4.3 Strategies for optimizing and minimizing risks of EN: Peptides vs. Whole Protein

Question: Does the use of peptide based enteral formula, compared to an intact protein formula, result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 8 level 2 studies that compared a peptide based enteral formula to one with intact proteins (also called polymeric or whole protein). Rice et al 2019 compared isonitrogenous hypocaloric feeding using a peptide-based formula to standard feeding using a polymeric formula in obese overweight critically ill patients (also included in section 3.3b Intentional Underfeeding: Hypocaloric Enteral Nutrition).

Mortality: Six studies reported mortality and when ethe data were aggregated, there were no differences between the groups that received peptide based vs. intact protein formulas (RR0.91, 95% CI 0.63, 1.31, p=0.62, test for heterogeneity I^2=0%; figure 1).

Infections: Based on the three studies that reported on infections, there were no difference between the groups (RR 0.95, 95% CI 0.77, 1.18, p=0.65, heterogeneity I^2=0%; figure 2).

LOS: Two studies reported on ICU LOS (Aguilar-Nascimento 2011, Jakob 2017) and neither found a difference between groups (p=0.97 and p=0.3, respectively). Three studies reported on hospital LOS (Meredith 1990, Jakob 2017, Rice 2019) and also found no difference between groups (p=0.NS, p=0.97, p=0.87 respectively). The data was not aggregated in a meta-analysis due to inconsistency in methods of reporting.

Ventilator days: Jakob 2017 and Rice 2019 reported ventilator days and found no difference between groups (p=0.23, p=0.52 respectively).

Other complications: A trend towards an increase in diarrhea with the use of peptides was seen in one study (Heimburger 1997; p =0.07), whereas another study showed a decrease in the incidence of diarrhea in the peptide group (Meredith 1990). Three studies found no significant differences in diarrhea between the two groups (Mowatt-Larsen 1992, Jakob 2017, Carteron 2021). In one study of hypoalbuminemic patients (Brinson 1988), 3/5 patients in the control group (standard) crossed over to the experimental group (peptide based) because of diarrhea. A meta analyses of the six studies showed no difference in diarrhea between the peptide based and standard groups (RR 1.06, 95% CI 0.61, 1.83, p=0.84, test for heterogeneity I^2=51%; figure 3). One study (Aguilar-Nascimento 2011) reported a significant decrease in IL-6 levels from day 1 to 5 with the use of a whey-based formula when compared to a casein based formula.

Energy and protein intake: When the data from the three studies that reported energy intake in kcal/kg/day were aggregated, the use of a peptide enteral formula compared to an intact protein formula had no effect on energy intake ((WMD -0.80, 95% CI -2.31, 0.70, p=0.29, heterogeneity I^2=0%; figure 4). The data from Rice 2019 was not included in this analysis due to the intentional hypocaloric feeding strategy. When the data from the four studies that reported protein intake were aggregated, the use of a peptide enteral formula had no effect on gm/kg/day of protein (WMD -0.01, 95% CI -0.20, 0.17, p=0.88, heterogeneity I^2=87%; figure 5).

Conclusions:

