3.3b Intentional Underfeeding: Hypocaloric Enteral Nutrition May 2015

2015 Recommendation: ***Based on 4 level 2 studies, intentional underfeeding of calories (not protein) should be considered in patients at low nutrition-risk. However, this recommendation does not apply to patients at high nutrition risk.***

2015 Discussion: The committee noted that with the inclusion of 3 new trials (Charles 2014, Petros 2014 and Arabi in press) the effect of hypocaloric enteral nutrition on mortality was associated with a trend towards a reduction in ICU and hospital mortality and a reduction in mechanical ventilation. There was no effect on length of stay outcomes. The differences in calories received were 42-50% in the hypocaloric group vs.72-75% energy needs in the comparison group yet protein delivery was not different. The committee struggled with the signal of benefit with restricting calories in a heterogeneous ICU patient population and a signal of benefit from optimizing caloric delivery in nutritionally high-risk patients. Given this, it was agreed that a weak recommendation be made for the use of hypocaloric nutrition without underfeeding of protein in nutritionally low-risk patients. It was agreed that the need for maintaining protein intake as demonstrated by recent evidence ought to be emphasized (1,2).

1) Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical outcomes related to protein delivery in critically ill population: A multicenter, multinational observational study. JPEN. [In Press].
2) Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr. 2012 Sep;96(3):591-600.

2013 Recommendation: ***There are insufficient data to make a recommendation on the use of hypocaloric enteral nutrition in critically ill patients.***

2013 Discussion: The committee noted the single centre nature of the one study (Arabi 2011) and agreed that the targeted intervention related to underfeeding of calories (60-70% calories) represented usual care in critically ill patients as evidenced by recent audits of clinical practices. The delivery of additional protein via supplementation was also noted. Despite the significant reduction in hospital and 180 day mortality and the modest sample size of the trial, the committee agreed to wait for the multicentre trial to be completed before putting forward a recommendation on the use of intentional underfeeding (i.e. hypocaloric enteral nutrition).

Semi Quantitative Scoring

Values	Definition	2013 Score (0,1,2,3)	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	**2 (mortality)**	**1 (mortality)**
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	**1**	**1**
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	**2**	**3**
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	**n/a**	**2**
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	**1**	**2**
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3)	**2**	**2**
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre=1, moderate likelihood i.e. multicentre with limited patient population or practice setting=2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings=3)	**1**	**2**
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	**3**	**3**
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	**3**	**3**
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	**2**	**2**

3.3b Intentional Underfeeding: Hypocaloric Enteral Nutrition

Question: Does the use of hypocaloric enteral nutrition vs full feeding result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 4 level 2 studies reviewed that compared starting at 50% caloric and 100% of protein goals (Charles 2014), 50% caloric and 50% of protein goals (Petros 2014), 60-70% of caloric goals plus protein supplements (Arabi 2011), and 40-60% of caloric goals (Arabi [in submission]). The actual amounts of calories received in the underfed group vs fully fed group ranged from 42.6% (Charles 2014) vs 75.5% (Petros 2014) to 59% vs 71.4% (Arabi 2011) while protein intakes were similar in the three studies that reported on this (Arabi 2011, Charles 2014, Arabi 2014). This is in contrast to the Taylor 1999 study that compared starting at full rate enteral nutrition to gradual introduction, in which the full rate group compared to the gradual introduction received 59% vs 37% calories and 69 vs 38% nitrogen in the first week post injury (refer to section 3.2 Achieving target dose of EN for more details). The Arabi2011 study also compared intensive insulin therapy to control in a 2 X 2 factorial design, refer to section 10.4 Insulin therapy data pertaining to these groups.

Mortality: When the data from the trials were aggregated, hypocaloric enteral nutrition was associated with a trend towards a reduction in ICU mortality (RR 0.85, 95% CI 0.67, 1.07, p =0.17, I^2= 0%) (figure 1) and hospital mortality (RR 0.85, 95% CI 0.71, 1.01, p = 0.07, I^2= 0%) (figure 2).

Infections: Hypocaloric enteral nutrition had no effect on the incidence of ICU-acquired infections (RR 1.05, 95% CI 0.77, 1.42,p =0.76 I^2= 47%) (figure 3).

