3.2 Nutritional Prescription of Enteral Nutrition: Enhanced Dose of Enteral Nutrition

Question: Does achieving target dose of enteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: All studies in this topic resulted in non-isocaloric and non-isonitrogenous nutrition delivery between the groups. If a strategy resulted in similar levels of protein intake but less calorie intake, it was included in section 3.2b. In this section, there were 7 level 2 studies that compared the use of enhanced enteral nutrition and/or feeding strategies to standard or reduced enteral nutrition. Four studies started the enhanced EN group at the patient's goal EN rate (Taylor 1999, Desachy 2008, Petros 2014, Allingstrup 2017), one study provided standard EN support (compared to a reduced EN strategy, Doig 2015), one study provided >75% of nutrition goals at initiation of EN (Braunschweig 2014), one study used a combined strategy of starting a denser EN formula at 50 mk/h, following a volume based feeding schedule, and using motility agents (Zavetailo 2010), and one study used a feeding protocol with a higher GRV threshold and motility agents (Pinilla 2001). In the Taylor study, 34% patients received small bowel feedings. Martin 2004 and Doig 2008 were previously included in this topic as well as topic 5.1 Feeding Protocols. We have since removed these two studies from this topic since they are cluster RCTs but they can still be found under topic 5.1. Peake 2014 was moved to topic 3.3b Hypocaloric EN due to its isonitrogenous, non-isocaloric study design.

Mortality: When the data from 7 trials was aggregated on overall mortality (Taylor 1999, Desachy 2008, Zaveteilo 2010, Petros 2014, Braunschweig 2014, Doig 2015, Allingstrup 2017), there was a trend towards a excess mortality in the enhanced EN group (RR 1.25 95% CI 0.89, 1.75, p = 0.19, test for heterogeneity I^2 = 33%) (figure 1). When the 3 studies that reported on ICU mortality were aggregated (Desachy 2008, Petros 2014, Doig 2015), enhanced dose of EN was associated with no effect on ICU mortality (RR 1.13, 95% CI 0.70, 1.82, p = 0.61, test for heterogeneity I^2 = 0%) (figure 2). When the 4 studies that reported on hospital mortality were aggregated (Desachy 2008, Petros 2014, Brauschweig 2014, Doig 2015), there again was a trend towards an increase in mortality associated with enhanced EN group (RR 1.49 95% CI 0.93, 2.40, p = 0.09, test for heterogeneity I^2 = 49%) (figure 3). It is important to note that the INTACT trial (Braunschweig 2014) was stopped early due to a significant increase in hospital mortality in the intensive medical nutrition therapy group (40% vs 16%, p=0.017).

Infections: Six studies reported on infectious complications (Taylor 1999, Pinilla 2001, Braunschweig 2014, Petros 2014, Doig 2015, Allingstrup 2017). When the data from these studies was aggregated, achieving enhanced dose of EN had no effect on the incidence of infections (RR 0.97, 95% CI 0.55, 1.70, p = 0.91, test for heterogeneity I^2 = 72) (figure 4).

LOS: In one study (Taylor 1999), length of stay was only reported on a sub group of patients and hence was not included. When the data from the 3 studies that reported LOS in mean and standard deviation was aggregated (Pinilla 2001, Desachy 2008, Zavetailo 2010, Braunschweig 2014), early EN had no effect on ICU LOS (Weighted Mean Difference WMD -1.42, 95% CI -4.28, 1.44, p = 0.33, test for test for heterogeneity I^2 =0) or hospital

LOS (WMD 4.44. 95% CI -2.55, 11.43, p = 0.21, test for heterogeneity I^2 =0) (figures 5, 6). Allingstrup 2017 only reported LOS results for 6 month survivors and found no difference in ICU and hospital LOS (p=0.21 and 1.0, respectively).

Ventilator duration

Taylor et al reported on ventilator days in mean and standard variation and found a reduction in ventilator days in the enhanced EN group (WMD -1.40. 95% CI -2.78, -0.02, p = 0.05). Three other studies reported (Braunschweig 2014, Petros 2014, Doig 2015) on mechanical ventilation duration (in days or hours, not reported as mean and SD) and none of the studies found an effect.

