3.3a Intentional Underfeeding: Trophic Feeds vs. Full Feeds May 2015

2015 Recommendation: *There were no new randomized controlled trials since the 2013 update but given the reporting of long term outcomes of previously included studies, the following changes to the following summary of evidence were made.*

2015 Discussion: The committee noted that there were no new studies in this section however there were two papers (Needham et al Am J Respir Crit Care Med 2013, Needham et al BMJ 2013) that reported long term outcomes of survivors of the EDEN study (Rice et al 2012 already included in this section). Initial trophic versus full enteral feeding did not have any significant effect on a wide spectrum of physical and cognitive performance based outcome measures as reported in both papers and the authors hypothesized the overall duration of difference in feeding strategies may not have been long enough to cause differences in patient outcomes. Concerns about the population not being at high nutrition risk, consistent with the 2013 discussions, were noted. It was also noted that Mental Health (Trophic 67(25) Full 63 (26) p=0.02) and mental health summary scores were higher in trophic feeding 46(15) than full feeding 43(15) p=0.01 yet trophic feeds were associated with poorer functional recovery at 12 months as seen by a trend towards a worse 6 minute walk test (p=0.136) and 4 minute timed walk speed (0=0.125). The committee downgraded the rating for safety but acknowledged that there was no reason to change the recommendation from 2013 in light of the lack of a strong effect on long term outcomes.

2013 Recommendation: *Based on 2 level 1 studies, in patients with Acute Lung Injury, an initial strategy of trophic feeds for 5 days should not be considered.*

2013 Discussion: The committee noted the lack of treatment effect of trophic feeds on clinical outcomes in the two studies (Rice 2011, Rice 2012). Although there were no safety concerns related to the use of trophic feeds for 5 days, the long term effects of this strategy (muscle mass, muscle function, functional recovery, etc.) are unknown. Despite the large multicentre nature of one of these studies (Rice 2012), the population studied (select patients, age ~ 52 yrs, high BMIs, no comorbidities) did not represent most critically ill patients that tend to benefit from nutritional therapy. Given this and the lack of effect on outcomes, the committee decided to recommend that this strategy not be used. The committee noted that if the recommendation was to be based on values other than the treatment effect alone (i.e. validity, homogeneity, plausibility, generalizability and cost)), a recommendation of "should be considered" would be appropriate.

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	0	0
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	0	0
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	3	3
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	3	3
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	3	3
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)	2	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	1

3.3a Intentional Underfeeding: Trophic Feeds vs Full Feeds March 6, 2015

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

Summary of evidence: There were two level 2 studies reviewed that compared trophic enteral feedings to feeding at full rate. Both studies compared starting at 10 ml/hr for the first 5-6 days to full feeds within 1-2 days (Rice 2011, Rice 2012). In the Rice 2012 study, the first 272 patients also received 240 mls/day of an omega-3 fatty acid supplement or control supplement (Rice 2011), refer to section 4.1 b Enteral Fish Oils for data pertaining to the omega-3 fatty acid vs control groups. Needham et al (2013 Crit Care Med, 2013 Am J Resp Care) further analysed the EDEN trial results (Rice 2011) with respect to patients' long term physical and cognitive performance.

Mortality: When the 2 studies by Rice were aggregated, trophic feeds had no effect on mortality (RR 1.06, 95% CI 0.86, 1.31, p=0.57; figure 1).

Infections, LOS & ventilator days: Both studies reported ventilator associated pneumonia (VAP) rates and when the data from these 2 studies were aggregated, trophic feeds had no effect on the incidence of VAP (RR 0.98, 95% CI 0.68, 1.43, p=0.94; figure 2). Both studies reported ICU free, hospital free and ventilator free days as medians and interquartile ranges instead of means and standard deviations, hence a meta-analysis was not possible. There were no significant differences in any of these outcomes between the 2 groups in Rice 2011 and Rice 2012 studies.

Other: Due to the study design, both studies reported a significant difference in calories between the trophic feeds and full feeds group. Trophic feeds were also associated with better gastrointestinal tolerance i.e. significantly lower % feedings days with diarrhea and high gastric residual volumes. Trophic vs full feeds may have no effect on longterm physical or cognitive function or survival. Results from the Needham et al analyses show EDEN trial survivors had substantial physical, psychological, and cognitive impairments, reduced quality of life, and impaired return to work. Trophic vs full feeds had no effect on physical or cognitive function at 6 and 12 months and no effect on 12-month survival yet Mental Health and mental health summary scores were higher in trophic feeding than full feeding (p=0.02 and 0.01, respectively). There was a worse 6 minute walk test (p=0.136) and 4 meter timed walk speed (p=0.125) in the trophic group.