1) A peptide based vs. standard EN formula has no effect on mortality, infections, or length of stay in ICU patients.
2) A peptide based vs. standard EN formula has no effect on diarrhea in ICU patients.
3) A peptide based vs. standard EN formula has no effect on energy or protein intake in ICU 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 peptide based vs. whole protein enteral formulas in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)	
				Peptide	Whole Protein	Peptide	Whole Protein
1. Brinson 1988	Mixed ICU's patients with MOF, hypoalbuminemia, malnutrition from 2 ICUs N=12	C.Random: no ITT: yes Blinding: nsingle (5)	Peptide based formula (vital HN) vs whole protein formula (Osmolite HN)	0/7 (0)	2/5 (40)	NR	NR
2. Meredith 1990	ICU patients, trauma, N=18	C.Random: yes ITT: yes Blinding: no (8)	Peptide based formula (Reabilan HN) vs whole protein formula (Osmolite HN)	1/9 (11)	1/9 (11)	NR	NR
3. Mowatt-Larsen 1992	Critically ill, acutely injured patients, albumin < 30 N=41	C.Random: not sure ITT: no Blinding: no (6)	Peptide based formula (Reabilan HN) vs whole protein formula (Isocal)	NR	NR	12/21 (60)	14/20 (70)
4. Heimburger 1997	ICU patients from 2 ICUs N=50	C.Random: not sure ITT: no Blinding: no (7)	Small peptide formula vs whole protein formula	NR	NR	17/26 (65)	18/24 (75)
5. de Aguilar-Nascimento 2011	Elderly patients with acute ischemic stroke in ICU N=31	C.Random: Yes ITT: No Blinding: No (7)	Hydrolyzed whey protein feed (Peptamen 1.5) vs. Hydrolyzed casein protein feed (Hiper Diet Energy Plus)	3/10 (30)	4/15 (27)	NR	NR
6. Jakob 2017	Medical and surgical ICU pts, expected LOS $\geq$ 5 days & EN for $\geq$ 3 days	C.Random: No ITT: Yes Blinding: double (11)	Semi-elemental formula (Peptamen AF) vs whole protein formula (Isosource Energy)	12/46	12/44	**Secondary infections** 19/46	**Secondary infections** 19/46
7. Rice 2019	Mechanically ventilated overweight/obese patients N=105	C.Random: no ITT: no Blinding: no (5)	Hypocaloric feeding with semi elemental (Peptamen Intense, 37% protein as whey peptides, 34% Fat, 29% CHO) vs. whole protein (Replete, 25%	**Hospital mortality or entered palliative care** 7/50 **Feeding protocol duration**	**Hospital mortality or entered palliative care** 8/52 **Feeding protocol duration**	NR	NR

			polymeric protein, 30% Fat, 45% CHO). Target for both1.5 g/kg/day protein for 7 days. Isonitrogenous, non isocaloric.	2/50	6/52		
8. Carteron 2021	Brain injured ICU patients expected to be ventilated >48 hrs N= 206	C.Random: Yes ITT: no Blinding: no (8)	Semi elemental formula (Peptamen AF 9.4 g/L protein) vs. whole protein formula (Sondalis High Protein 7.5 g/L protein) Isocaloric, non isonitrogenous formulas	**28 day** 20/100 (20%) **60 day** 23/100 (23%)	**28 day** 21/95 (22%); p=0.71 **60 day** 23/95 (24%); p=0.81	**Pneumonia** 47/100 (47%)	**Pneumonia** 41/95 (43%); p=0.59

Table 1. Randomized studies evaluating peptide based vs. whole protein enteral formulas in critically ill patients (continued)

Study	**LOS days**		**Ventilator days**		**Other**	
	Peptide	**Whole Protein**	**Peptide**	**Whole Protein**	**Peptide**	**Whole Protein**
1. Brinson 1988	NR	NR	NR	NR	**Diarrhea** 1/7 (14) **Energy intake (kcal/day)** 649 ± 4 **Nitrogen balance (gm /day)** -11.2 ± 2.3	3/5 (60) 737 ± 50 -9.6 ± 2.5
2. Meredith 1990	**Hospital** 32.4 ± 5.9 P=NS	**Hospital** 47.6 ± 8.7	NR	NR	**Diarrhea** 0/9 (0) **Energy intake (kcal/kg/day)** 26.2 ± 3.7 **Protein intake (gm/kg/day)** 1.14 ± 0.17 **Nitrogen balance (gm/day)** -0.14 ± 1.5	4/9 (44) 27.8 ± 3.0 1.15 ± 0.12 -0.24 ± 0.9

