4.2a Composition of Enteral Nutrition: (Carbohydrate/fat): High fat/low CHO

Question: Does a high fat/low CHO enteral formula affect outcomes in the critically ill adult patient?

Summary of evidence: There were eight level 2 studies and one level 1 study that compared a high fat, low CHO formula to a standard formula. Two studies compared Pulmocare (55% fat, 28 % CHO); one compared Novasource Diabetic Plus (40% fat, 40 % CHO), one compared Diben (45% fat, 37% CHO), one compared Glucerna 1.5 (46% fat, 33% CHO) to standard formula (up to 35% fat and 53% CHO) and one compared Glucerna select (50 % fat, 30% CHO, 20 % protein1 Kcal/mL) to Nutrison Protein Plus (35% fat, 45 % CHO, 20 % protein, 1.25 Kcal/mL). One study compared two hospital made formulas (45% fat, 35% CHO vs. 30% fat, 50% CHO). Two studies compared two different high fat formulas to a standard formula: Mesejo 2015's experimental EN formulas were Diaba HP (40% fat, 33% CHO) and Glucerna Select (49% fat, 30% CHO) and Nourohommadi 2017's experimental formulas contained 45% fat (50:50 olive and sunflower oil), 35% CHO and 45% fat (100% sunflower oil), 35% CHO. The data for the two intervention arms in Mesejo 2015 and Nourohommadi 2017 have been combined in the meta-analyses.

Mortality: Eight studies reported on mortality and there were no differences between the groups for overall mortality when the data were aggregated (RR 1.12, 95% CI 0.82, 1.55, p=0.45, test for heterogeneity I^2=0%; Figure 1) and for ICU mortality (RR 1.12, 05% CI 0.78, 1.62, p=0.52, test for heterogeneity I^2=0%; Figure 2).

Infections: Three studies (Mesejo 2003. Mesejo 2015 and Vahabzadeh 2019) reported infectious complications and found no differences between the two groups (RR 0.94, 95% CI 0.67, 1.33, p=0.74, test for heterogeneity I^2 =0%; Figure 3).

LOS: Two studies (Mesejo 2003, Nourohommadi 2017) reported on ICU length of stay as means and standard deviations and no differences were seen between the two groups when the data were aggregated (WMD -2.07, 95% CI -6.98, 2.84, p=0.41; figure 4). Data from four studies were not included in the analyses due to carrying reporting outcomes (three reported median and ranges, one reported ICU free days).

Ventilator days: Duration of mechanical ventilation was significantly lower in the high fat group in one study (Al Saady 1994 p<0.001), no difference found in the van de Berg 1994 study or the Mesejo 2003 study. For the two studies that reported ventilation duration in mean and standard deviation, a significant reduction in duration was seen in the high fat group (WMD -2.87, 95% CI -3.59, -1.14, p=0.0002; Figure 5).

Other complications: Six studies reported on glycemic control or glucose levels, three reported significantly lower blood sugars in the group receiving the higher fat, lower CHO formula (Mesejo 2003, Mesejo 2015 [Diaba HP group], Doola 2019). Wewalka 2018 and Vahabzadeh 2019 found no statistically significant differences in fasting blood glucose levels between groups. Van Steen 2018 showed a trend in a reduction of hyperglycemic events in the high fat group, but there was no difference between groups regarding hypoglycemic events. Insulin use was significantly lower in the high fat, low CHO group compared to the lower fat, higher CHO group in one study (Doola 2019) but not in the other study (Vahabzadeh 2019). Four studies reported on diarrhea and there was a trend towards a reduction in diarrhea in the high fat, low CHO formula fed groups (RR 0.81, 95% CI 0.64, 1.04, p=0.10, test for heterogeneity I^2 =0%; Figure 6).