Other complications and nutritional outcomes: In one study (Taylor 1999), early enhanced enteral nutrition was associated with a trend towards fewer major complications and better neurological outcome at 3 months (p =0.08). Of the 2 studies that reported caloric and protein adequacy (percent adequacy in mean and SD, Taylor 1999, Braunschweig 2014), the enhanced EN group received significantly more calories (WMD 25.19. 95% CI 16.14, 34.24, p < 0.00001, figure 7) and protein (WMD 21.05. 95% CI 14.22, 27.88, p <0.0001, figure 8), as would be expected with this intervention. Pinilla et al saw a trend in greater overall nutritional adequacy in the enhanced EN group (p<0.2). The remaining five trials reported significantly greater calorie and protein delivery in the enhanced EN group (see Table 1). It is important to note that by day 7 in one study, protein intake was no longer significant (p=0.6698) since the standard/reduced EN group's feeding protocol had the patients reaching goal nutrition targets by that time.

Quality of Life (QOL) Outcomes: Doig 2015 followed up with survivors at day 90 to obtain QOL outcome data. They found significantly better general health in the group that received higher amounts of nutrition according to the RAND-36 general health (p=0.014) and a trend towards better performance and physical functions in the group that received higher amounts of nutrition according to the ECOG performance status (p=0.18) and RAND-36 physical function (p=0.13). At 6 month follow up, Allingstrup 2017 found no significant difference in the physical composite score (PCS) between groups.

Conclusions:

1) Early enhanced EN, compared to slower rate of advancement of EN, has no effect on ICU mortality but may be associated with an increase in hospital and overall mortality.
2) Early enhanced EN, compared to slower rate of advancement of EN, has no effect on infections, ICU LOS, hospital LOS or ventilator duration in the critically ill patient.
3) Early enhanced EN, compared to a slower rate of advancement of EN, is associated with higher calorie and protein intake in critically ill patients.
4) Early enhanced EN, compared to a slower rate of advancement of EN, may be associated with better long term QOL, especially in patients with hypophosphatemia at ICU admission.

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 target dose of enteral nutrition in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡		LOS days		Other outcomes	
				Enhanced EN	Standard	Enhanced EN	Standard	Enhanced EN	Standard	Enhanced EN	Standard
1) Taylor 1999	Head injured ventilated > 10 yrs n = 82	C.Random: not sure ITT: yes Blinding: no (10)	EN at Goal rate on Day 1 vs. 15 ml/hr day 1 and gradual increase. Both on standard formula. Non-isocaloric, non-isonitrogenous.	6 months 5/41(12.2)	6 months 6/41 (14.6)	25/41 (61) Pneumonia 18/41 (44)	35/41 (85) Pneumonia 26/41 (63)	NR*	NR*	% Energy needs met (mean) 59.2 Nitrogen needs met (mean) 68.7 Major complications 37 % Better neurological outcome at 3 mo 61% Better neurological outcome at 6 mo 68% Ventilator days 3.8±2.4 (41)	36.8 37.9 61% 39% 61% 5.2 ± 3.8 (41)
2) Pinilla 2001	Mixed ICU's N = 96	C.Random: not sure ITT: yes Blinding:no (9)	Feeding protocol with a higher gastric RV threshold (250 mls) + prokinetics vs feeding protocol with lower GRV (150 mls). Both groups received polymeric formula vis gastric feeds. Non-isocaloric, non-isonitrogenous	NR	NR	1/44 (2)	0/36 (0)	ICU 9.5 ± 6.4 (44)	ICU 13.2 ± 18.3 (36)	Hours to reach goal rate 15 ± 10 P<0.09 % nutritional needs met 76 ± 18 P<0.2 intolerances 20/44 (45) P=NS High GRV aspirations 10/44 (23) P<0.005	22 ± 22 70 ± 25 21/36 (58) 19/36 (53)
3) Desachy 2008	Patients from two mixed ICUs N =100	C.Random: not sure ITT: yes Blinding: no (8)	Goal rate EN on day 1 vs. 25 ml/hr day 1 and gradual increase. Both on standard formula, goal rate 25 kcal/kg. Non-isocaloric, non-isonitrogenous.	Hospital 14/50 (28) ICU 6/50 (12)	Hospital 11/50 (22) ICU 8/50 (16)	NR	NR	ICU 15 ± 11 Hospital 56 ± 59 *Mean and SD*	ICU 15 ± 11 Hospital 51 ± 75 *Mean and SD*	Energy intake (mean) 1715 ± 331 Cumulative calorie Deficit 406 ±729 % Energy needs met (mean) 95	1297 ± 331 p < 0.001 2310 ± 1340, p < 0.0001 76, p < 0.0001

