3.2a Nutritional Prescription of Enteral Nutrition: Achieving Target Dose of Enteral Nutrition

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

Summary of evidence: In this section, there were 11 level 2 studies that compared achieving target dose of EN (via the use of early enhanced enteral nutrition and/or feeding strategies) to standard feeding strategies or reduced enteral nutrition (referred in this document as a standard underfeeding). All studies in this topic resulted in non-isocaloric and non-isonitrogenous nutrition delivery between the groups. If a trial evaluated similar levels of protein intake but less calorie intake, it was included in section 3.3b. Hypocaloric Enteral Nutrition. If a trial evaluated similar levels of caloric intake but different levels of protein intake, it was included in section 4.2c High Protein vs. Low Protein.

Six studies started the enhanced EN group at 75-100% of the patient's goal EN rate (Taylor 1999, Desachy 2008, Petros 2014, Allingstrup 2017, McKeever 2019, Mousavian 2020); one study compared a higher calorie and protein, glutamine & omega 3 enriched enteral formula to a standard formula at the same rate (Efremov 2017); one study provided standard EN support (compared to a reduced EN strategy, Doig 2015) and one study provided >75% of nutrition goals at initiation of EN and intervention patients received more PN and more IV lipids compared to standard feed patients (Braunschweig 2014). Another study used a combined strategy of starting a denser EN formula at 50 ml/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 randomized controlled trials, 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 10 trials was aggregated on overall mortality (Taylor 1999, Desachy 2008, Zaveteilo 2010, Petros 2014, Braunschweig 2014, Doig 2015, Allingstrup 2017, Efremov 2017, McKeever 2019, Mousavian 2020), there was a trend towards an increase in mortality in the achieving target dose group (RR 1.23, 95% CI 0.94, 1.59, p=0.12, test for heterogeneity I^2 = 7%), figure 1. When the 4 studies that reported on ICU mortality were aggregated (Desachy 2008, Petros 2014, Doig 2015, McKeever 2019), achieving target dose of EN had no effect on ICU mortality (RR 1.12, 95% CI 0.72, 1.76, p = 0.61, test for heterogeneity I^2 = 0%), figure 2. When the data on hospital mortality were aggregated (Desachy 2008, Petros 2014, Brauschweig 2014, Doig 2015, Efremov 2017), a trend towards an increase in mortality was seen in the achieving target dose group (RR 1.49 95% CI 1.00. 2.21, p = 0.05, test for heterogeneity I^2 = 32%), 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: Seven studies reported on infectious complications (Taylor 1999, Pinilla 2001, Braunschweig 2014, Petros 2014, Doig 2015, Allingstrup 2017, McKeever 2019). When the data from these studies was aggregated, achieving target dose of EN had no effect on the incidence of infections (RR 0.97, 95% CI 0.61, 1.54, p = 0.90, test for heterogeneity I^2 = 66%) (figure 4). When the data from two studies that reported on ventilator associated pneumonia were aggregated (Taylor 1999, Mousavian 2020), there were no differences between the target dose or standard underfeeding groups (RR 1.11, 95%CI 0.33, 3.67, p=0.87, test for heterogeneity I^2 = 71%) (figure 5).

LOS: In one study (Taylor 1999), length of stay was only reported on a subgroup of patients and hence was not included. When the data from the studies that reported LOS in mean and standard deviation were aggregated, target dose of EN had no effect on ICU LOS (Weighted Mean Difference WMD -0.88, 95% CI -3.60, 1.84, p = 0.53, test for heterogeneity I^2 =0) (figure 6) and a trend towards an increase in hospital LOS (WMD 4.61, 95% CI -0.92, 10.14, p=0.10, test for heterogeneity I^2 =0) (figure 7). 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: Only two studies reported ventilator days as means and standard deviation (Taylor et al 1990 and McKeever 2019) and when the data from these studies was aggregated, there was no difference between the groups (WMD 0.03, 95% CI -3.87, 3.93, p = 0.99, test for heterogeneity I^2 =62%, figure not shown). Other studies also reported a lack of significant difference between the groups with the exception of one study (Mousavian 2020), in which achieving target dose of EN was associated with a significant increase in mechanical ventilation duration, compared to standard underfeeding (p = 0.014).