Conclusions:

1) A high fat, low CHO enteral formula may be associated with a reduction in ventilated days in medical ICU patients with respiratory failure and better glycemic control in critically ill patients with hyperglycemia.
2) A high fat, low CHO enteral formula has no effect on mortality, infections or LOS found between the critically ill patients receiving high fat/low CHO formula or standard.
3) A high fat, low CHO formula may be associated with less diarrhea in critically ill 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 High Fat/Low CHO Enteral Nutrition In Critically ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)**		RR (CI) or p value	Infections # (%)		RR (CI) or p value
1. van den Berg 1994	Medical ICU patients with COPD Chronically ventilated N=32	C.Random: not sure ITT: yes Blinding: no (5)	55% fat, 28 % CHO (Pulmocare) vs 30 % fat, 53 % CHO (standard, Ensure Plus)	**High fat/low CHO** NR	**Standard** NR	NR	**High fat/low CHO** NR	**Standard** NR	NR
2. Al Saady 1994	Ventilated patients Acute respiratory failure N=40	C.Random: not sure ITT: no Blinding: double (9)	55% fat, 28 % CHO (Pulmocare) vs 30 % fat, 53 % CHO (standard, Ensure Plus)	3/9 (33)	3/11 (27)	1.22 (0.32-4.65)	NR	NR	NR
3. Mesejo 2003	Critically ill pts with Diabetes or hyperglycemia from 2 different centers N=50	C.Random: not sure ITT: yes Blinding: single (9)	40% fat, 40 % CHO (Novasource Diab Plus) vs. 29 % fat, 49 % CHO (Standard, Isosource Protein)	**ICU** 8/26 (31)	**ICU** 7/24 (29)	1.05 (0.45, 2.47)	10/26 (38.5)	8/24 (33)	1.15 (0.55, 2.43)
4) Mesejo 2015	Critically ill patients meeting ADA criteria for diabetes/hyperglycemia. Multi-centre. N=157	C.Random: yes ITT: no Blinding: single (11)	40% fat, 33% CHO (Diaba HP - experimental) vs 49% fat, 30% CHO (Glucerna Select – experimental) vs 34% fat, 44% CHO (Isosource Protein Fibra – control)	Diaba HP **28 day** 11/52 (21.1) **6 Month** 16/52 (30.7) Glucerna Select **28 day** 13/52 (25) **6 Month** 18/52 (34.6)	**28 day** 10/53 (18.9) **6 Month** 20/53 (37.7)		Diaba HP 18/52 (34.6) Glucerna Select 23/52 (44.2)	23/53 (43.3)	
5) Nourohammadi 2017	Mixed ICU patients. Single centre. N=42	C.Random: yes ITT: yes Blinding: double (10)	45% fat (half olive, half sunflower oil), 35% CHO vs 45% fat (all sunflower oil), 35% CHO vs 30% fat, 50% CHO.	**Olive/Sunflower ICU** 3/16 (18.7) **Sunflower ICU** 6/16 (37.5)	6/16 (37.5)		NR	NR	NR
6) Wewalka 2018	Medical ICU pts. Single centre. N=60	C.Random: no ITT: yes Blinding: no (9)	45% fat, 37% CHO (Diben) vs 30% fat, 55% CHO (Fresubin original fibre). Formulas contain 2.3 g fibre/100ml and 1.5 g fibre/100 ml, respectively.	**ICU** 13/30 (43)	**ICU** 9/30 (30)		NR	NR	

7) Van Steen 2018	Medical and surgical critically ill patients N=170	C.Random: yes ITT: no Blinding: no (8)	46% fat, 33% CHO, 21% protein (Glucerna 1.5) vs 35% fat, 50% CHO, 15% protein (Fresubin Energy Fibre + protein supplement (Resource Instant Protein) 3x qd to make relatively equal in protein to intervention group.	**ICU** 9/52 (17)	**ICU** 8/49 (16)		NR	NR	
8) Doola 2019	Critically ill patients requiring insulin for hyperglycemia while on EN N=42	C.Random: yes ITT: no Blinding: double (8)	50 % fat, 30% CHO, 20 % protein (Glucerna select 1 Kcal/mL) vs. 35% fat, 45 % CHO, 20 % protein (Nutrison Protein Plus (1.25 Kcal/mL) Target for both 25 kcal/kg; 1.2 g protein/kg for 2 days	**28 day** **1/21 (5%)**	**28 day** **2/20 (10%)**	0.60	NR	NR	
9) Vahabzadeh 2019	Critically ill patients with hyperglycemia while on EN N=88	C.Random: no ITT: no Blinding: double (5)	45% fat,35% CHO, 20% protein hospital made formula vs. 30% fat, 50% CHO, 20% protein hospital made formula. Target for both 25-30 Kcal/kg for up to 15 days	**ICU** 6/41 (14%)	**ICU** 4/39 (10%)		**Sepsis** 0/41	**Sepsis** 1/39 (2.6%)	