LOS: Hypocaloric enteral nutrition had no effect on ICU LOS (WMD 0.16, 95% CI -3.29, 3.61, p=0.93, I^2= 93%) (figure 4) or hospital LOS (0.74, 95%CI -7.09, 8.57, p = 0.85, I^2= 56%) (figure 5).

Ventilator days: When the data from the 2 studies that reported this outcome were aggregated, hypocaloric enteral nutrition was associated with a significant reduction in ventilator days (WMD -2.34, 95% CI -4.15, -0.53, p = 0.01, I^2= 0%) (figure 6).

Other: Due to the intended study designs, the hypocaloric enteral nutrition groups received significantly fewer calories than the full feeds groups (p 0.003) (figure 7) but received the same amount of protein (p=0.73) (figure 8).

Conclusions:

1. The use of hypocaloric enteral nutrition vs full feeds is associated with a trend towards a reduction in ICU mortality and hospital mortality in critically ill patients.
2. The use of hypocaloric enteral nutrition vs full feeds has no effect on ICU or hospital LOS

3. The use of hypocaloric enteral nutrition vs full feeds is associated with a decrease in length of ventilator support.

Note: Risk ratios, mean differences, confidence intervals and p-values indicated above were calculated using Review Manager 5.3.
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 hypocaloric vs. full feeding in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Hypocaloric Feeds	Full Feeds	HypocaloricFeeds	Full Feeds
1) Arabi 2011*	ICU patients ~30% brain trauma 40% Type 2 diabetes N=240 **BMI (kg/m²)** Trophic feeds pts: 28.5±7.4 Full feeds pts: 28.5±8.4 **Age** Trophic feeds pts: 50.3±21.3 Full feeds pts: 51.9±22.1	C.Random: Yes ITT: Yes Blinding: No (9)	Underfed: 60-70% goal + protein supplements vs.90-100% goal Calories actually received 59.0% vs 71.4% Protein actually received 65.2% vs 63.7% Isonitrogenous, non-isocaloric	**ICU** 21/120 (18) **28 Day** 22/120 (18) **Hospital** 36/120 (30) **180 Day** 38/120 (32)	**ICU** 26/120 (22) **28 Day** 28/120 (23) **Hospital** 51/120 (43) **180 Day** 52/120 (43)	**All Infections/1000 days** 54.7 **VAP/1000 vent days** 14 **Sepsis** 53/120 (44)	**All infections/1000 days** 53.6 **VAP/1000 vent days** 10 **Sepsis** 56/120 (47)
2) Charles 2014	Adults admitted to surgical ICU, included operative and non-operative trauma pts, abdominal vascular liver transplant, and ortho non-trauma surgical pts. N=83	C.Random: Yes ITT: Yes Blinding: single (11)	50% of caloric goal (12.5-15 kcal/kg/d) and protein 1.5 g/kg/d vs 100% of goal calories and protein 1.5 g/kg/d. Calories received 12.3 vs 17.2 kcal/kg/d, protein 1.1 vs 1.1 g/kg/d. Isonitrogenous, non-isocaloric	**Hospital** 3/41 (7.3)	**Hospital** 4/42 (9.5)	**Pts w ICU acquired** 23/41 (56.1) **Pneumonia** 18/41 (43.9) **Bloodstream** 10/41 (24.4) **Central Line** 2/41 (4.9) **UTI** 6/41 (14.6) **Wound** 5/41 (12.2)	**Pts w ICU acquired** 24/42 (57.1) **Pneumonia** 20/42 (47.6) **Bloodstream** 8/42 (19.1) **Central Line** 2/42 (4.8) **UTI** 6/42 (14.3) **Wound** 3/42 (7.1)
3) Petros 2014	ICU patient population, with sepsis, acute cardiovascular dysfunction, acute respiratory insufficiency N=100	C.Random: Yes ITT: Yes Blinding: no (10)	50% of caloric and protein goal initiated within 24 hrs of ICU admission to increase to goal hypo feeds by day 3. vs 100% of goal calories and protein initiated within 24 hrs of ICU admission to increase to goal by day 3. Calories received: 42.2% vs 75.5% or 11.3 kcal.kg/d vs	**ICU** 10/46 (21.7) **Hospital** 17/46 (37.0) **28-day** 18/46 (39.1)	**ICU** 12/54 (22.2) **Hospital** 17/54 (31.5) **28-day** 18/54 (33.3)	**Infections** 12/46 (26.1)	**Infections** 6/54 (11.1)