4) Zavetailo 2010	Traumatic brain injury or hemorrhagic stroke w anticipated vent >5 days N=56	C.Random: Not sure ITT: yes Blinding: no (7)	Feeding protocol with erythromycin 300 mg first 3 days, target feeding volumes per day, starting EN at 50 ml/hr and increasing by 25 ml/hr daily, introduction of fibre formula on day 3, use of hypercaloric hypernitrogenous formula starting day 1 vs fibre free formula, isotonic, no erythromycin, starting EN at 50 ml/hr and increasing by 25 ml/hr daily. Non-isocaloric, non-isonitrogenous.	30 Day 3/28 (10.7)	30 Day 3/28 (10.7)	NR	NR	ICU 25.8±14 P=0.22	ICU 32.6±25.4	Calories received per kg/d 31.8±10.5 kcal/kg/d 20.6±10.1 kcal/kg/d P<0.01
5) Braunschweig 2014	Acute lung injury, single center ICU N= 78	C.Random: yes ITT: yes Blinding: No (7)	Intensive Medical Nutrition Therapy >75% of energy and protein goal (continuous feed), vs standard nutrition support (bolus, intermittent or continuous feed). Goal 30 kcal/kg/d, 1.5g/kg/d protein. Non-isocaloric, non-isonitrogenous.	Hospital 16/40 (40)	Hospital 6/38 (15.8)	5/40 (12)	8/38 (21)	ICU 15.5 ± 12.8 Hospital 27.2 ± 18.2	ICU 16.1 ± 11.5 Hospital 22.8 ± 14.3	Ventilator days (mean) 6 (4-10) 7 (3-14) p<0.25 Caloric adequacy 84.7 ± 22 55.4 ± 19 Protein adequacy 76.1 ± 18 54.4 ± 21
6) Petros 2014	ICU patient population, with sepsis, acute cardiovascular dysfunction, acute respiratory insufficiency N=100	C.Random: Yes ITT: Yes Blinding: no (10)	100% of goal calories and protein initiated within 24 hrs of ICU admission to increase to goal by day 3 vs 50% of caloric and protein goal initiated within 24 hrs of ICU admission to	ICU 12/54 (22.2) Hospital 17/54 (31.5) 28-day 18/54 (33.3)	ICU 10/46 (21.7) Hospital 17/46 (37.0) 28-day 18/46 (39.1)	Infections 6/54 (11.1)	Infections 12/46 (26.1)	NR	NR	Hypoglycemia 8/54 (14.8) 12/46 (26.1) Diarrhea Increased incidence in normocaloric group (p=0.036) Caloric intake (kcal/kg/d) 19.7 ± 5.7 11.3 ± 3.1, p=0.0001 Caloric adequacy (%) 75.5 42.6 Daily protein intake (g/kg) Group values not provided

			increase to goal hypo feeds by day 3. Non-isocaloric, non-isonitrogenous.							P<0.0001 Ventilator hours 178.5 (69.5-403.3) 254.5 (115.5-686.3) p=NS
7) Doig 2015	Multicentre ICU adults with hypophosphatemia within 72h of starting nutrition support in ICU N=339	C.Random: Yes ITT: no Blinding: single (9)	Continued nutrition support as planned before study enrollment vs 20 kcal/h for at least 2 days, then, if PO4 not needing replacement, the nutrition goal is reached over 2-3 days. Non-isocaloric, non-isonitrogenous	ICU 15/165 Hospital 30/165 60 day 35/165 90 day 35/165	ICU 9/166 Hospital 15/166 60 day 15/166 90 day 21/166	Infections 27/165	Infections 13/166	ICU 10.0 (9.2-10.9) Hospital 21.7 (20.0-23.5)	ICU 11.4 (10.5-12.4) P=0.14 Hospital 27.9 (25.7-30.3) P=0.003	Caloric targets (kcal/h), mean and SD Day 7 83.6 (14.2) 62.4 (23.2), p=0.0001 Protein targets (g/d), mean and SD Day 7 53.89 (38.6) 51.5 (37.8), p=0.6698 Patients developing hypoglycemia days 1-7 P=1.0 on each study day Daily lowest PO4, days 1-7 P>0.05 on each study day Patients with hyperglycemia Day 1 70/165 45/166, p=0.004 Day 2 62/265 30/166, p<0.001 Day 3 64/157 31/159, p<0.001 Day 4 47/138 33/141, p=0.06 Day 5-7 P>0.05 Mechanical ventilation, days 7.45 (7.16-7.65) 7.86 (7.54-8.18) P=0.21
8) Allingstrup 2017	Mixed ICU patients. Single centre. N=203	C.Random: Yes ITT: No Blinding: single (8)	Feeding protocol with calories determined by indirect calorimetry, protein dosed at 1.5 g/kg/d, 100% of nutrition prescription given on first full study day, EN started within 24h of randomization, sPN if needed, protocol for hyperglycemia and increased plasma urea vs	Day 28 20/100 (20) Day 90 30/100 (30) 6 Months 37/100 (37)	Day 28 21/99 (21) Day 90 32/99 (32) 6 Months 34/99 (34)	Any nosocomial infection 19/100 (19)	Any nosocomial infection 12/99 (12)	ICU, among 6 month survivors 7 (5-22) p=0.21 Hospital, among 6 month survivors 30 (12-53) p=1.0	ICU, among 6 month survivors 7 (4-11) Hospital, among 6 month survivors 34 (14-53)	% of energy goals 97 (91-100) 64 (40-84), p<0.001 % of protein goals 97 (75-115) 45 (27-62) p<0.001 Protein intake g/kg/d 1.47 (1.13-1.69) 0.5 (0.29-0.69) Highest blood glucose in ICU, mmol/L 11.0 (9.3-12.4) 9.4 (8.5-10.9)

