9.5 Composition of PN: Protein and Amino Acids

There were no new randomized controlled trials since the 2015 update and hence there are no changes to the following summary of evidence.

Question: Do higher or lower IV amino acid doses result in improved clinical outcomes in the critically ill adult patient?

Summary of evidence: This is a new topic in 2018. There is one level 1 (Ferrie 2016) and 1 level 2 (Doig 2015) study included in this topic. Ferrie et al studied a higher amino acid concentration of PN aimed to provide 1.2 g/kg/d protein vs a lower amino acid concentration of PN aimed to provide 0.8 g/kg/d protein. Nutrition provision was intended to be non-isonitrogenous, isocaloric (25 kcal/kg/d). Doig et al studied standard nutrition care plus IV amino acids with a max dose of 2 g/kg/d protein vs standard nutrition care. Nutrition provision was intended to be non-isonitrogenous, non-isocaloric.

Mortality: When the two trials were aggregated, a higher protein dose had no effect on ICU mortality (RR 0.99, 95% CI 0.60, 1.62, p=0.96, heterogeneity I^2=0%; figure 1) or hospital mortality (RR 0.92, 95% CI 0.59, 1.43, p=0.70, heterogeneity I^2=2%; figure 2).

Infections: No data available.

LOS: Though both studies reported on ICU and hospital LOS, data was not reported in mean and standard deviation and, therefore, could not be meta-analyzed. Ferrie et al found a trend towards a reduced ICU LOS in the higher amino acid group (p=0.16) but there was no effect on hospital LOS (p=0.41). Doig et al found no effect on ICU or hospital LOS (p=0.26 and 0.49, respectively).

Ventilator Days: Though both studies reported on ventilation duration, data was not reported in mean and standard deviation and, therefore, could not be meta-analyzed. Both Ferrie et al and Doig et al found no effect on ventilation duration (p=0.22 and 0.84, respectively).

Other: Ferrie et al measured hand grip strength at study day 7 and at ICU discharge. They found a significant difference favouring the higher amino acid group at study day 7 (p=0.025) and a trend towards improvement in the higher amino acid group at ICU discharge (p=0.054). They also measured muscle area and thickness using ultrasound on day 7 and found a significantly greater forearm muscle thickness (p<0.0001) and thigh muscle area (p=0.02) in the higher amino acid group, but there was no difference in bicep muscle thickness (p=0.21). The sum of the 3 muscle sites on ultrasound at day 7 was significantly greater in the higher amino acid group (p=0.02). Doig et al conducted quality of life (QOL) questionnaires and found no difference between groups on the RAND-36 General Health questionnaire and the ECOG Performance Status questionnaire (p=0.41 and 0.21, respectively). They observed a trend towards improvement in the higher amino acid group (p=0.11) on the RAND-36 Physical Function questionnaire.

Conclusions:

1) A higher vs lower IV amino acid dose has no effect on ICU and hospital mortality, ICU and hospital LOS and mechanical ventilation duration in critically ill patients.

2) A higher vs lower IV amino acid dose may be associated with improved muscle mass, strength and functional performance.

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/Amino Acids vs. Low Protein/Amino Acids in Critically ill Patients receiving PN

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)		Mechanical Ventilation	
				Additional protein	Control	Additional protein	Control	Additional protein	Control
1) Doig 2015	Mixed ICU patients with an expected LOS of at least 2 days. Multi centre. N=474	C. Random: yes ITT: no Blinded: no (7)	100 g/L L-amino acids (Synthamin 17 electrolyte free, max 100 g/d from supplement) + standard nutrition care (max 2 g/kg/d protein from all sources combined) vs standard nutrition care	**ICU** 28/239 (11.7) **Hospital** 37/239 (15.5) **90 day** 42/236 (17.8)	**ICU** 30/235 (12.8) **Hospital** 43/235 (18.3) **90 day** 47/235 (20)	NR	NR	7.33 (7-7.68)	7.26 (6.94-7.61)
2) Ferrie 2016	ICU patients requiring PN. Single centre. N=120	C. Random: yes ITT: yes Blinded: double (12)	Olimel N9 (57 g amino acids/L), goal protein 1.2 g/kg/d vs Oli-Clinomel N7 (40 g amino acids/L), goal protein 0.8 g/kg/d. Both groups aimed for 25 kcal/kg/d.	**ICU** 8/59 (14) **Hospital** 12/60 (20) **6 Month** 15/60 (25)	**ICU** 6/60 (10) **Hospital** 9/60 (15) **6 Month** 9/60 (15)	NR	NR	2.0 (1.0-3.0)	2.0 (1.0-5.0)

C.Random: concealed randomization ± : mean ± standard deviation NR: Not Reported

Table 1. Randomized Studies Evaluating Higher Protein/Amino Acids vs. Low Protein/Amino Acids in Critically ill Patients receiving PN (continued)