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 studies that reported caloric and/or protein adequacy (percent adequacy in mean and SD, Taylor 1999, Braunschweig 2014), the achieving target dose groups received significantly more calories (WMD 22.83, 95% CI 17.97, 27.70, p <0.00001, test for heterogeneity I^2 =26%, figure 8) and protein (WMD 21.05, 95% CI 14.22, 27.88, p <0.00001, test for heterogeneity I^2 =0%, figure 9), as would be expected with this intervention. All studies reported significantly greater calorie and protein delivery in the achieving target dose group compared to the standard underfeeding group (see table 1).

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: In heterogenous critically ill patient populations, achieving target dose of EN, compared to standard underfeeding with EN:

1) Is associated with higher calorie and protein intake.

2) Has no effect on ICU mortality but may be associated with an increase in hospital and overall mortality.
3) Has no effect on infections, ICU LOS or ventilator duration but may increase hospital LOS.
4) May be associated with better long term QOL in patients with hypophosphatemia at ICU admission but there seems to be no effect in other 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 target dose of enteral nutrition in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%) Target Dose vs. Std underfeeding	Infections # (%)‡ Target Dose EN vs. Std underfeeding	LOS days Target Dose EN vs. Std underfeeding	Other outcomes Target Dose EN vs. Std underfeeding
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) vs. 6/41 (14.6)	25/41 (61) vs. 35/41 (85) **Pneumonia** 18/41 (44) vs. 26/41 (63)	NR*	**% Energy needs met (mean)** 59.2 vs. 36.8 **Nitrogen needs met (mean)** 68.7vs. 37.9 **Major complications** 37 % vs. 61% **Better neurological outcome at 3 mo** 61% vs. 39% **Better neurological outcome at 6 mo** 68% vs. 61% **Ventilator days** 3.8±2.4 (41) vs. 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	1/44 (2) vs.0/36 (0)	**ICU** 9.5 ± 6.4 (44) vs. 13.2 ± 18.3 (36)	**Hours to reach goal rate** 15 ± 10 vs. 22 ± 22; p<0.09 **% nutritional needs met** 76 ± 18 vs.70 ± 25, p<0.02 **intolerances** 20/44 (45) vs. 21/36 (58) p=NS **High GRV aspirations** 10/44 (23) vs.19/36 (53) p<0.005
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) vs. 11/50 (22) **ICU** 6/50 (12) vs. 8/50 (16)	NR	**ICU** 15 ± 11 vs.15 ± 11 **Hospital** 56 ± 59 vs. 51 ± 75	**Energy intake (mean)** 1715 ± 331 vs. 1297 ± 331 p < 0.001 **Cumulative calorie Deficit** 406 ±729 vs. 2310 ± 1340 p < 0.0001 **% Energy needs met (mean)** 95 vs. 76, p < 0.0001
4) Zavetailo 2010	Traumatic brain injury or hemorrhagic	C.Random: Not sure ITT: yes	Feeding protocol with erythromycin 300 mg first 3 days, target feeding volumes per day,	**30 Day** 3/28 (10.7) vs. 3/28 (10.7)	NR	**ICU** 25.8±14 vs. 32.6±25.4	**Calories received per kg/d** 31.8±10.5 vs. 20.6±10.1 p<0.01