3. Mowatt-Larsen 1992	NR	NR	NR	NR	**Diarrhea** 6/21 (29) 6/20 (30) **Elevated gastric residuals** 8/21 (38) 7/20 (35) **Energy intake (kcal/kg/day)** 34.2 ± 11.3 32.4 ± 6.8 **Protein intake (gm/kg/day)** 1.5 ± 0.5 1.7 ± 0.3
4. Heimburger 1997	NR	NR	NR	NR	**Diarrhea** 10/26 (39) 4/24 (17)
5. de Aguilar-Nascimento 2011	**ICU** 16 ± 8 Mean and SEM P=0.97	**ICU** 16 ± 5 Mean and SEM	NR	NR	**Glutathione peroxidase - Day 1 (U/G Hb)** 32.2 ± 2. 30.0 ± 5.0 **Glutathione peroxidase - Day 5 (U/G Hb)** 39.9 ± 4.8 26.2 ± 6.7 **Interleukin 6 - Day 1 (pg/dL)** 62.7 ± 56.2 64.3 ± 40.3 **Interleukin 6 - Day 5 (pg/dL)** 20.6 ± 10.3 42.0 ± 2.7 All reported as mean and SEM
6. Jakob 2017	**ICU** 7.0 (5.3-8.7) P=0.3 **Hospital** 31.0 (27.0-35.0) P=0.97	**ICU** 10.0 (6.6-13.4) **Hospital** 36.0 (29.9-42.1)	6.2 (4.8-7.7)	7.0 (4.7-9.3); p=0.23	**Diarrhea** 29/46 (64) 31/44 (70); p=0.83 **Percent of prescribed kcal received** 85% (71-95) 90% (84-96); p=0.07 **Median intake, kcal/kg/d** 18.0 (12.5-20.9) 19.7 (17.3-23.1); p=0.08 **Protein intake, g/kg/d** 1.13 (0.78-1.31) 0.8 (0.7-0.94); p <0.001

7. Rice 2019	**Hospital** 4.12 ± 2.32	**Hospital** 4.17 ± 2.37; p=0.87	NR	NR	**Difference in mean rate of glycemic events >110 and 150 mg/dL between groups** 2.7% (95% CI −6% to 11.5%; p = .54) **mean glucose, first week, mg/dL** 138 126; p=0.004 **Insulin use (IU/day)** 43.8±95.8 52.9±93.2; p=0.25 **Protein, g/kg IBW** 1.1±0.3 1.2±0.4; p=0.83 **Energy, kcal/kg IBW** 12.5±3.7 18.2±6.0; p <0.0001 **CHO, g/d** 61±22 126±48; p <0.0001
8. Carteron 2021	**ICU** 14 (8-21)	**ICU** 15 (10-23); p=0.18	10 (6-16)	11 (6-17); p=0.52	**Diarrhea** 16/100 (16%) 8/95 (8%); p=0.11 **GRV > 500 mL** 18/100 (18%) 11/95 (12%); p=0.21 **Daily energy (kcal/kg)** 20.2 ±6.3 21.0 ±6.5; p=0.42 **Daily protein (g/kg)** 1.3±0.3 1.1 ±0.3; p<0.0001

C.Random: concealed randomization
ITT: intent to treat
NR : Not reported
MOF: multiorgan failure

± : mean ± standard deviation
† presumed ICU mortality unless otherwise specified
** RR= relative risk, CI= Confidence intervals
ICU: intensive care unit

Figure 1. Mortality

Study or Subgroup	Peptide Events	Peptide Total	Whole Protein Events	Whole Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brinson	0	7	2	5	1.6%	0.15 [0.01, 2.58]	1988
Meredith	1	9	1	9	1.9%	1.00 [0.07, 13.64]	1990
Aguilar-Nascimento	3	10	4	15	8.3%	1.13 [0.32, 3.99]	2011
Jakob	12	46	12	44	28.3%	0.96 [0.48, 1.90]	2017
Rice	7	50	8	52	15.1%	0.91 [0.36, 2.32]	2019
Carteron	20	100	21	95	44.8%	0.90 [0.53, 1.56]	2021
Total (95% CI)		**222**		**220**	**100.0%**	**0.91 [0.63, 1.31]**	
Total events	43		48				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.69$, df = 5 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 0.50 (P = 0.62)