			19.7 kcal/kg/d Non-isocaloric, non-isonitrogenous.				
4) Arabi (unpublished)	Multicenter. ICU adult patients with LOS ≥72 hrs, requiring EN. N=894	C.Random: Yes ITT: no Blinding: no (8)	40-60% of calorie goals x 14 days and 1.2-1.5 g/kg/d protein achieved with EN and protein supplements vs 70-100% of calorie goals and 1.2-1.5 g/kg/d protein x 14 days. Calories received: 46.2% vs 72% adequacy. No difference in protein. Non-isocaloric, isonitrogenous.	**ICU** 72/448 (16.1) **Hospital** 108/447 (24.2) **28 day** 93/447 (20.8) **90 day** 121/445 (27.2) **180 day** 131/438 (29.9)	**ICU** 85/446 (19.1) **Hospital** 123/445 (27.6) **28 day** 97/444 (21.8) **90 day** 127/440 (28.9) **180 day** 140/436 (32.1)	**Infections** 161/448 (35.9) **VAP** 81/448 (18.1)	**Infections** 169/446 (37.9) **VAP** 90/446 (20.2)

Table 2. Randomized studies evaluating hypocaloric vs full feeding in critically ill patients

Study	LOS days		Ventilator days		Other	
	Hypocaloric Feeds	Full Feeds	Hypocaloric Feeds	Full Feeds	Hypocaloric Feeds	Full Feeds
1)Arabi 2011*	**ICU** 11.7 ±8.1 (120) **Hospital** 70.2 ±106.9 (120)	**ICU** 14.5 ±15.5 (120) **Hospital** 67.2 ±93.6(120)	10.6 ±7.6 (120)	13.2 ±15.2 (120)	**Kcal/day** 1067 ± 306	1252 ± 432, p=0.0002 **Caloric Adequacy (%)** 59 ± 16.1 71.4 ± 22.8, p=<0.0001 **Protein adequacy (%)** 65.2 ± 25.7 63.7 ± 25, p=0.63
2) Charles 2014	**ICU** 16.7 ± 2.7 (41) **Hospital** 35.2 ± 4.9 (41)	**ICU** 13.5 ± 1.1 (42) **Hospital** 31.0 ± 2.5 (42)	NR	NR	**Kcal/d** 982 ±61 **Kcal/kg/d** 12.3 ±0.7 **Protein g/d** 86 ±6 **Protein g/kg/d** 1.1 ±0.1	1338 ±92 17.1 ±1.1 83 ±6 1.1 ±0.1

3) Petros 2014	NR	NR	254.5 hours (115.5-686.3)	178.5 hours (69.5-403.3)	**Hypoglycemia** 12/46 (26.1) 8/54 (14.8) **Diarrhea** Increased incidence in normocaloric group (p=0.036) **Caloric intake (kcal/kg/d)** 11.3 ± 3.1 19.7 ± 5.7 **Caloric adequacy (%)** 42.6 75.5
4) Arabi	**ICU**+ 15.8 ± 11.6 (444) **Hospital**+ 48.3 ±67.5 (444)	**ICU**+ 16.4± 12.1 (443) **Hospital**+ 54.4±73.9 (443)	11.3±9.2 (444)+	13.5±22.3 (443)+	**Kcal/d (p=<0.001)** 835.2±297 1299±467 **% Caloric adequacy (p=<0.001)** 46±14 71±22 **Protein g/d (p=0.29)** 57±24 59±25 **% Protein adequacy (p=0.56)** 68±24 69±25 **No. feeding intolerance (p=0.26)** 67/448 (15) 79/446 (17.7) **No. Diarrhea p=0.11)** 97/448 (21.7) 117/446 (26.2)

C.Random: concealed randomization
† presumed hospital mortality unless otherwise specified
± ( ) : mean ± Standard deviation (number)

ITT: intent to treat; NA: not available
+Data obtained from author in mean and standard deviation
‡ refers to the # of patients with infections unless specified

***** Data shown here for underfed group and full fed groups include patients randomized to the intensive insulin and conventional insulin therapy within these 2 groups. Refer to the intensive insulin therapy section for data on intensive insulin vs conventional groups.
****** Includes 272 patients that also randomized to an experimental arm of omega 3fatty acids arm.