	stroke anticipated vent >5 days N=56	Blinding: no (7)	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.				
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) vs. 6/38 (15.8)	5/40 (12) vs.8/38 (21)	**ICU** 15.5 ± 12.8 vs. 16.1 ± 11.5 **Hospital** 27.2 ± 18.2 vs. 22.8 ± 14.3	**Ventilator days (mean)** 6 (4-10) vs. 7 (3-14) p<0.25 **Caloric adequacy %** 84.7 ± 22 vs.55.4 ± 19 **Protein adequacy %** 76.1 ± 18 vs. 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 increase to goal hypo feeds by day 3. Non-isocaloric, non-isonitrogenous.	**ICU** 12/54 (22.2) vs. 10/46 (21.7) **Hospital** 17/54 (31.5) vs. 17/46 (37.0) **28-day** 18/54 (33.3) **vs.** 18/46 (39.1)	**Infections** 6/54 (11.1) vs. 12/46 (26.1)	NR	**Hypoglycemia** 8/54 (14.8) vs. 12/46 (26.1) **Diarrhea** Increased incidence in normocaloric group (p=0.036) **Caloric intake (kcal/kg/d)** 19.7 ± 5.7 vs. 11.3 ± 3.1, p=0.0001 **Caloric adequacy (%)** 75.5 vs. 42.6% **Daily protein intake (g/kg)** Group values not provided p<0.0001 **Ventilator hours** 178.5 (69.5-403.3) vs. 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 reduced calorie intake of 20 kcal/h for at least 2 days, then, if PO4 not needing replacement, the nutrition goal is reached over	**ICU** 15/165 vs. 9/166 **Hospital** 30/165 vs.15/166 **60 day** 35/165 vs. 15/166 **90 day**	**Infections** 27/165 vs.13/166	**ICU** 10.0 (9.2-10.9) vs.11.4 (10.5-12.4) p=0.14 **Hospital**	**Day 7 Caloric targets (kcal/h), mean and SD** 83.6 (14.2) vs. 62.4 (23.2), p=0.0001 **Day 7Protein targets (g/d), mean and SD** 53.89 (38.6) vs 51.5 (37.8), p=0.6698 **Patients developing hypoglycemia days 1-7**

			2-3 days. Non-isocaloric, non-isonitrogenous	35/165 vs. 21/166		21.7 (20.0-23.5) vs. 27.9 (25.7-30.3) p=0.003	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 vs. 45/166, p=0.004 **Day 2** 62/265 vs.30/166, p<0.001 **Day 3** 64/157 vs. 31/159, p<0.001 **Day 4** 47/138 vs. 33/141, p=0.06 **Day 5-7** P>0.05 **Mechanical ventilation, days** 7.45 (7.16-7.65) vs. 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 feeds dosed at 25 kcal/kg, EN started within 24h and gradually increased, sPN only after day 7 if needed. Non-isocaloric, non-isonitrogenous	**Day 28** 20/100 (20) vs, 21/99 (21) **Day 90** 30/100 (30) vs. 32/99 (32) **6 Months** 37/100 (37) vs. 34/99 (34)	**Any nosocomial infection** 19/100 (19) vs. 12/99 (12)	**ICU, 6 month survivors** 7 (5-22) vs. 7 (4-11) p=0.21 **Hospital, 6 month survivors** 30 (12-53) vs, 34 (14-53) p=1.0	**% 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)
9) Efremov 2017	Mechanically ventilated, critically ill patients undergoing elective cardiac surgery N=40	C.Random: Yes ITT: yes Blinding: no (10)	High calorie, glutamine & omega 3 enriched EN (Nutricomp immune with 1.33 Kcal/mL,6.7 gm/L protein) vs. standard (Nutricomp standard with 1 Kcal/mL, 3.8 gm/lL protein) EN. Both started within 48 hrs of surgery at 25 mL/hr and increasing at same rates for 14 days, PN used to supplement. Non-isocaloric, non-isonitrogenous	**Hospital** 6/20 (30) vs. 4/20 (20)	**NR**	**Hospital** 30 (25-33) vs. 26 (19-21) **ICU** 11 (7-23) vs. 9 (7-11)	**Enteral nutrition Day 7, Kcal/day** 1950 (1300-2600) 1250 (1000-1500); p <0.05 **EN plus PN Day 7, Kcals/day** 1950 (1300-2600) 1500 (1000=2059), p<0.05 **Protein (EN + PN) Day 7, g/day** 100 (67-133) 57 (38-90), p<0.01 **Prealbumin Day 7, g/L** 0.21±0.1 0.13±0.01, p<0.05 **C-reactive protein Day 7, mg/L** 4.5(2.8-8.6) 3.2(2.1-7.9) **Mechanical ventilation, days**