Risk Ratio
M-H, Random, 95% CI

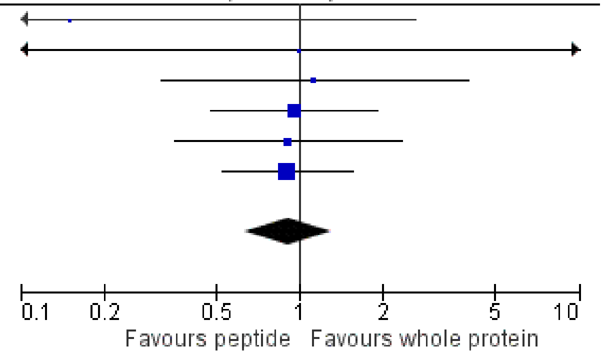


Figure 2. Infections

Study or Subgroup	Peptide Events	Peptide Total	Whole Protein Events	Whole Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Mowatt-Larsen	12	21	14	20	20.2%	0.82 [0.51, 1.30]	1992
Heimburger	17	26	18	24	33.8%	0.87 [0.61, 1.25]	1997
Carteron	47	100	41	95	46.0%	1.09 [0.80, 1.49]	2021
Total (95% CI)		**147**		**139**	**100.0%**	**0.95 [0.77, 1.18]**	
Total events	76		73				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.44$, df = 2 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 0.45 (P = 0.65)

Risk Ratio
M-H, Random, 95% CI

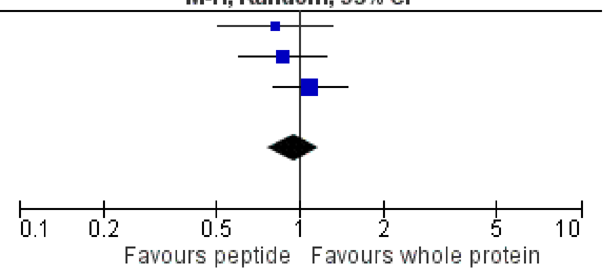


Figure 3. Diarrhea

Study or Subgroup	Peptide Events	Peptide Total	Whole Protein Events	Whole Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brinson	1	7	3	5	6.6%	0.24 [0.03, 1.67]	1988
Meredith	0	9	4	9	3.5%	0.11 [0.01, 1.80]	1990
Mowatt-Larsen	6	21	6	20	17.8%	0.95 [0.37, 2.47]	1992
Heimburger	10	26	4	24	16.5%	2.31 [0.83, 6.39]	1997
Jakob	29	46	31	44	34.6%	0.89 [0.67, 1.20]	2017
Carteron	16	100	8	95	21.1%	1.90 [0.85, 4.23]	2021
Total (95% CI)		**209**		**197**	**100.0%**	**1.06 [0.61, 1.83]**	
Total events	62		56				

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 10.27$, df = 5 (P = 0.07); $I^2 = 51\%$
Test for overall effect: Z = 0.20 (P = 0.84)

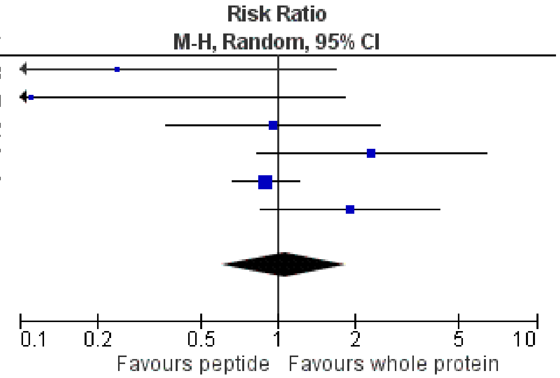


Figure 4. Energy intake Kcal/kg/day

Study or Subgroup	Peptide Mean	Peptide SD	Peptide Total	Whole protein Mean	Whole protein SD	Whole protein Total	Weight	Mean Difference IV, Random, 95% CI	Year
Meredith	26.2	3.7	9	27.8	3	9	23.3%	-1.60 [-4.71, 1.51]	1990
Mowatt-Larsen	34.2	11.3	21	32.4	6.8	20	7.0%	1.80 [-3.88, 7.48]	1992
Carteron	20.2	6.3	100	21	6.5	95	69.7%	-0.80 [-2.60, 1.00]	2021
Total (95% CI)			**130**			**124**	**100.0%**	**-0.80 [-2.31, 0.70]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.06$, df = 2 (P = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 1.05 (P = 0.29)

