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

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 6 level 2 studies that compared a peptide based enteral formula to one with intact proteins.

Mortality: Only four studies reported mortality and found no differences between the groups (Meredith, Brinson, Aguilar-Nascimento, Jakob) (RR 0.92, 95% CI 0.52, 1.63, p=0.77, heterogeneity I^2=0%; figure 1).

Infections: Based on the two studies that reported on infections, there were no difference between the groups (RR 0.85, 95% CI 0.64, 1.13, p=0.27, heterogeneity I^2=0%; figure 2).

LOS: Two studies reported on ICU LOS (Aguilar-Nascimento, Jakob) and neither found a difference between groups (p=0.97 and p=0.3, respectively). Two studies reported on hospital LOS (Meredith, Jakob) and also found no difference between groups (p=0.NS and p=0.97, respectively).

Ventilator days: Jakon et al reported on ventilator days and found no difference between groups (p=0.23).

Other complications: A trend towards an increase in diarrhea with the use of peptides was seen in one study (Heimburger p =0.07), whereas another study showed a decrease in the incidence of diarrhea in the peptide group (Meredith). Two studies found no differences in diarrhea between the two groups (Mowatt-Larsen, Jakob). In one study of hypoalbuminemic patients (Brinson et al), 3/5 patients in the control group (standard) crossed over to the experimental group (peptide based) because of diarrhea. Meta analysis showed no difference in diarrhea between the peptide based and standard groups (RR 0.91, 95% CI 0.49, 1.66, p=0.75, heterogeneity I^2=45%; figure 3). One study (Aguilar-Nascimento) 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 two 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 -0.76, 95% CI -3.63, 2.11, p=0.60, heterogeneity I^2=6% (figure 4). Similarly, when the data from the two studies that reported protein intake were aggregated, the use of a peptide enteral formula had no effect on protein intake (WMD -0.09, 95% CI -0.27, 0.10, p=0.35, heterogeneity I^2=54%) (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 enteral PROTEIN vs. PEPTIDES 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 ≥ 5 days, needing EN for ≥ 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

Table 1. Randomized studies evaluating enteral PROTEIN vs. PEPTIDES in critically ill patients (continued)

Study	LOS days		Ventilator days		Cost		Other		RR (CI) **
	Peptide	Whole Protein	Peptide	Whole Protein	Peptide	Whole Protein	Peptide	Whole Protein	
1. Brinson 1988	NR	NR	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	0.24 (0.03, 1.67)
2. Meredith 1990	Hospital 32.4 ± 5.9 P=NS	Hospital 47.6 ± 8.7	NR	NR	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	0.11 (0.01, 1.80)
3. Mowatt-Larsen 1992	NR	NR	NR	NR	NR	NR	Diarrhea 6/21 (29) Elevated gastric residuals 8/21 (38) Energy intake (kcal/kg/day) 34.2 ± 11.3 Protein intake (gm/kg/day) 1.5 ± 0.5	6/20 (30) 7/20 (35) 32.4 ± 6.8 1.7 ± 0.3	0.95 (0.37, 2.47)
4. Heimburger 1997	NR	NR	NR	NR	NR	NR	Diarrhea 10/26 (39)	4/24 (17)	2.31 (0.83, 6.39)

5. de Aguilar-Nascimento 2011	ICU 16 ± 8 Mean and SEM P=0.97	ICU 16 ± 5 Mean and SEM	NR	NR	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) P=0.23	7.0 (4.7-9.3)			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 Proetein intake, g/kg/d 1.13 (0.78-1.31) 0.8 (0.7-0.94) P <0.001	

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	Standard Events	Standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brinson	0	7	2	5	4.1%	0.15 [0.01, 2.58]	1988
Meredith	1	9	1	9	4.8%	1.00 [0.07, 13.64]	1990
Aguilar-Nascimento	3	10	4	15	20.7%	1.13 [0.32, 3.99]	2011
Jakob	12	46	12	44	70.4%	0.96 [0.48, 1.90]	2017
Total (95% CI)		**72**		**73**	**100.0%**	**0.92 [0.52, 1.63]**	
Total events	16		19				

Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)

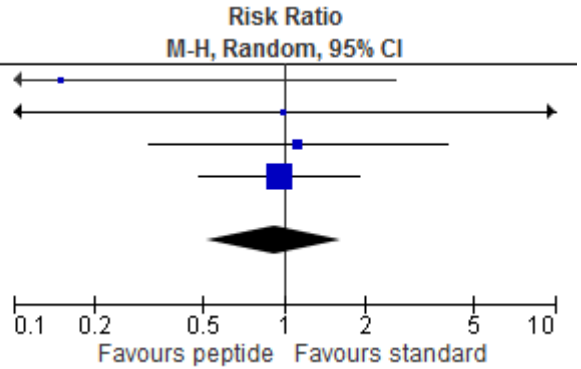

Figure 2. Infections

Study or Subgroup	Peptide Events	Peptide Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Mowatt-Larsen	12	21	14	20	37.5%	0.82 [0.51, 1.30]	1992
Heimburger	17	26	18	24	62.5%	0.87 [0.61, 1.25]	1997
Total (95% CI)		**47**		**44**	**100.0%**	**0.85 [0.64, 1.13]**	
Total events	29		32				