							4.75 (3-11.4) vs. 5.25 (3.4-6.37), p=NS
10) McKeever 2019	Critically ill patients with systemic inflammatory response syndrome N=34	C.Random: Yes ITT: no Blinding: double (10)	100% energy needs (25-30 Kcal/kg/day) via high calorie Jevity 1.5 Kcal/mL vs. 40% energy needs (10-12 Kcal/kg/day) for 7 days Non-isocaloric, non-isonitrogenous	**ICU** 4/19 (21.1) vs. 3/15 (18.8)	10/19 (52.6) vs. 8/15 (50)	**Hospital** 25.3 ±18.4 (19) vs. 20.4 ± 7.2 (15) **ICU** 22 ±17.9 (19) vs. 17.7 ±7.3 (15)	**Calorie intake, Kcal/kg/day** 16.1±6 10.9±5.4, p=0.01 **Protein intake, gm/day** 0.63±0.27 0.46±0.31, p=0.08 **Mechanical Ventilation, days** 13.1 ± 8.6 (19) vs. 10.3±5.8 (15) p=0.22
11) Mousavian 2020	Neurosurgical intensive care patients with glasgow coma scale 4-10 N=68	C.Random: no ITT: no Blinding: single (7)	Starting at 75% energy needs via standard enteral formula (1 Kcal/mL 0.035 g protein/mL) and increasing to 90-100% vs. starting at 30% energy needs of same formula and increasing to 75% by day 7 Non-isocaloric, non-isonitrogenous	**28 day** 2/29 (6.9) vs 3/29 (10.3)	**Pneumonia** 7/29 (25.9) vs. 3/29 (11.5) p=NS	**Hospital** 28 (28-28) vs. 25 (19.75-28) p=0.046 **ICU** 28 (17-28) vs. 20 (14-28). p=0.163	**% calorie intake, 1st week** 75 47, p<0.001 **% protein intake, 1st week** 70.1 44 , p<0.001 **% calorie intake, 2nd week** 79.2 86, p=NS **% protein intake, 2nd week** 73.96 80.3, p=NS Gastrointestinal intolerance, days 3 (104) 0 (0-1), p<0.001 **Mechanical Ventilation, days** 28 (8.75-28) vs. 11 (7-23) p=0.014

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

Figure 1: Overall Mortality

	Achieving Target Dose EN		Standard Underfeeding			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Taylor	5	41	6	41	5.4%	0.83 [0.28, 2.52]	1999	
Desachy	14	50	11	50	13.2%	1.27 [0.64, 2.53]	2008	
Zavetailo	3	28	3	28	2.9%	1.00 [0.22, 4.54]	2010	
Braunschweig	16	40	6	38	9.4%	2.53 [1.11, 5.79]	2014	
Petros	17	54	17	46	19.9%	0.85 [0.49, 1.47]	2014	
Doig	30	165	15	166	17.8%	2.01 [1.13, 3.60]	2015	
Allingstrup	20	100	21	99	19.9%	0.94 [0.55, 1.63]	2015	
Efremov 2017	6	20	4	20	5.4%	1.50 [0.50, 4.52]	2017	
McKeever 2019	4	19	3	15	3.7%	1.05 [0.28, 4.00]	2019	
Mousavian 2020	2	29	3	29	2.3%	0.67 [0.12, 3.70]	2020	
Total (95% CI)		**546**		**532**	**100.0%**	**1.23 [0.94, 1.59]**		
Total events	117		89					

