.6	40	9.7	4.9	40	59.4%	-1.20 [-3.28, 0.88]	2013
Fetterplace 2018	8.7	7.5	30	7	5	30	40.6%	1.70 [-1.53, 4.93]	2018
Total (95% CI)			**70**			**70**	**100.0%**	**-0.02 [-2.81, 2.77]**	

Heterogeneity: Tau² = 2.29; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.02 (P = 0.99)