Figure 1: ICU Mortality

Study or Subgroup	Hypocaloric Events	Hypocaloric Total	Normocaloric Events	Normocaloric Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Arabi 2011	21	120	26	120	21.0%	0.81 [0.48, 1.35]	2011
Petros	10	46	12	54	10.2%	0.98 [0.47, 2.05]	2014
Arabi (unpublished)	72	448	85	446	68.8%	0.84 [0.63, 1.12]	2015
Total (95% CI)		**614**		**620**	**100.0%**	**0.85 [0.67, 1.07]**	
Total events	103		123				

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)

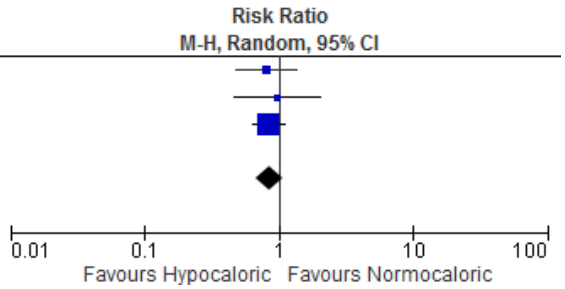

Figure 2: Hospital Mortality

Study or Subgroup	Hypocaloric Events	Hypocaloric Total	Normocaloric Events	Normocaloric Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Arabi 2011	36	120	51	120	26.1%	0.71 [0.50, 1.00]	2011
Charles	3	41	4	42	1.5%	0.77 [0.18, 3.22]	2014
Petros	17	46	17	54	10.4%	1.17 [0.68, 2.03]	2014
Arabi (unpublished)	108	447	123	445	62.1%	0.87 [0.70, 1.09]	2015
Total (95% CI)		**654**		**661**	**100.0%**	**0.85 [0.71, 1.01]**	
Total events	164		195				

Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)

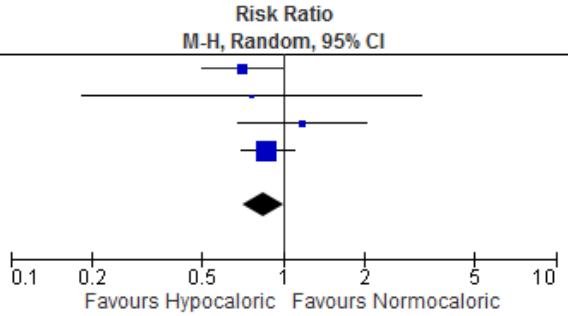

Figure 3: Infectious complications

Study or Subgroup	Trophic Events	Total	Full Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Petros	23	41	24	42	33.4%	0.98 [0.67, 1.43]	2014
Charles	12	46	6	54	9.7%	2.35 [0.96, 5.76]	2014
Arabi (unpublished)	161	448	169	446	56.8%	0.95 [0.80, 1.13]	2015
Total (95% CI)		**535**		**542**	**100.0%**	**1.05 [0.77, 1.42]**	
Total events	196		199				

Heterogeneity: Tau² = 0.03; Chi² = 3.80, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 0.30 (P = 0.76)

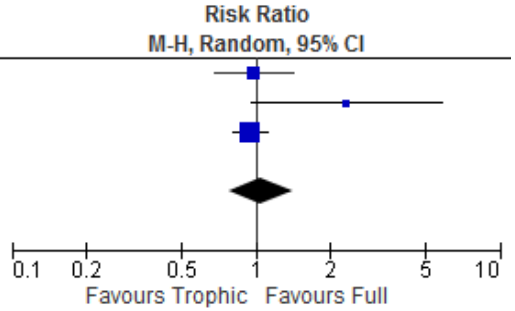

Figure 4 ICU LOS

Study or Subgroup	Hypocaloric Mean	SD	Total	Normocaloric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	11.7	8.1	120	14.5	15.5	120	28.6%	-2.80 [-5.93, 0.33]	2011
Charles	16.7	2.7	41	13.5	1.1	42	36.6%	3.20 [2.31, 4.09]	2014
Arabi (unpublished)	15.8	11.6	444	16.4	12.1	443	34.8%	-0.60 [-2.16, 0.96]	2015
Total (95% CI)			**605**			**605**	**100.0%**	**0.16 [-3.29, 3.61]**	