Heterogeneity: Tau² = 0.01; Chi² = 9.63, df = 9 (P = 0.38); I² = 7%
Test for overall effect: Z = 1.54 (P = 0.12)

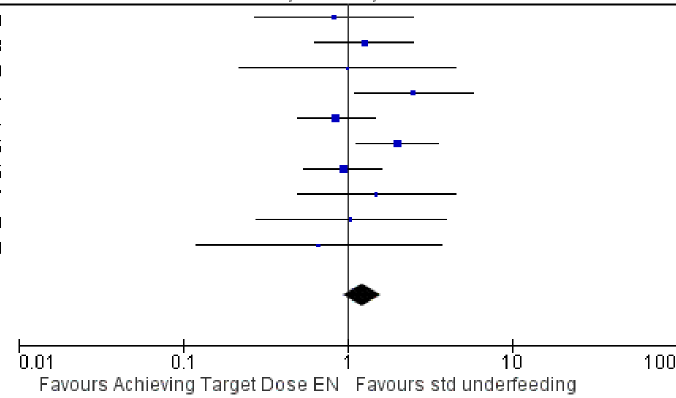


Figure 2: ICU Mortality

	Achieving Target Dose EN		Standard underfeeding			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Desachy	6	50	8	50	20.7%	0.75 [0.28, 2.00]	2008	
Petros	12	54	10	46	36.5%	1.02 [0.49, 2.15]	2014	
Doig	15	165	9	166	31.5%	1.68 [0.76, 3.72]	2015	
McKeever 2019	4	19	3	15	11.3%	1.05 [0.28, 4.00]	2019	
Total (95% CI)		**288**		**277**	**100.0%**	**1.12 [0.72, 1.76]**		
Total events	37		30					

Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)

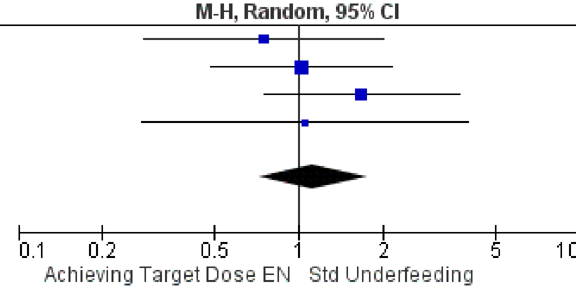


Figure 3: Hospital Mortality

	Achieving Target Dose EN		Standard underfeeding			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Desachy	14	50	11	50	21.7%	1.27 [0.64, 2.53]	2008
Petros	14	54	14	46	24.3%	0.85 [0.45, 1.60]	2014
Braunschweig	16	40	6	38	16.8%	2.53 [1.11, 5.79]	2014
Doig	30	165	15	166	26.6%	2.01 [1.13, 3.60]	2015
Efremov 2017	6	20	4	20	10.7%	1.50 [0.50, 4.52]	2017
Total (95% CI)		**329**		**320**	**100.0%**	**1.49 [1.00, 2.21]**	
Total events	80		50				

Heterogeneity: Tau² = 0.07; Chi² = 5.91, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 1.97 (P = 0.05)

