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 six 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) and one compared Glucerna 1.5 (46% fat, 33% CHO) to standard formula (29-30 % fat, 49-53% 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-analysis.

Mortality: Six studies reported on mortality (Al Saady, Mesejo 2003, Mesejo 2015, Nourohammadi 2017, Van Steen 2018, Wewalka 2018) and found no differences between the groups for overall mortality (RR 1.13, 95% CI 0.81, 1.57, p=0.47, I^2 heterogeneity=0%; Figure 1) and for ICU mortality (RR 1.10, 95% CI 0.75, 1.61, p=0.63, I^2 heterogeneity=0%; Figure 2).

Infections: Two studies (Mesejo 2003 and 2015) reported infectious complications and found no differences between the two groups (RR 0.96, 95% CI 0.68, 1.35, p=0.80, I^2 heterogeneity=0%; Figure 3).

LOS: Two studies (Mesejo 2003, Nourohommadi 2017) reported on ICU length of stay and found no differences between the two groups (WMD -2.07, 95% CI -6.98, 2.84, p=0.41; figure 4).

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: In the four studies that reported on glycemic control, glucose levels and the dose of insulin needed were significantly lower in the group receiving the higher fat, lower CHO formula (Mesejo 2003), and Mesejo 2015 reported similar findings between one of their experimental groups (Diaba HP) and the control group. Wewalka 2018 found no statistical significance 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. Three studies reported on diarrhea and no difference was found between groups (RR 0.77, 95% CI 0.49, 1.20, p=0.25, I^2 heterogeneity=16%; 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.

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)	Infections # (%)		RR (CI)
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%	Olive/Sunflower ICU 3/16 (18.7) Sunflower	6/16 (37.5)		NR	NR	NR

			CHO.	ICU 6/16 (37.5)					
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	

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

Study	LOS days		Ventilator days		Cost		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 NR	Standard NR	High fat/low CHO Gastric retention 1/15 (7)	Standard 1/17 (6)

2. Al Saady 1994	NR	NR	3.6 ± 0.7	6.2 ± 1.5	NR	NR	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	NR	NR	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) +	NR	NR	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	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	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+	NR	NR	Patients with hypoglycemia 0/51 1/49 Patients with hyperglycemia 2/51 7/49

C.Random: concealed randomization
ITT: intent to treat
NR: Not reported
± : Mean ± Standard deviation
RR= relative risk, CI= Confidence intervals
+Unable to obtain data from author in 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	6.1%	1.22 [0.32, 4.65]	1994
Mesejo 2003	8	26	7	24	15.2%	1.05 [0.45, 2.47]	2003
Mesejo 2015	24	104	10	53	25.2%	1.22 [0.63, 2.36]	2015
Nourohammadi	9	32	6	16	15.5%	0.75 [0.32, 1.74]	2017
Van Steen	9	52	8	49	14.5%	1.06 [0.44, 2.53]	2018
Wewalka	13	30	9	30	23.5%	1.44 [0.73, 2.86]	2018
Total (95% CI)		**253**		**183**	**100.0%**	**1.13 [0.81, 1.57]**	
Total events	66		43				

Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 5 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

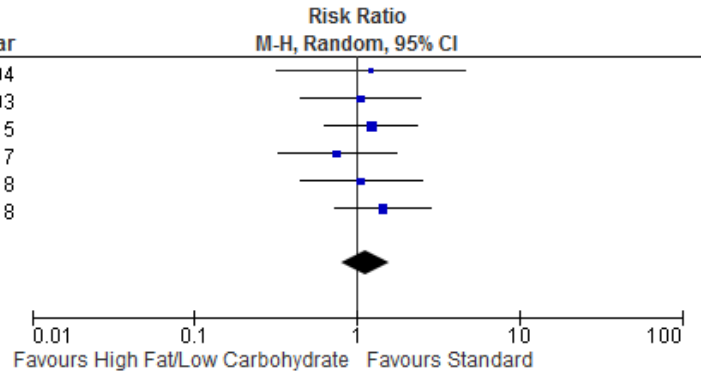

Figure 2. ICU Mortality

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	8.2%	1.22 [0.32, 4.65]	1994
Mesejo 2003	8	26	7	24	20.3%	1.05 [0.45, 2.47]	2003
Nourohammadi	9	32	6	16	20.7%	0.75 [0.32, 1.74]	2017
Wewalka	13	30	9	30	31.4%	1.44 [0.73, 2.86]	2018
Van Steen	9	52	8	49	19.4%	1.06 [0.44, 2.53]	2018
Total (95% CI)		**149**		**130**	**100.0%**	**1.10 [0.75, 1.61]**	
Total events	42		33				

Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 4 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

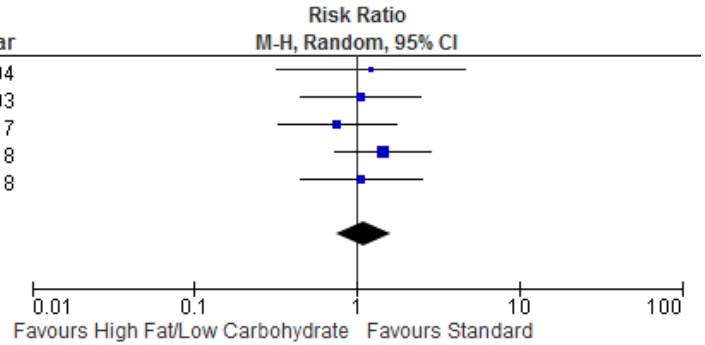

Figure 3. Infections

Study or Subgroup	High Fat/Low Carbohydrate Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Mesejo 2003	10	26	8	24	21.4%	1.15 [0.55, 2.43]	2003
Mesejo 2015	41	104	23	53	78.6%	0.91 [0.62, 1.34]	2015
Total (95% CI)		**130**		**77**	**100.0%**	**0.96 [0.68, 1.35]**	
Total events	51		31				

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

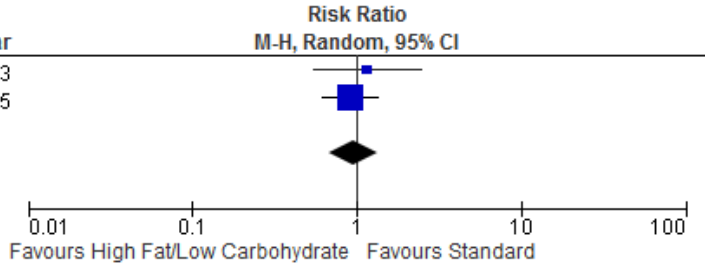

Figure 4. ICU LOS

Study or Subgroup	High Fat/Low Carbohydrate Mean	SD	Total	Standard Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mesejo 2003	14.8	9.4	26	14.8	8.8	24	59.4%	0.00 [-5.04, 5.04]	2003
Nourohammadi	18.1	7.5	32	23.2	12.5	16	40.6%	-5.10 [-11.75, 1.55]	2017
Total (95% CI)			**58**			**40**	**100.0%**	**-2.07 [-6.98, 2.84]**	

Heterogeneity: Tau² = 3.93; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 0.83 (P = 0.41)

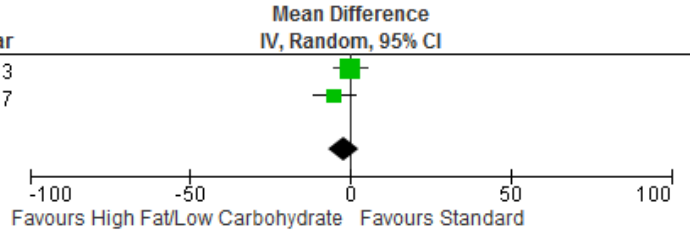

Figure 5. Mechanical Ventilation

Study or Subgroup	High Fat/Low Carbohydrate Mean	SD	Total	Standard Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Al Saady	3.6	0.7	9	6.2	1.5	11	87.7%	-2.60 [-3.60, -1.60]	1994
Mesejo 2003	8.7	6.2	26	9.4	6	24	12.3%	-0.70 [-4.08, 2.68]	2003
Total (95% CI)			**35**			**35**	**100.0%**	**-2.37 [-3.59, -1.14]**	

Heterogeneity: Tau² = 0.19; Chi² = 1.12, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 3.79 (P = 0.0002)