			feeds dosed at 25 kcal/kg, EN started within 24h and gradually increased, sPN only after day 7 if needed. Non-isocaloric, non-isonitrogenous							

C.Random: concealed randomization ITT: intent to treat NR: not reported ‡ refers to the # of patients with infections unless specified * only reported on a subgroup of patients hence not included
**NA : methodological scoring not applicable as cluster RCTs ICU: intensive care unit

Table 2. Quality of Life Outcomes

Study	QOL Outcome Enhanced EN Standard
7) Doig 2015	RAND-36 General Health 53.4 (22.6), n=124/128 46.0 (26.0), n=136/143 P=0.014 RAND-36 Physical Function 47.3 (35.0), n=123/128 40.9 (33.4), n=135/143 P=0.13 ECOG Performance Status 1.3 (1.0), n=125/128 1.5 (1.1), n=135/143 P=0.18
8) Allingstrup 2017	PCS score at 6 months adjusted for presence of haematologic malignancy, mean (SD) 22.9 (21.8), n=51 23.0 (22.3), n=53 P=0.99

Figure 1: Overall Mortality

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Taylor	5	41	6	41	7.7%	0.83 [0.28, 2.52]	1999
Desachy	14	50	11	50	15.6%	1.27 [0.64, 2.53]	2008
Zavetailo	3	28	3	28	4.4%	1.00 [0.22, 4.54]	2010
Petros	17	54	17	46	20.5%	0.85 [0.49, 1.47]	2014
Braunschweig	16	40	6	38	12.1%	2.53 [1.11, 5.79]	2014
Doig	30	165	15	166	19.1%	2.01 [1.13, 3.60]	2015
Allingstrup	20	100	21	99	20.5%	0.94 [0.55, 1.63]	2015
Total (95% CI)		**478**		**468**	**100.0%**	**1.25 [0.89, 1.75]**	
Total events	105		79				

Heterogeneity: Tau² = 0.07; Chi² = 8.98, df = 6 (P = 0.17); I² = 33%
Test for overall effect: Z = 1.31 (P = 0.19)

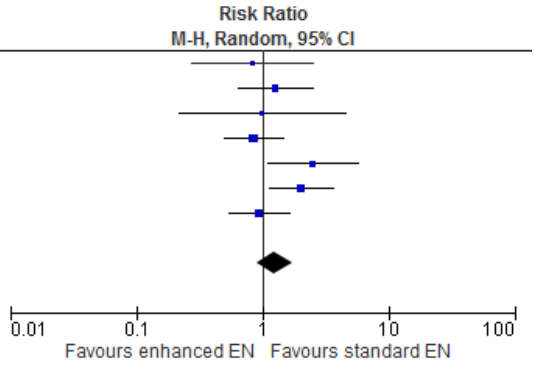

Figure 2: ICU Mortality

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Desachy	6	50	8	50	23.4%	0.75 [0.28, 2.00]	2008
Petros	12	54	10	46	41.1%	1.02 [0.49, 2.15]	2014
Doig	15	165	9	166	35.5%	1.68 [0.76, 3.72]	2015
Total (95% CI)		**269**		**262**	**100.0%**	**1.13 [0.70, 1.82]**	
Total events	33		27				

Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.61)