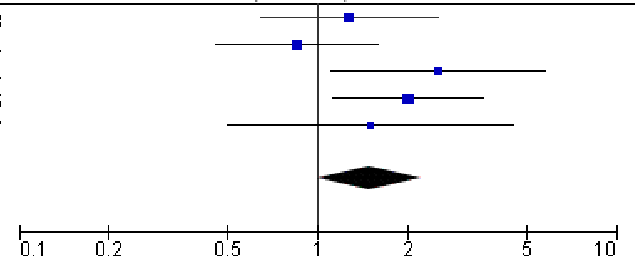


Figure 4: Infectious complications

	Achieving Target Dose EN		Standard Underfeeding			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Taylor	25	41	35	41	23.2%	0.71 [0.54, 0.94]	1999
Pinilla	1	44	0	36	1.9%	2.47 [0.10, 58.78]	2001
Braunschweig	5	40	8	38	11.2%	0.59 [0.21, 1.66]	2014
Petros	6	54	12	46	12.9%	0.43 [0.17, 1.05]	2014
Allingstrup	19	100	12	99	16.5%	1.57 [0.80, 3.05]	2015
Doig	27	165	13	166	17.2%	2.09 [1.12, 3.91]	2015
McKeever 2019	10	19	8	15	17.0%	0.99 [0.52, 1.87]	2019
Total (95% CI)		**463**		**441**	**100.0%**	**0.97 [0.61, 1.54]**	
Total events	93		88				

Heterogeneity: Tau² = 0.22; Chi² = 17.81, df = 6 (P = 0.007); I² = 66%
Test for overall effect: Z = 0.13 (P = 0.90)

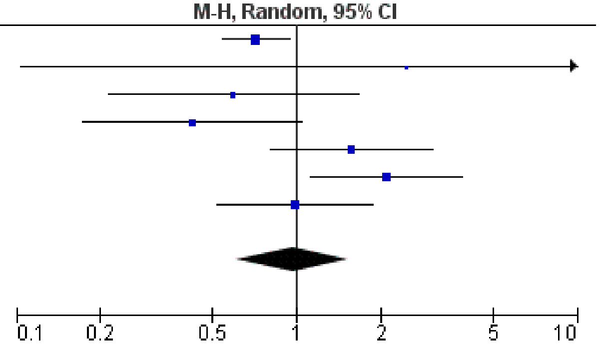


Figure 5: Ventilator Associated Pneumonia

Study or Subgroup	Achieving Target Dose EN Events	Achieving Target Dose EN Total	Standard Underfeeding Events	Standard Underfeeding Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Taylor	18	41	26	41	61.4%	0.69 [0.46, 1.05]	1999
Mousavian 2020	7	29	3	29	38.6%	2.33 [0.67, 8.15]	2020
Total (95% CI)		**70**		**70**	**100.0%**	**1.11 [0.33, 3.67]**	
Total events	25		29				

Heterogeneity: Tau² = 0.57; Chi² = 3.50, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.16 (P = 0.87)

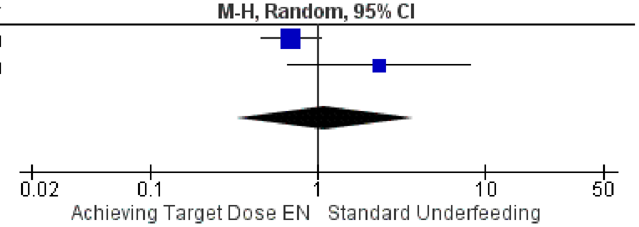


Figure 6: ICU LOS

Study or Subgroup	Achieving Target dose EN Mean	SD	Total	Standard Underfeeding Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Pinilla	9.5	6.4	44	13.2	18.3	36	18.8%	-3.70 [-9.97, 2.57]	2001
Desachy	15	11	50	15	11	50	39.8%	0.00 [-4.31, 4.31]	2008
Zavetailo	25.8	14	28	32.6	25.4	28	6.4%	-6.80 [-17.54, 3.94]	2010
Braunschweig	15.5	12.8	40	16.1	11.5	38	25.5%	-0.60 [-5.99, 4.79]	2014
McKeever 2019	22	17.9	19	17.7	7.3	15	9.4%	4.30 [-4.56, 13.16]	2019
Total (95% CI)			**181**			**167**	**100.0%**	**-0.88 [-3.60, 1.84]**	

Heterogeneity: Tau² = 0.00; Chi² = 3.43, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

