9.1a Composition of PN: Protein and Amino Acids

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

Summary of evidence: This was introduced as a new topic in 2018 and includes one level 1 (Ferrie 2016) and 2 level 2 studies (Doig 2015, Singer 2007) . Singer at al 2007 examined the effect of an isocaloric approach of 150 g/day amino acids vs. 75 g/day amino acids for 3 days. Ferrie et al 2016 studied an isocaloric, 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. Doig et al 2015 studied standard nutrition care plus IV amino acids with a max dose of 2 g/kg/d protein vs. standard nutrition care (non isocaloric).

Mortality: When the data from the trials were aggregated, a higher protein dose had no effect on ICU mortality (RR 1.00, 95% CI 0.66, 1.51, p=1.00, test for heterogeneity I^2=0%; figure 1) or hospital mortality (RR 0.93, 95% CI 0.65, 1.34, p=0.70, heterogeneity I^2=2%; figure 2).

Infections: No data available.

LOS: Two studies reported on ICU and hospital LOS, however data was not reported in mean and standard deviation and therefore, could not be meta-analyzed. Ferrie et al 2016 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 2015 found no effect on ICU or hospital LOS (p=0.26 and 0.49, respectively).

Ventilator Days: Two studies reported on ventilation duration, data was not reported in mean and standard deviation hence could not be meta-analyzed. Both Ferrie et al 2016 and Doig et al 2015 found no effect on ventilation duration (p=0.22 and 0.84, respectively).

Other: In the Singer 2007 study, a significant improvement in cumulative nitrogen balance was seen in non oliguric patients with acute renal failure receiving 150 gms of amino acids/day with 2000 non protein kcals/day compared to those that received 75 gms amino acids and same non protein kcals (p<0.001). Doig et al 2015 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. Ferrie et al 2016 measured hand grip strength at study day 7 and at ICU discharge and reported a significant difference favouring the higher amino acid group at study day 7 (p=0.025) with a trend towards improvement in the higher amino acid group at ICU discharge (p=0.054). A significantly greater forearm muscle thickness (p<0.0001) and thigh muscle area (p=0.02) was found 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).

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, functional performance and improved nitrogen balance .

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	
				Higher amino acids	Lower amino acids	Higher amino acids	Lower amino acids	Higher amino acids	Lower amino acids
1) Singer 2007	Mechanically ventilated patients requiring PN with non-oliguric acute renal failure N=14	C. Random: no ITT: yes Blinded: not (5)	150 g/day amino acids (Aminoplasmal 10%) vs. 75 g/day amino acids (Aminoplasmal 10%) for 3 days. Both aimed to receive 2000 kcal/day of non-protein calories via dextrose and Intralipid (isocaloric)	**ICU** 3/8 (37.5%)	**ICU** 2/6 (33.3%)	NR	NR	NR	
2) 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 Non isocaloric	**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)
3) 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 (isocaloric)	**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) 4.87±14.37*	2.0 (1.0-5.0) 2.67±6.16*

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

Study	LOS Higher amino acids Lower amino acids	Nutritional outcomes Higher amino acids Lower amino acids	QOL Outcomes Higher amino acids Lower amino acids	Physical Outcomes Higher amino acids Lower amino acids
1) Singer 2007	NR	**Cumulative Nitrogen balance** 2.9 ± 8.3 vs. -10.5 ± 17; p<0.001	NR	NR
2) Doig 2015	**ICU** 11.6 (10.8-12.5) 10.7 (10-11.5) **Hospital** 26 (24.2-28) 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) 52.8 ± 25.9 (n=180) **ECOG Performance Status** 1.31 ± 1 (n=192) 1.18 ± 1 (n=181) **RAND-36 physical function** 47.4 ± 33.7 (n=192) 53.2 ± 33 (n=180)	NR
3) Ferrie 2016	**ICU** 5.0 (3.0-8.0) 6.0 (3.8-10.0) 9.85±14.83* 7.27±7.84* **Hospital** 25.0 (16.8-41.3) 27.5 (18.8-55.8) 41.75±37.36* 37.70±35.88*	**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

C.Random: concealed randomization ± : mean ± standard deviation NR: Not Reported
* Data was obtained from the author

Figure 1. ICU Mortality

Study or Subgroup	Higher Protein/Amino Acids Events	Total	Low Protein/Amino Acids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Singer	3	8	2	6	8.3%	1.13 [0.27, 4.76]	2007
Doig	28	239	30	235	74.3%	0.92 [0.57, 1.49]	2015
Ferrie	8	59	6	60	17.4%	1.36 [0.50, 3.67]	2016
Total (95% CI)		**306**		**301**	**100.0%**	**1.00 [0.66, 1.51]**	
Total events	39		38				

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

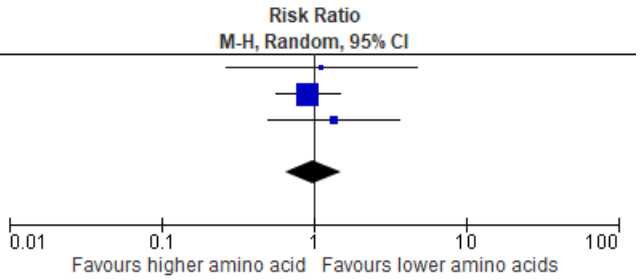
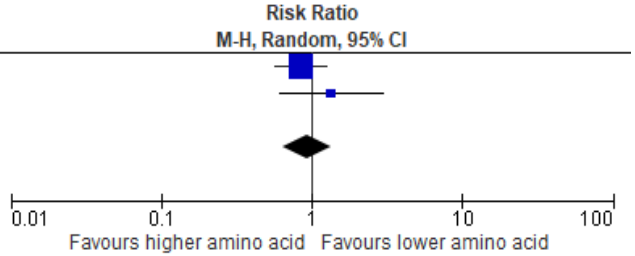


Figure 2. Hospital Mortality

Study or Subgroup	Higher Protein/Amino Acids Events	Total	Low Protein/Amino Acids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Doig	37	239	43	235	78.8%	0.85 [0.57, 1.26]	2015
Ferrie	12	60	9	60	21.2%	1.33 [0.61, 2.93]	2016
Total (95% CI)		**299**		**295**	**100.0%**	**0.93 [0.65, 1.34]**	
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. Singer P. High-dose amino acid infusion preserves diuresis and improves nitrogen balance in non-oliguric acute renal failure. Wien Klin Wochenschr. 2007;119(7-8):218-222. doi:10.1007/s00508-007-0794-3
2. Doig GS, Simpson F, Bellomo R, et al. Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. Intensive Care Med. 2015;41(7):1197-1208. doi:10.1007/s00134-015-3827-9
3. 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;40(6):795-805. doi:10.1177/0148607115618449