

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 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)	3/5 (60)	0.24 (0.03, 1.67)
							Energy intake (kcal/day) 649 ± 4	737 ± 50	
							Nitrogen balance (gm /day) -11.2 ± 2.3	-9.6 ± 2.5	
2. Meredith 1990	Hospital 32.4 ± 5.9 P=NS	Hospital 47.6 ± 8.7	NR	NR	NR	NR	Diarrhea 0/9 (0)	4/9 (44)	0.11 (0.01, 1.80)
							Energy intake (kcal/kg/day) 26.2 ± 3.7	27.8 ± 3.0	
							Protein intake (gm/kg/day) 1.14 ± 0.17	1.15 ± 0.12	
							Nitrogen balance (gm/day) -0.14 ± 1.5	-0.24 ± 0.9	
3. Mowatt-Larsen 1992	NR	NR	NR	NR	NR	NR	Diarrhea 6/21 (29)	6/20 (30)	0.95 (0.37, 2.47)
							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	NR	NR	Diarrhea 10/26 (39)	4/24 (17)	2.31 (0.83, 6.39)

<p>5. de Aguilar-Nascimento 2011</p>	<p>ICU 16 ± 8 Mean and SEM P=0.97</p>	<p>ICU 16 ± 5 Mean and SEM</p>	<p>NR</p>	<p>NR</p>	<p>NR</p>	<p>NR</p>	<p>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</p>	
<p>6. Jakob 2017</p>	<p>ICU 7.0 (5.3-8.7) P=0.3 Hospital 31.0 (27.0-35.0) P=0.97</p>	<p>ICU 10.0 (6.6-13.4) Hospital 36.0 (29.9-42.1)</p>	<p>6.2 (4.8-7.7) P=0.23</p>	<p>7.0 (4.7-9.3)</p>			<p>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</p>	