Study	LOS		Nutritional outcomes		QOL Outcomes		Physical Outcomes	
	Additional protein	Control	Additional protein	Control	Additional protein	Control	Additional protein	Control
1) Doig 2015	**ICU** 11.6 (10.8-12.5) **Hospital** 26 (24.2-28)	10.7 (10-11.5) 24.8 (23-26.6)	Intervention group received "significantly more protein" during first 7 days. **Requiring RRT at day 90** 0/191	1/183	**RAND-36 General Health** 50.5 ± 27.2 (n=192) **ECOG Performance Status** 1.31 ± 1 (n=192) **RAND-36 physical function** 47.4 ± 33.7 (n=192)	52.8 ± 25.9 (n=180) 1.18 ± 1 (n=181) 53.2 ± 33 (n=180)	NR	

2) Ferrie 2016	**ICU** 5.0 (3.0-8.0) 6.0 (3.8-10.0) **Hospital** 25.0 (16.8-41.3) 27.5 (18.8-55.8)	**Protein g/kg/d, mean first 7 days** 1.09 ± 0.22 0.9 ± 0.21 **Kcal/kg/d, mean first 7 days** 23.2 ± 3.0 24.9 ± 4.2 **Dialysis days, median (Q1-Q3)** 7.0 (2.0-8.8) 6.0 (5.4-7.0)	NR	**Hand grip strength at day 7, kg** 22.1 ± 10.1 18.5 ± 11.8, p=0.025 **Hand grip strength at ICU d/c, kg** 18.5 ± 10.4 15.8 ± 10.3, p=0.054 **Forearm muscle thickness on ultrasound, cm, day 7** 3.2 ± 0.4 2.8 ± 0.4, p<0.0001 **Bicep muscle thickness on ultrasound, cm, day 7** 2.5 ± 0.6 2.4 ± 0.4, p=0.21 **Thigh muscle area on ultrasound, cm, day 7** 6.8 ± 2.1 5.8 ± 1.9, p=0.02 **Sum of 3 muscle sites on ultrasound, cm, day 7** 8.4 ± 1.0 7.9 ± 1.1, p=0.02

Figure 1. ICU Mortality

Study or Subgroup	Higher Protein/Amino Acids Events	Total	Low Protein/Amino Acids Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Doig 2015	28	239	30	235	80.7%	0.91 [0.52, 1.57]
Ferrie 2016	8	59	6	60	19.3%	1.41 [0.46, 4.35]
Total (95% CI)		**298**		**295**	**100.0%**	**0.99 [0.60, 1.62]**
Total events	36		36			

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

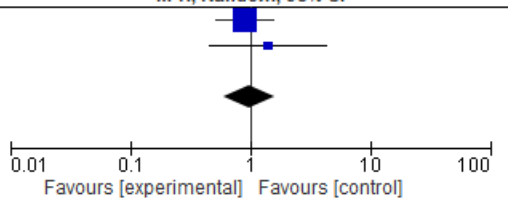
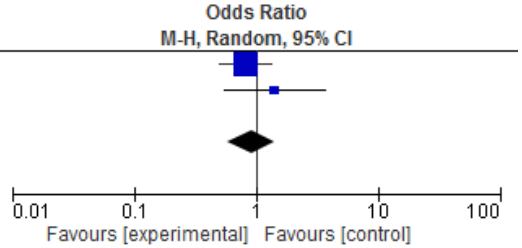


Figure 2. Hospital Mortality

Study or Subgroup	Higher Protein/Amino Acids Events	Total	Low Protein/Amino Acids Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Doig 2015	37	239	43	235	78.9%	0.82 [0.51, 1.32]
Ferrie 2016	12	60	9	60	21.1%	1.42 [0.55, 3.66]
Total (95% CI)		**299**		**295**	**100.0%**	**0.92 [0.59, 1.43]**
Total events	49		52			

Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 0.38 (P = 0.70)



Reference:
Included Articles

1. Doig GS, Simpson F, Bellomo R, Heighes PT, Sweetman EA, Chesher D, Pollock C, Davies A, Botha J, Harrigan P, Reade MC. Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. Intensive Care Med. 2015 Jul;41(7):1197-208.
2. Ferrie S, Allman-Farinelli M, Daley M, Smith K. Protein Requirements in the Critically Ill: A Randomized Controlled Trial Using Parenteral Nutrition. JPEN J Parenter Enteral Nutr. 2016 Aug;40(6):795-805. doi: 10.1177/0148607115618449. Epub 2015 Dec 3. PubMed PMID: 26635305.

Excluded Articles

#	Reason excluded	Citation
1	Not critically ill pts	Liebau F, Sundström M, van Loon LJ, Wernerman J, Rooyackers O. Short-term amino acid infusion improves protein balance in critically ill patients. Critical Care. 2015;19(1):106. doi:10.1186/s13054-015-0844-6.