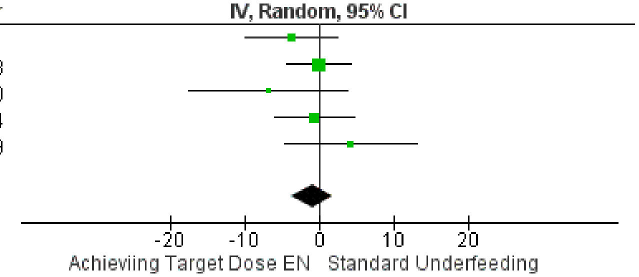


Figure 7: Hospital LOS

Study or Subgroup	Achieving Target Dose EN Mean	SD	Total	Standard Underfeeding Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Desachy	56	59	50	51	75	50	4.4%	5.00 [-21.45, 31.45]	2008
Braunschweig	27.2	18.2	40	22.8	14.3	38	58.2%	4.40 [-2.84, 11.64]	2014
McKeever 2019	25.3	18.4	19	20.4	7.2	15	37.4%	4.90 [-4.14, 13.94]	2019
Total (95% CI)			**109**			**103**	**100.0%**	**4.61 [-0.92, 10.14]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)

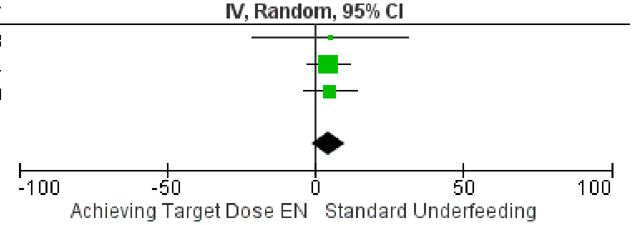


Figure 8: Caloric Adequacy

	Achieving Target Dose EN			Standard Underfeeding				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Taylor	60	30	41	40	20	41	16.5%	20.00 [8.96, 31.04]	1999
Braunschweig	84.7	22	40	55.4	19	38	22.6%	29.30 [20.19, 38.41]	2014
Doig	83.6	14.2	165	62.4	23.2	166	60.9%	21.20 [17.06, 25.34]	2015
Total (95% CI)			**246**			**245**	**100.0%**	**22.83 [17.97, 27.70]**	

Heterogeneity: Tau² = 5.64; Chi² = 2.71, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 9.20 (P < 0.00001)

Mean Difference
IV, Random, 95% CI

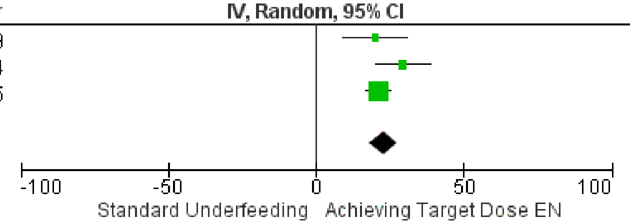
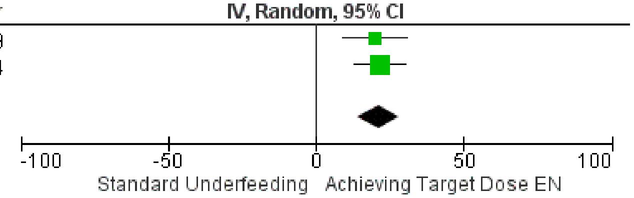


Figure 9: Protein Adequacy

	Achieving Target Dose EN			Standard Underfeeding				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Taylor	60	30	41	40	20	41	38.3%	20.00 [8.96, 31.04]	1999
Braunschweig	76.1	18	40	54.4	21	38	61.7%	21.70 [13.00, 30.40]	2014
Total (95% CI)			**81**			**79**	**100.0%**	**21.05 [14.22, 27.88]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 6.04 (P < 0.00001)

Mean Difference
IV, Random, 95% CI



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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.	Earlier work of Petros 2014 JPEN
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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.	Systematic review
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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.	Systematic Review