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

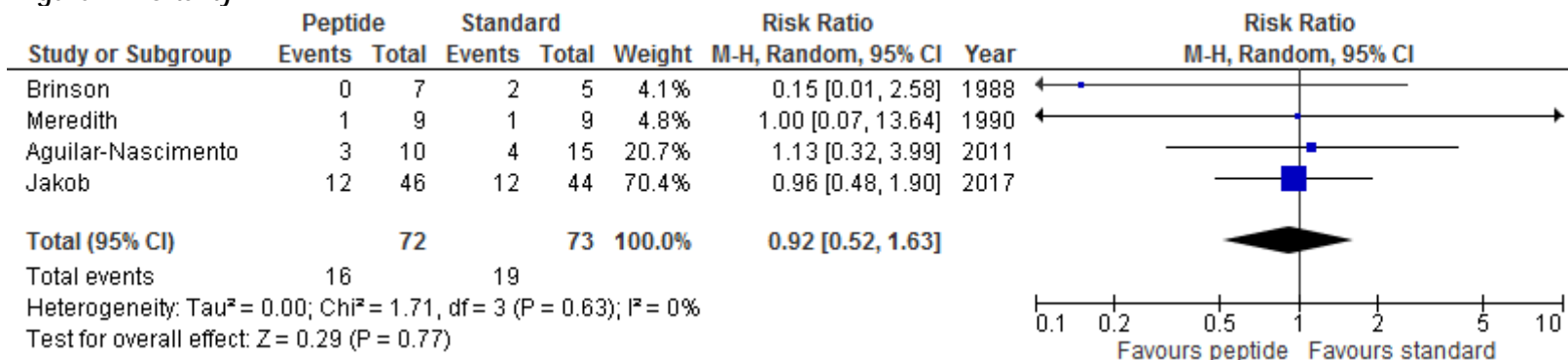


Figure 2. Infections

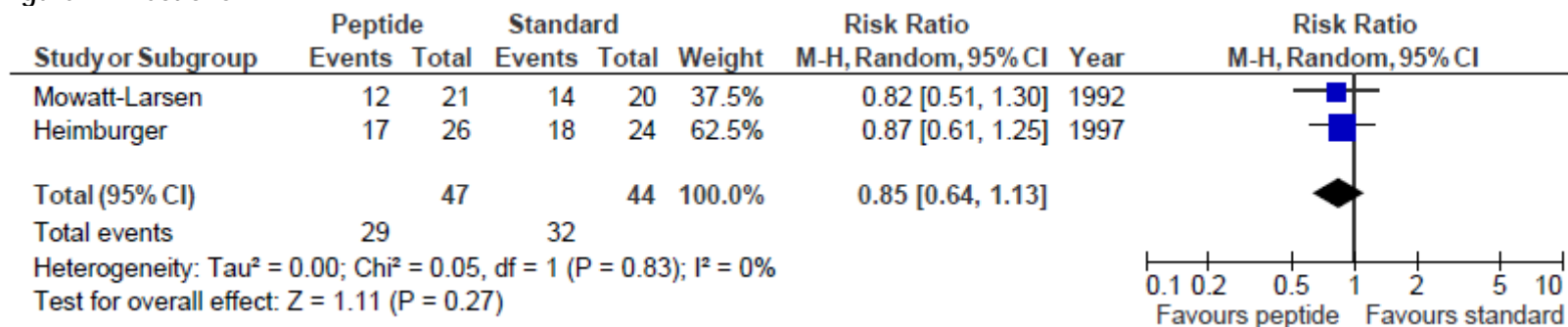


Figure 3. Diarrhea

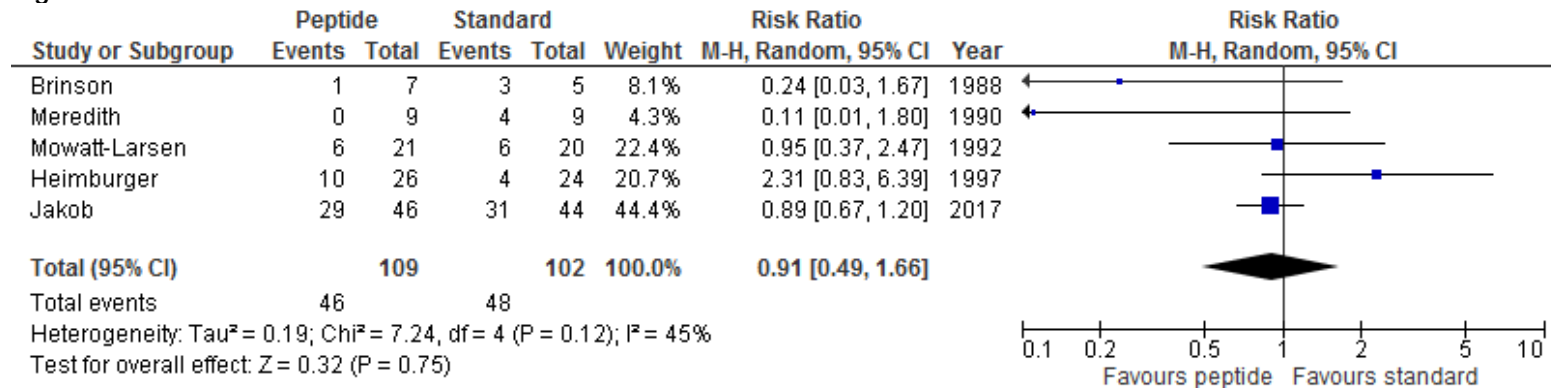


Figure 4. Energy intake

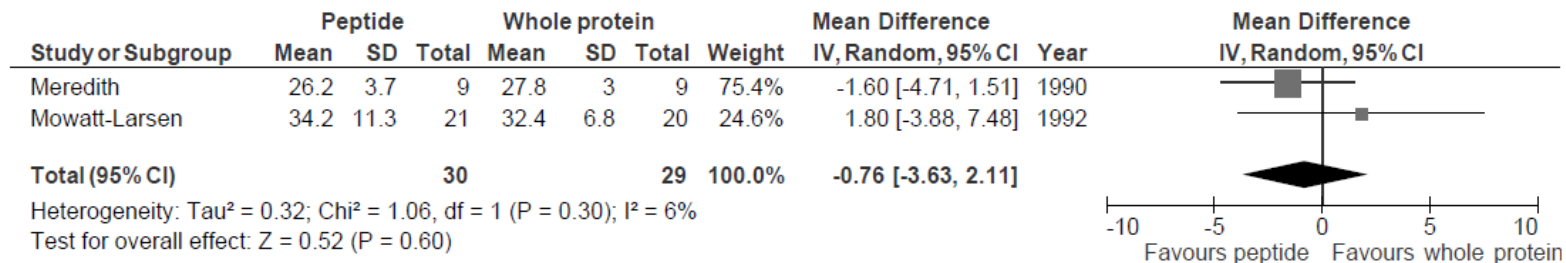


Figure 5. Protein intake