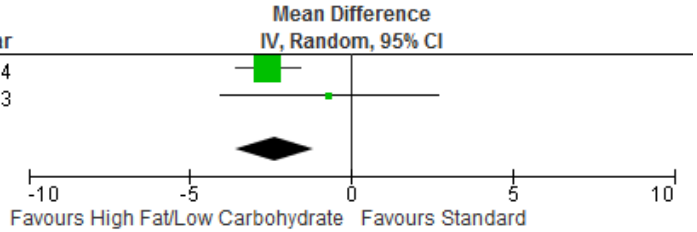

Figure 6. Diarrhea

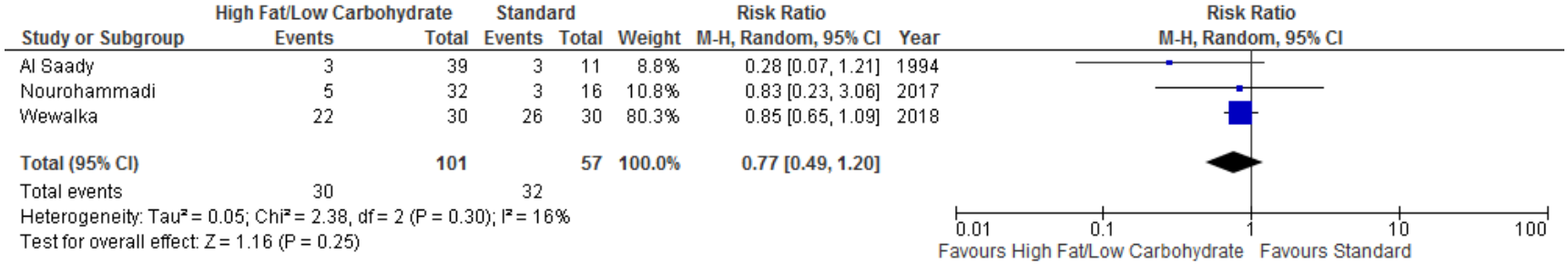

Table 2. Excluded Articles

#	Reason excluded	Citation
1	No clinical outcomes	Schneeweiss B, Graninger W, Ferenci P, Druml W, Ratheiser K, Steger G, Grimm G, Schurz B, Laggner AN, Siostrzonek, et al. Short-term energy balance in patients with infections: carbohydrate-based versus fat-based diets. Metabolism. 1992 Feb; 41(2): 125-30.
2	No clinical outcomes	Diboune M, Ferard G, Ingenbleek Y, Tulasne PA, Calon B, Hasselmann M, Sauder P, Spielmann D, Metais P. Composition of phospholipid fatty acids in red blood cell membranes of patients in intensive care units: effects of different intakes of soybean oil, medium-chain triglycerides, and black-currant seed oil. JPEN J Parenter Enteral Nutr 1992 Mar-Apr; 16(2): 136-41.
3	No clinical outcomes	Adams S, Yeh YY, Jensen GL. Changes in plasma and erythrocyte fatty acids in patients fed enteral formulas containing different fats. JPEN J Parenter Enteral Nutr. 1993 Jan-Feb; 17(1): 30-
4	No clinical outcomes	Tappy L, Berger M, Schwarz JM, McCamish M, Revelly JP, Schneiter P, Jequier E, Chiolero R. Hepatic and peripheral glucose metabolism in intensive care patients receiving continuous high- or low-carbohydrate enteral nutrition. JPEN 1999 Sep-Oct; 23(5): 260-7; discussion 267-8.
5	Not ICU pts	Pohl M, Mayr P, Mertl-Roetzer et al. Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. Eur J Clin Nutr 2005;59:1221-1232.
6	No clinical outcomes	ZHANG Y, QIN D, NI X. Clinical effect of enteral nutrient solution in improving chronic obstructive pulmonary disease patients under mechanical ventilation [J]. Chinese Journal of Clinical Nutrition. 2006;1:011.
7	Irreproducible findings (blenderized feeds) and possible erroneous stats (SE not SD reported?)	Faramawy MAES, Allah AA, Batrawy SE , Amer H. Impact of high fat low carbohydrate enteral feeding on weaning from mechanical ventilation. Egyptian Journal of Chest Diseases and Tuberculosis. 2014;63(4):931-938.