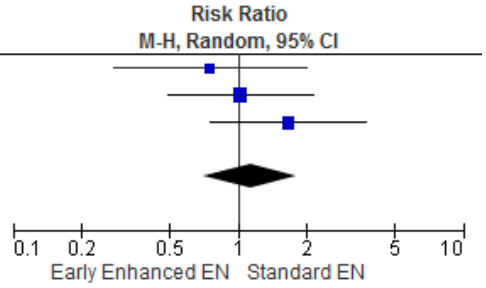

Figure 3: Hospital Mortality

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Desachy	14	50	11	50	24.6%	1.27 [0.64, 2.53]	2008
Petros	14	54	14	46	26.8%	0.85 [0.45, 1.60]	2014
Braunschweig	16	40	6	38	19.9%	2.53 [1.11, 5.79]	2014
Doig	30	165	15	166	28.8%	2.01 [1.13, 3.60]	2015
Total (95% CI)		**309**		**300**	**100.0%**	**1.49 [0.93, 2.40]**	
Total events	74		46				

Heterogeneity: Tau² = 0.11; Chi² = 5.91, df = 3 (P = 0.12); I² = 49%
Test for overall effect: Z = 1.67 (P = 0.09)

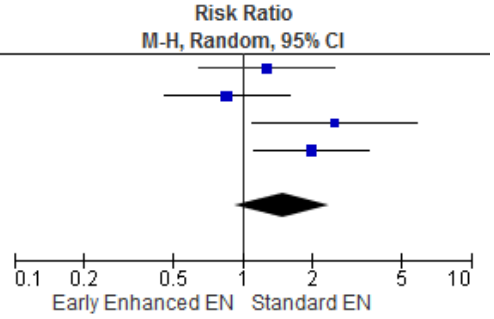

Figure 4: Infectious complications

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Taylor	25	41	35	41	25.8%	0.71 [0.54, 0.94]	1999
Pinilla	1	44	0	36	2.9%	2.47 [0.10, 58.78]	2001
Braunschweig	5	40	8	38	14.5%	0.59 [0.21, 1.66]	2014
Petros	6	54	12	46	16.3%	0.43 [0.17, 1.05]	2014
Doig	27	165	13	166	20.6%	2.09 [1.12, 3.91]	2015
Allingstrup	19	100	12	99	19.9%	1.57 [0.80, 3.05]	2015
Total (95% CI)		**444**		**426**	**100.0%**	**0.97 [0.55, 1.70]**	
Total events	83		80				

Heterogeneity: Tau² = 0.30; Chi² = 17.86, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 0.12 (P = 0.91)

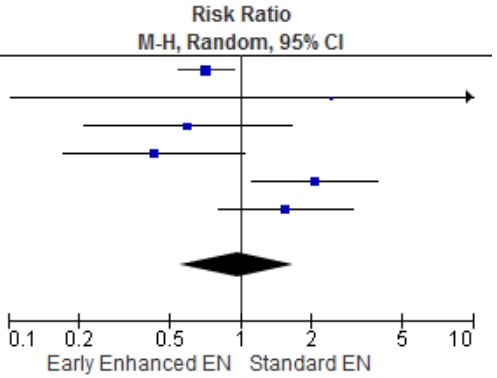

Figure 5: ICU LOS

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Pinilla	9.5	6.4	44	13.2	18.3	36	20.8%	-3.70 [-9.97, 2.57]	2001
Desachy	15	11	50	15	11	50	44.0%	0.00 [-4.31, 4.31]	2008
Zavetailo	25.8	14	28	32.6	25.4	28	7.1%	-6.80 [-17.54, 3.94]	2010
Braunschweig	15.5	12.8	40	16.1	11.5	38	28.1%	-0.60 [-5.99, 4.79]	2014
Total (95% CI)			**162**			**152**	**100.0%**	**-1.42 [-4.28, 1.44]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

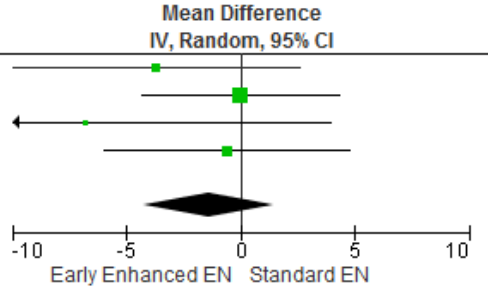

Figure 6: Hospital LOS

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Desachy 2008	56	59	50	51	75	50	4.0%	5.00 [-21.45, 31.45]	2008
Peake 2014	33.3	25.3	57	24	17.6	55	43.0%	9.30 [1.25, 17.35]	2014
Braunschweig 2014	27.2	18.2	40	22.8	14.3	38	53.0%	4.40 [-2.84, 11.64]	2014
Total (95% CI)			**147**			**143**	**100.0%**	**6.53 [1.25, 11.81]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.02)