Table 1. Randomized Studies Evaluating High Fat/Low CHO Enteral Nutrition In Critically ill Patients (continued)

Study	LOS days		Ventilator days		Other
1. van den Berg 1994	**High fat/low CHO** NR	**Standard** NR	**High fat/low CHO** 4 (median)	**Standard** 6 (median)	**High fat/low CHO** **Standard** **Gastric retention** 1/15 (7) 1/17 (6)
2. Al Saady 1994	NR	NR	3.6 ± 0.7	6.2 ± 1.5	**Diarrhea** 3/9 (33) 3/11 (27)
3. Mesejo 2003	**ICU** 14.8 ± 9.4	**ICU** 14.8 ± 8.8	8.7 ± 6.2	9.4 ± 6.0	**Plasma Glucose Levels (mmol/L)** 9.8 ± 2.4 12.4 ± 2.6
4) Mesejo 2015	Diaba HP **ICU**+ 13 (9-20) **Hospital**+ 27 (18-50) Glucerna Select **ICU**+ 11.5 (7.5-18) **Hospital**+ 30.5 (14 – 46.5)	**ICU**+ 12 (7-21) **Hospital**+ 25 (17-51)	Diaba HP+ 7 (4-13) Glucerna Select+ 6 (3-12)	6 (2-11) +	**Plasma Glucose Levels (mg/dL)** Diaba HP: 138.6 (39.1) Glucerna Select: 143.9 (45.9) Isocource: 146.1 (49.9
5) Nourohammadi 2017	**Olive/Sunflower** **ICU*** 16.6 ± 6.7 **Sunflower** **ICU*** 19.6 ± 8.3	**ICU*** 23.2 ± 12.5	NR	NR	**Diarrhea** Olive/sunflower: 2/16 (13.5) Sunflower: 3/16 (19.7) Control: 3/16 (19.7)
6) Wewalka 2018	NR	NR	NR	NR	**Fasting Plasma Glucose (mg/dL)** 128 (110-170) 123 (98-153) **Diarrhea** 22/30 26/30
7) Van Steen 2018	**ICU** 4.6 (2-12.6) +	**ICU** 4.2 (2.4-11.4) +	NR+	NR+	**Patients with hypoglycemia** 0/51 1/49 **Patients with hyperglycemia** 2/51 7/49
8) Doola 2019	**ICU** 7 (4-11)* **Hospital** 18 (14-30)*	**ICU** 8 (6-11)*; p=0.80 **Hospital** 15 (11-20)*; p=0.10	141 [94-184]*	160 [106-219]*; p=0.70	**Mean insulin use, units per hour** 1.01 2.31 (p=0.017) **Patients with Glycemic variability** 12.6% 15.9%; p=0.01 **Mean glucose control, mmol/L** 8.7 10.1; p=0.002 **Diarrhea** 2/21 (9.5) 3/20 (15); p=0.70

9) Vahabzadeh 2019	**ICU free days** 0 (0-0)	**ICU free days** **0 (0-1); p=0.11**	**Ventilator dependency** 35/41 (85.4%)	**Ventilator dependency** 34/39 (87.2%); p=0.81	**Reduction in blood glucose by end of study, mg/dL** 66.75 51.74; p=0.35 **Insulin use, IU/day by end of study** 0 (0-6) 0 (0-8); p=0.18

C.Random: concealed randomization
ITT: intent to treat
NR: Not reported
± : Mean ± Standard deviation
RR= relative risk, CI= Confidence intervals
+not able to analyze as not reported as mean and SD
*data obtained from correspondence with author
**presumed to be ICU mortality unless otherwise stated

Figure 1. Overall Mortality

Study or Subgroup	High Fat/Low Carbohydrate Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Al Saady	3	9	3	11	5.6%	1.22 [0.32, 4.65]	1994
Mesejo 2003	8	26	7	24	13.8%	1.05 [0.45, 2.47]	2003
Mesejo 2015	24	104	10	53	22.9%	1.22 [0.63, 2.36]	2015
Nourohammadi	9	32	6	16	14.1%	0.75 [0.32, 1.74]	2017
Van Steen	9	52	8	49	13.2%	1.06 [0.44, 2.53]	2018
Wewalka	13	30	9	30	21.4%	1.44 [0.73, 2.86]	2018
Doola	1	21	2	20	1.9%	0.48 [0.05, 4.85]	2019
Vahabzadeh	6	41	4	39	7.1%	1.43 [0.44, 4.67]	2019
Total (95% CI)		**315**		**242**	**100.0%**	**1.13 [0.82, 1.55]**	
Total events	73		49				

Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 7 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)

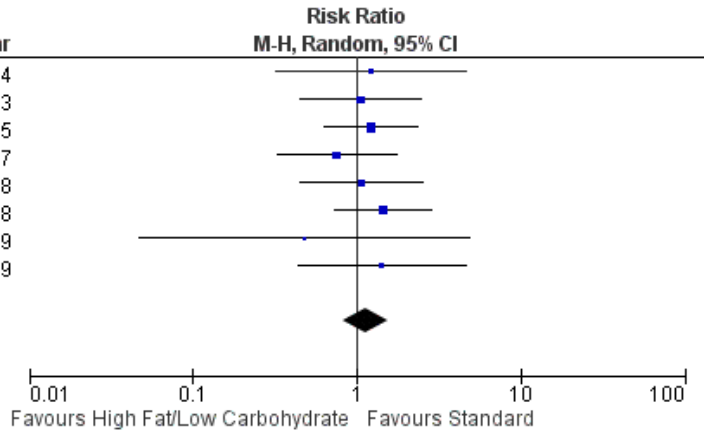


Figure 2. ICU Mortality

Study or Subgroup	High Fat/Low Carbohydrate Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Al Saady	3	9	3	11	7.4%	1.22 [0.32, 4.65]	1994
Mesejo 2003	8	26	7	24	18.4%	1.05 [0.45, 2.47]	2003
Nourohammadi	9	32	6	16	18.8%	0.75 [0.32, 1.74]	2017
Wewalka	13	30	9	30	28.4%	1.44 [0.73, 2.86]	2018
Van Steen	9	52	8	49	17.6%	1.06 [0.44, 2.53]	2018
Vahabzadeh	6	41	4	39	9.4%	1.43 [0.44, 4.67]	2019
Total (95% CI)		**190**		**169**	**100.0%**	**1.13 [0.78, 1.62]**	
Total events	48		37				

Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 5 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)