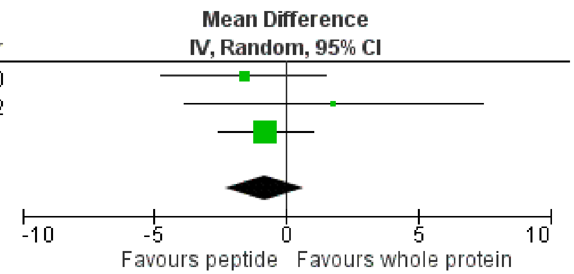
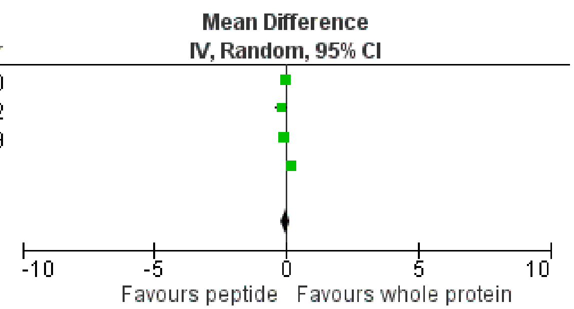


Figure 5. Protein intake gm/kg/day

Study or Subgroup	Peptide Mean	Peptide SD	Peptide Total	Whole protein Mean	Whole protein SD	Whole protein Total	Weight	Mean Difference IV, Random, 95% CI	Year
Meredith	1.14	0.17	9	1.15	0.12	9	25.5%	-0.01 [-0.15, 0.13]	1990
Mowatt-Larsen	1.5	0.5	29	1.7	0.3	30	21.2%	-0.20 [-0.41, 0.01]	1992
Rice	1.1	0.3	50	1.2	0.4	52	25.4%	-0.10 [-0.24, 0.04]	2019
Carteron	1.3	0.3	100	1.1	0.3	95	27.9%	0.20 [0.12, 0.28]	2021
Total (95% CI)			**188**			**186**	**100.0%**	**-0.01 [-0.20, 0.17]**	

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 22.66$, df = 3 (P < 0.0001); $I^2 = 87\%$
Test for overall effect: Z = 0.16 (P = 0.88)



References:

Included Studies

1. Brinson RR, Kolts BE. Diarrhea associated with severe hypoalbuminemia: a comparison of a peptide-based chemically defined diet and standard enteral alimentation. Crit Care Med. 1988 Feb;16(2):130-6.
2. Meredith JW, Ditesheim JA, Zaloga GP. Visceral protein levels in trauma patients are greater with peptide diet than with intact protein diet. J Trauma. 1990 Jul;30(7):825-8; discussion 828-9.
3. Mowatt-Larssen CA, Brown RO, Wojtysiak SL, Kudsk KA. Comparison of tolerance and nutritional outcome between a peptide and a standard enteral formula in critically ill, hypoalbuminemic patients. JPEN J Parenter Enteral Nutr. 1992 ;16(1):20-4.
4. Heimburger DC, Geels VJ, Bilbrey J, Redden DT, Keeney C. Effects of small-peptide and whole-protein enteral feedings on serum proteins and diarrhea in critically ill patients: a randomized trial. JPEN 1997;21(3):162-7.
5. de Aguilar-Nascimento JE, Prado Silveira BR, Dock-Nascimento DB. Early enteral nutrition with whey protein or casein in elderly patients with acute ischemic stroke: a double-blind randomized trial. Nutrition. 2011 Apr;27(4):440-4. Epub 2010 Dec 16. Erratum in: Nutrition. 2011 Sep;27(9):982. PubMed PMID: 21167685.
6. Jakob SM, Bütikofer L, Berger D, Coslovsky M, Takala J. A randomized controlled pilot study to evaluate the effect of an enteral formulation designed to improve gastrointestinal tolerance in the critically ill patient-the SPIRIT trial. Crit Care. 2017 Jun 10;21(1):140.
7. Carteron L, Samain E, Winiszewski H, et al. Semi-elemental versus polymeric formula for enteral nutrition in brain-injured critically ill patients: a randomized trial. Crit Care. 2021;25(1):31. Published 2021 Jan 20. doi:10.1186/s13054-020-03456-7
8. Rice, T. W.; Files, D. C.; Morris, P. E.; Bernard, A. C.; Ziegler, T. R.; Drover, J. W.; Kress, J. P.; Ham, K. R.; Grathwohl, D. J.; Huhmann, M. B.; Gautier, J. B. O. Dietary Management of Blood Glucose in Medical Critically Ill Overweight and Obese Patients: An Open-Label Randomized Trial. JPEN. Journal of parenteral and enteral nutrition 2019, 43 (4), 471–480. https://doi.org/10.1002/jpen.1447.