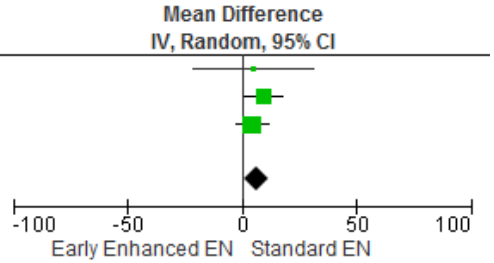

Figure 7: Caloric Adequacy

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor	60	30	41	40	20	41	44.2%	20.00 [8.96, 31.04]	1999
Braunschweig	84.7	22	40	55.4	19	38	55.8%	29.30 [20.19, 38.41]	2014
Total (95% CI)			**81**			**79**	**100.0%**	**25.19 [16.14, 34.24]**	

Heterogeneity: Tau² = 16.59; Chi² = 1.62, df = 1 (P = 0.20); I² = 38%
Test for overall effect: Z = 5.46 (P < 0.00001)

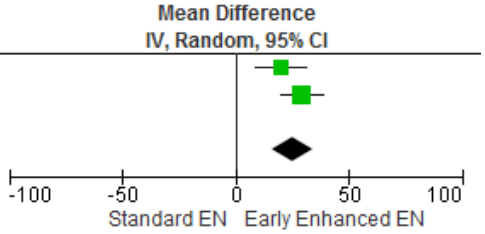

Figure 8: Protein Adequacy

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	60	30	41	40	20	41	33.0%	20.00 [8.96, 31.04]	1999
Peake 2014	82	23.6	57	88.2	39.1	55	32.1%	-6.20 [-18.21, 5.81]	2014
Braunschweig 2014	76.1	18	40	54.4	21	38	34.9%	21.70 [13.00, 30.40]	2014
Total (95% CI)			**138**			**134**	**100.0%**	**12.18 [-4.45, 28.81]**	

Heterogeneity: Tau² = 186.58; Chi² = 14.99, df = 2 (P = 0.0006); I² = 87%
Test for overall effect: Z = 1.44 (P = 0.15)

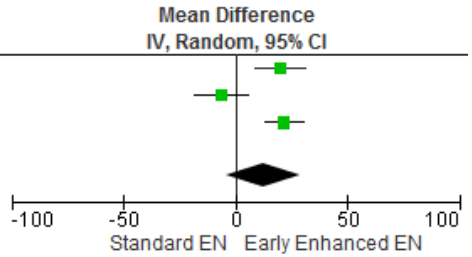

Table 3. Excluded Articles

#	Reason excluded	Citation
1	Earlier work of Petros 2014 JPEN	Petros S, Horbach M, Weidhase L, Seidel F, Schwabe K, Vogel I, Dafova E. Hypocaloric versus normocaloric nutrition in critically ill patients. Int Care Med. S259:0691.
2	Meta-analysis	Al-Dorzi HM, Albarrak A, Ferwana M, Murad MH, Arabi YM. Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis. Crit Care. 2016 Nov 4;20(1):358. PubMed PMID: 27814776; PubMed Central PMCID: PMC5097427.
3	Post-hoc/subset analysis	Braunschweig CL, Freels C, Sheean PM, Peterson SJ, Perez SG, McKeever L, Lateef O, Gurka D, Fantuzzia G. Role of timing and dose of energy received in patients with acute lung injury on mortality in the Intensive Nutrition in Acute Lung Injury Trial (INTACT): A post hoc analysis. Am J Clin Nutr 2017;105:411–6
4	Not a RCT	Akbay Harmandar F, Gömceli I, Yolcular BO, Çekin AH. Importance of target calorie intake in hospitalized patients. Turk J Gastroenterol. 2017 Jul;28(4):289-297.
5	Not a RCT	Charrière M, Ridley E, Hastings J, Bianchet O, Scheinkestel C, Berger MM. Propofol sedation substantially increases the caloric and lipid intake in critically ill patients. Nutrition. 2017 Oct;42:64-68.
6	Meta-analysis	Ridley EJ, Davies AR, Hodgson CL, Deane A, Bailey M, Cooper DJ. Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of randomised controlled trials. Clin Nutr. 2017 Oct 9. pii: S0261-5614(17)31358-4.