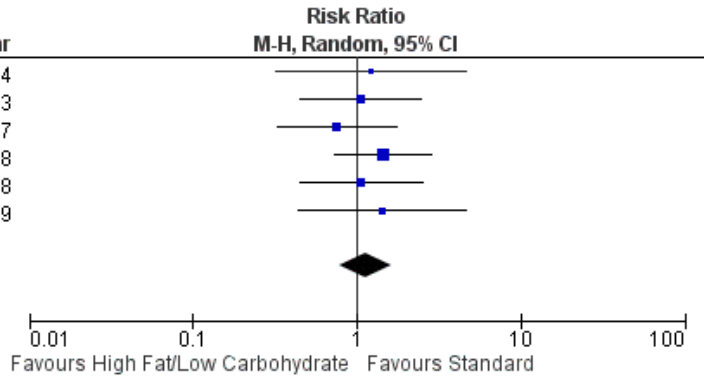


Figure 3. Infections

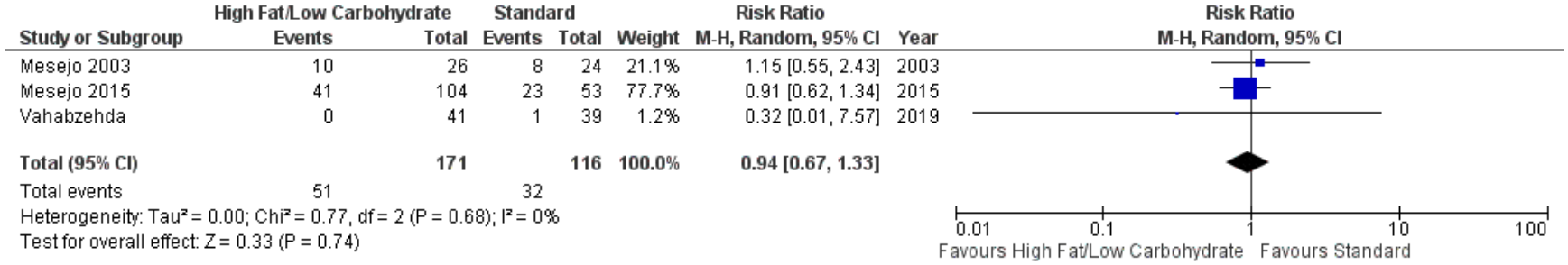


Figure 4. ICU LOS

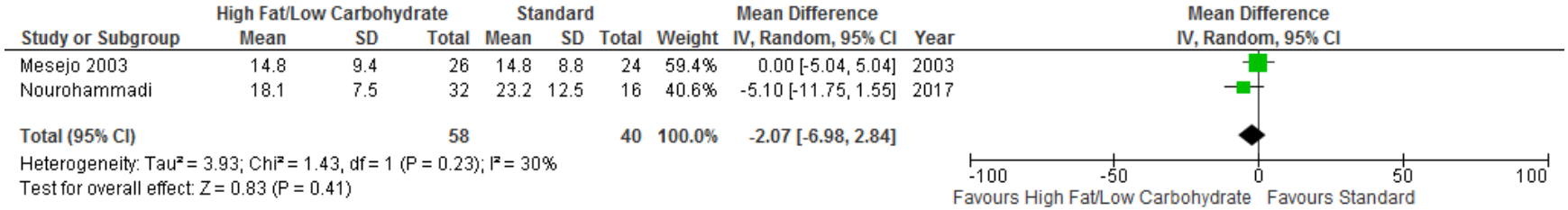


Figure 5. Mechanical Ventilation

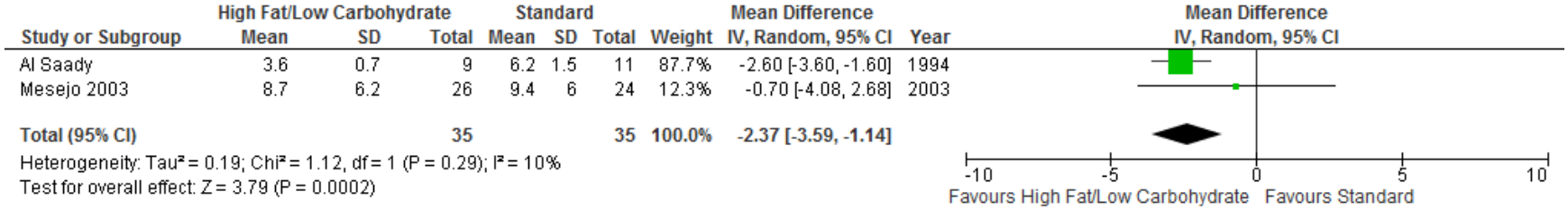
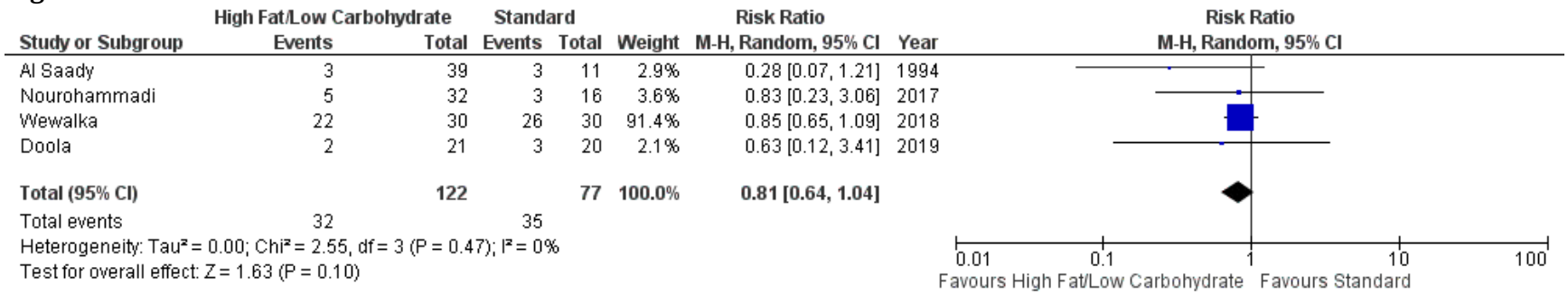


Figure 6. Diarrhea



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