Excluded Articles

#	Reason excluded	Citation
1	Surgical patients	Sagar S, Harland P, Shields R. Early postoperative feeding with elemental diet. Br Med J. 1979 Feb 3;1(6159):293-5.
2	Crossover study	Wolfe RR, Goodenough RD, Burke JF, Wolfe MH. Response of protein and urea kinetics in burn patients to different levels of protein intake. Ann Surg. 1983 Feb;197(2):163-71.
3	Elective surgery patients	Cerra FB, Shronts EP, Konstantinides NN et al. Enteral feeding in sepsis: a prospective, randomized, double-blind trial. Surgery 1985;98(4):632-9.
4	Elective surgery patients	Ziegler F, Ollivier JM, Cynober L, Masini JP, Coudray-Lucas C, Levy E, Giboudeau J. Efficiency of enteral nitrogen support in surgical patients: small peptides v non-degraded proteins. Gut. 1990 Nov;31(11):1277-83.
5	Elective surgery patients	Borlase BC, Bell SJ, Lewis EJ et al. Tolerance to enteral tube feeding diets in hypoalbuminemic critically ill, geriatric patients. Surg Gynecol Obstet1992;174:181-188.
6	Elective surgery patients	Donald P, Miller E, Schirmer B. Repletion of nutritional parameters in surgical patients receiving peptide versus amino acid elemental feedings. Nut Res. 1994; 14: 3-12
7	No clinical outcome	Rowe B et al. Effects of whey- and casein-based diets on glutathione and cysteine metabolism in ICU patients. J Am Coll Nutr. 1994; 13(suppl): 535A (Abstract 62)
8	No clinical outcome	Dietscher JE, Foulks CJ, Smith RW. Nutritional response of patients in an intensive care unit to an elemental formula vs a standard enteral formula. JADA 1998;98(3):335-336.
9	Not ICU patients	Tiengou LE, Gloro R, Pouzoulet J, Bouhier K, Read MH, Arnaud-Battandier F, Plaze JM, Blaizot X, Dao T, Piquet MA. Semi-elemental formula or polymeric formula: is there a better choice for enteral nutrition in acute pancreatitis? Randomized comparative study. JPEN J Parenter Enteral Nutr. 2006 Jan-Feb;30(1):1-5.
10	No clinical outcomes	Mansoor O, Breuillé D, Béchereau F, Buffière C, Pouyet C, Beaufrère B, Vuichoud J, Van't-Of M, Obled C. Effect of an enteral diet supplemented with a specific blend of amino acid on plasma and muscle protein synthesis in ICU patients. Clin Nutr. 2007 Feb;26(1):30-40. Epub 2006 Sep 25.
11	No clinical outcome per group	Seres DS, Ippolito PR. Pilot study evaluating the efficacy, tolerance and safety of a peptide-based enteral formula versus a high protein enteral formula in multiple ICU settings (medical, surgical, cardiothoracic). Clin Nutr. 2017 Jun;36(3):706-709.