4.3 Strategies for optimizing and minimizing risks of EN: Whole Protein vs. Peptides March 2013

2013 Recommendation: *Based on 5 level 2 studies, when initiating enteral feeds, the use of whole protein formulas (polymeric) should be considered.*

2013 Discussion: The committee noted that with the addition of one study (de Aguilar-Nascimento 2011) there was no change in the effect of peptide based formulas on clinical or nutritional outcomes. The trend towards a reduction in hospital length of stay was based on sparse data with statistical heterogeneity. In summary, there is no evidence of treatment effect to give a recommendation for one product over another but given the higher cost of peptide based formulas, a weak recommendation for the use of polymeric products, in general, was put forward. This recommendation was downgraded from past recommendations to be consistent with other content areas that have no evidence for superiority based on evidence and recommendations are based on values such as safety and costs, etc. The committee also noted that peptide based formulas may be considered for their other components i.e. fat content, MCT, glutamine composition, etc and that patients with gastrointestinal complications (short bowel syndrome, pancreatitis, etc.) may benefit from peptide based formulas but in the absence of positive effects on clinical outcomes, this did not result in a recommendation for these formulas.

2009 Recommendation: *Based on 4 level 2 studies, when initiating enteral feeds, we recommend the use of whole protein formulas (polymeric).*

2009 Discussion: The committee noted that despite no safety concerns and the ease of implementation of peptide based enteral formulas, there were no studies demonstrating any favourable treatment effects with their use. The higher cost of peptide based formulas compared to standard was noted. The committee also noted that peptide based formulas may be considered for their other components i.e. fat content, MCT, glutamine composition, etc and that patients with gastrointestinal complications (short bowel syndrome, pancreatitis, etc.) may benefit from peptide based formulas but there are insufficient data to put forward a recommendation.

Semi Quantitative Scoring

Values	Definition	2009 Score	2013 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0	1
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	1	0
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1	3
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	1
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogeneous patients, diverse practice settings =3.	1	1
Cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3	3
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	3	3

4.3 Strategies for optimizing and minimizing risks of EN: Protein vs Peptides March 2013

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

Mortality: Only three studies reported mortality and found no differences between the groups (Meredith, Brinson, Aguilar-Nascimento) (RR 0.84, 95% CI 0.29, 2.41, p=0.74, 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: When the data from the two studies (Meredith, Aguilar-Nascimento) that reported length of stay were aggregated, peptide based enteral formula was associated with a trend towards fewer hospital days (WMD -7.46, 95% CI -22.35, 7.43, p=0.33, heterogeneity I^2=91%; figure 3).

Ventilator days: Not reported.

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). A third study found no differences in diarrhea between the two groups in another study (Mowatt-Larsen). 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 0.76, 95% CI 0.25, 2.33, p=0.63, heterogeneity I^2=58%; figure 4). 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 5). 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 6).

Conclusions:

1) No difference in mortality, infections, or length of stay between patients receiving a peptide based vs. a standard formula.
2) No difference in diarrhea between the groups receiving peptides vs. standard formula.
3) No difference in energy or protein intake patients receiving a peptide based vs. a standard formula.

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 (Peptamin 1.5) vs. Hydrolyzed casein protein feed (Hiper Diet Energy Plus)	3/10 (30)	4/15 (27)	NR	NR

Table 2. 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	32.4 ± 5.9	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	ICU 16 ± 5	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	

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

Figure 1. Mortality

Study or Subgroup	Peptide Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brinson	0	7	2	5	13.8%	0.15 [0.01, 2.58]	1988
Meredith	1	9	1	9	16.4%	1.00 [0.07, 13.64]	1990
Aguilar-Nascimento	3	10	4	15	69.8%	1.13 [0.32, 3.99]	2011
Total (95% CI)		26		29	100.0%	0.84 [0.29, 2.41]	
Total events	4		7				