Conclusions:

1. The use of trophic vs full feeds has no effect on mortality in critically ill patients
2. The use of trophic vs full feeds has no effect on VAP in critically ill patients
3. The use of trophic vs full feeds may be associated with significant underfeeding but better gastrointestinal tolerance in critically ill patients.
4. The use of trophic vs full feeds has no effect on longterm physical or cognitive function or survival but may be associated with poorer functional outcome at 12 months

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 trophic vs full feeding in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Trophic Feeds	Full Feeds	Trophic Feeds	Full Feeds
1) Rice 2011	Mechanically ventilated with acute respiratory failure N=200	C.Random: Yes ITT: Yes Blinding: No (10)	Underfed: 10ml/hr for first 5 days vs. full feed: increased by 25 mls q6h, received 74.8% target. Non isocaloric, non-isonitrogenous	Hospital 22/98 (22)	Hospital 20/102 (17)	30/98 (31) VAP 14/98 (14)	33/102 (32) VAP 18/102 (18)
2) Rice 2012**:	Acute Lung Injury patients from 44 ICUs N=1000	C.Random: Yes ITT: Yes Blinding: No (12)	Underfed 10ml/hr ~400kcal/day x 6 days vs. Full feed: ~1300kcal/day, 90% reached goal in 1.3 days; 25ml/hr advanced q6h Non isocaloric, non isonitrogenous	60 Day 118/508 (23)	60 Day 109/492 (27)	VAP 37/508 (7)	VAP 33/492 (7)

Table 1. Randomized studies evaluating trophic vs full feeding in critically ill patients (continued)

Study	LOS days		Ventilator days		Cost		Other	
	Trophic Feeds	Full Feeds	Trophic Feeds	Full Feeds	Trophic Feeds	Full Feeds	Trophic Feeds	Full Feeds
2) Rice 2011	ICU-free Days 21.0 (6.5-24) Hospital-free Days 12.0 (0-21)	ICU-free Days 21.0 (9.3-24) Hospital-free Days 16.5 (0-21)	Vent-free Days 23 (10.5-26)	Vent-free Days 23 (9.3-26)	NR	NR	Kcal/day 300 ± 149	1481 ± 686 p<0.001 Diarrhea (% feeding days) 19% 24% p 0.08 High Gastric Residuals (% feeding days) 2% 8% p<0.001

3) Rice 2012	ICU-free Days 14.4 (13.5-15.3)	ICU-free Days 14.7 (13.8-15.6)	Vent-free Days 14.9 (13.9-15.8)	Vent-free Days 15.0 (14.9-15.8)	NR	NR	Kcal/day 400 (25) 1300 (82), p=0.001 Time to goal rate (days) 6.7 ± 1.8 1.3 ± 1.2, p=0.001 Diarrhea (% feeding days) 16.5% 18.7%, p=0.16 High Gastric Residuals (% feeding days) 2.2% 4.9%, p<0.001 Vomiting (% feeding days) 1.7% 2.2%, p=0.05 Quality of Life, Physical function – SF-36 55 (33) 55(31), p=0.54 Quality of Life, mental health – SF-36 67 (25) 63 (26), p=0.02 Quality of Life, mental health summary-SF-36 46 (15) 43 (15), p=0.01 Functional Activities – functional performance inventory 2.0 (0.7) 2.1 (0.7), p=0.28 Fatigue – FACIT 63(19) 61 (17), p=0.16 Mini Mental Score 25 (2) 26 (2), p=0.45 6 min walk test @ 12 months 63 (25) 70 (24), p=0.136 4 min timed walk speed 0.98 (0.29) 1.08 (0.29), p=0.125 Hand grip strength 82 (27) 85 (26), p=0.462 Max inspiratory pressure 97 (33) 99(31), p=0.421 Cognitive Impariment, no. (%) 22 (29) 15 (20), p=0.311

C.Random: concealed randomization ITT: intent to treat; NA: not available

† presumed hospital mortality unless otherwise specified

± ( ) : mean ± Standard deviation (number) ‡ 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. Mortality

Study or Subgroup	Trophic Events	Trophic Total	Full Events	Full Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Rice 2011	22	98	20	102	15.3%	1.14 [0.67, 1.96]	2011
Rice 2012	118	508	109	492	84.7%	1.05 [0.83, 1.32]	2012
Total (95% CI)		**606**		**594**	**100.0%**	**1.06 [0.86, 1.31]**	
Total events	140		129				

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)

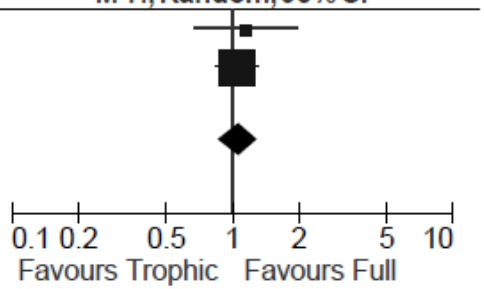

Figure 2. Ventilator Associated Pneumonia

Study or Subgroup	Trophic Events	Trophic Total	Full Events	Full Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Rice 2011	14	98	18	102	33.3%	0.81 [0.43, 1.54]	2011
Rice 2012	37	508	33	492	66.7%	1.09 [0.69, 1.71]	2012
Total (95% CI)		**606**		**594**	**100.0%**	**0.98 [0.68, 1.43]**	
Total events	51		51				

Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)