Heterogeneity: Tau² = 8.27; Chi² = 26.67, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 0.09 (P = 0.93)

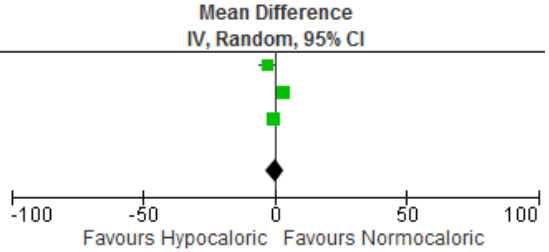

Figure 5 Hospital LOS

Study or Subgroup	Hypocaloric Mean	SD	Total	Normocaloric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	70.2	106.9	120	67.2	93.6	120	8.2%	3.00 [-22.42, 28.42]	2011
Charles	35.2	4.9	41	31	2.5	42	59.1%	4.20 [2.52, 5.88]	2014
Arabi (unpublished)	48.3	67.5	444	54.4	73.9	443	32.7%	-6.10 [-15.42, 3.22]	2015
Total (95% CI)			**605**			**605**	**100.0%**	**0.74 [-7.09, 8.57]**	

Heterogeneity: Tau² = 26.26; Chi² = 4.55, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 0.18 (P = 0.85)

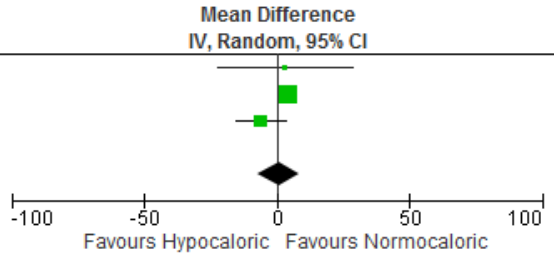

Figure 7 Ventilator Days

Study or Subgroup	Hypocaloric Mean	SD	Total	Normocaloric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	10.6	7.6	120	13.2	15.2	120	35.3%	-2.60 [-5.64, 0.44]	2011
Arabi (unpublished)	11.3	9.2	444	13.5	22.3	443	64.7%	-2.20 [-4.45, 0.05]	2015
Total (95% CI)			564			563	100.0%	**-2.34 [-4.15, -0.53]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)

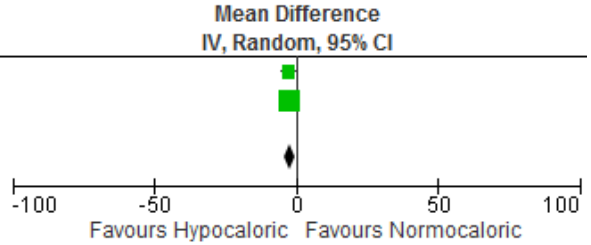

Figure 8 Caloric Adequacy

Study or Subgroup	Hypocaloric Mean	SD	Total	Normocaloric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	59	16.1	120	71.4	22.8	120	48.4%	-12.40 [-17.39, -7.41]	2011
Arabi (unpublished)	46	14	448	71	22	446	51.6%	-25.00 [-27.42, -22.58]	2015
Total (95% CI)			568			566	100.0%	**-18.90 [-31.24, -6.56]**	

Heterogeneity: Tau² = 75.37; Chi² = 19.81, df = 1 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.00 (P = 0.003)

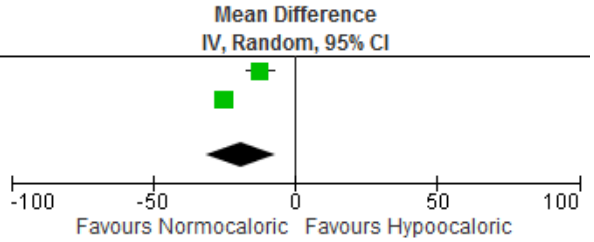

Figure 9 Protein Adequacy

Study or Subgroup	Hypocaloric Mean	SD	Total	Normocaloric Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Arabi 2011	65.2	25.7	120	63.7	25	120	20.1%	1.50 [-4.91, 7.91]	2011
Arabi (unpublished)	68	24	448	69	25	446	79.9%	-1.00 [-4.21, 2.21]	2015
Total (95% CI)			568			566	100.0%	**-0.50 [-3.37, 2.37]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)