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

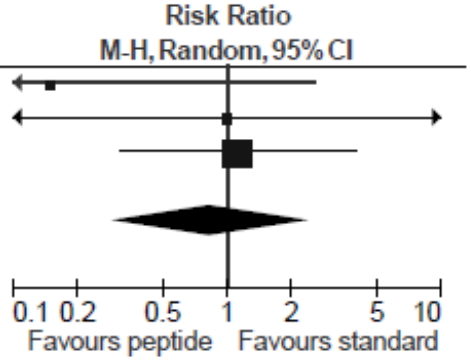

Figure 2. Infections

Study or Subgroup	Peptide Events	Total	Standard Events	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)

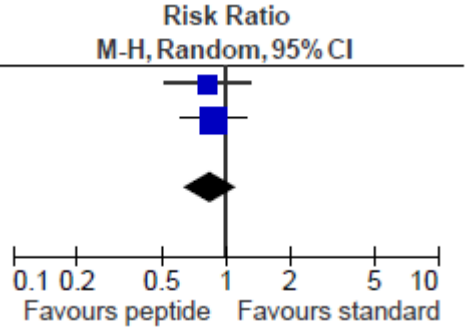

Figure 3. Hospital LOS

Study or Subgroup	Peptide Mean	Peptide SD	Peptide Total	Standard Mean	Standard SD	Standard Total	Weight	Mean Difference IV, Random, 95% CI	Year
Meredith	32.4	5.9	9	47.6	8.7	9	49.1%	-15.20 [-22.07, -8.33]	1990
Aguilar-Nascimento	16	8	10	16	5	15	50.9%	0.00 [-5.57, 5.57]	2011
Total (95% CI)			19			24	100.0%	-7.46 [-22.35, 7.43]	

Heterogeneity: Tau² = 105.35; Chi² = 11.36, df = 1 (P = 0.0008); I² = 91%
Test for overall effect: Z = 0.98 (P = 0.33)

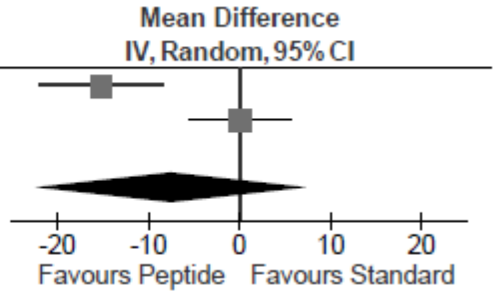

Figure 4. Diarrhea

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	19.4%	0.24 [0.03, 1.67]	1988
Meredith	0	9	4	9	12.0%	0.11 [0.01, 1.80]	1990
Mowatt-Larsen	6	21	6	20	34.9%	0.95 [0.37, 2.47]	1992
Heimburger	10	26	4	24	33.7%	2.31 [0.83, 6.39]	1997
Total (95% CI)		63		58	100.0%	0.76 [0.25, 2.33]	
Total events	17		17				

Heterogeneity: Tau² = 0.70; Chi² = 7.20, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 0.48 (P = 0.63)

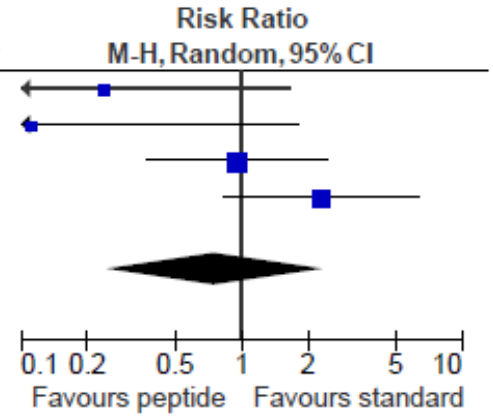

Figure 5. Energy intake

	Peptide			Whole protein				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	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)

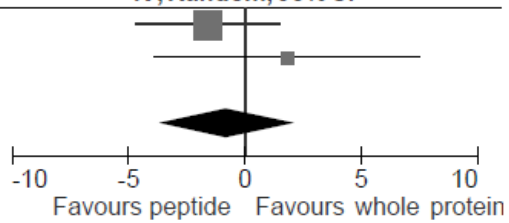

Figure 6. Protein intake

	Peptide			Whole protein				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	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)