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)

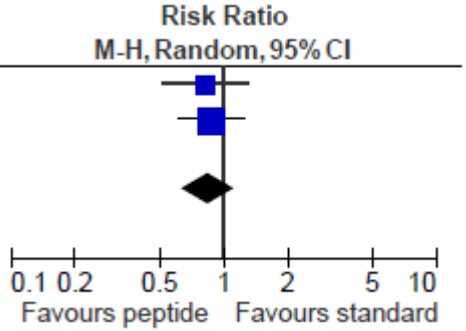

Figure 3. Diarrhea

Study or Subgroup	Peptide Events	Peptide Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brinson	1	7	3	5	8.1%	0.24 [0.03, 1.67]	1988
Meredith	0	9	4	9	4.3%	0.11 [0.01, 1.80]	1990
Mowatt-Larsen	6	21	6	20	22.4%	0.95 [0.37, 2.47]	1992
Heimburger	10	26	4	24	20.7%	2.31 [0.83, 6.39]	1997
Jakob	29	46	31	44	44.4%	0.89 [0.67, 1.20]	2017
Total (95% CI)		**109**		**102**	**100.0%**	**0.91 [0.49, 1.66]**	
Total events	46		48				

Heterogeneity: Tau² = 0.19; Chi² = 7.24, df = 4 (P = 0.12); I² = 45%
Test for overall effect: Z = 0.32 (P = 0.75)

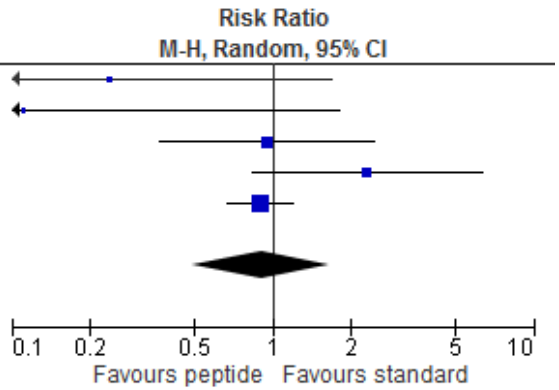

Figure 4. Energy intake

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	75.4%	-1.60 [-4.71, 1.51]	1990
Mowatt-Larsen	34.2	11.3	21	32.4	6.8	20	24.6%	1.80 [-3.88, 7.48]	1992
Total (95% CI)			**30**			**29**	**100.0%**	**-0.76 [-3.63, 2.11]**	

Heterogeneity: Tau² = 0.32; Chi² = 1.06, df = 1 (P = 0.30); I² = 6%
Test for overall effect: Z = 0.52 (P = 0.60)

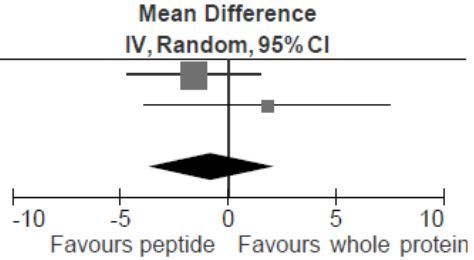

Figure 5. Protein intake

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	59.4%	-0.01 [-0.15, 0.13]	1990
Mowatt-Larsen	1.5	0.5	29	1.7	0.3	30	40.6%	-0.20 [-0.41, 0.01]	1992
Total (95% CI)			**38**			**39**	**100.0%**	**-0.09 [-0.27, 0.10]**	

Heterogeneity: Tau² = 0.01; Chi² = 2.20, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.93 (P = 0.35)

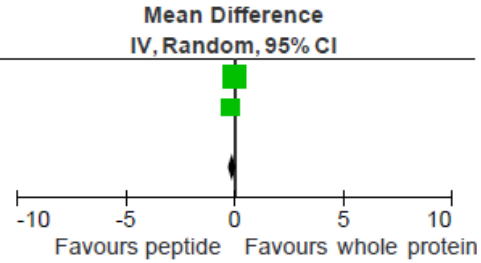

Table 2. Exluded Articles

#	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 elementa feedings. Nut Res. 1994; 14: 3-12
7	No clinical outcomes	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 outcomes	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.
11	No clinical outcomes	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.