3.2 Nutritional Prescription of Enteral Nutrition: Achieving Target Dose of Enteral Nutrition March 2013

There were no new randomized controlled trials since the 2009 update and hence there are no changes to the following summary of evidence.

Recommendation: *Based on 2 level 2 studies and 2 cluster randomized controlled trials , when starting enteral nutrition in critically ill patients, strategies to optimize delivery of nutrients (starting at target rate, higher threshold of gastric residual volumes, use of prokinetics and small bowel feedings) should be considered.*

Discussion: The committee noted that across the four disparate studies, there were large improvements in calorie/protein intake/calorie deficit, decreased complications and reduced mortality with the use of enhanced enteral nutrition. Cost and feasibility concerns were also favourable. These favourable signals are tampered by the probability of harm associated with aggressive enteral nutrition as illustrated by non-randomized studies ([1,2]). Given the recent mixed signals from observational studies on the association of calorie deficit and outcomes [3,4], the committee felt that a stronger recommendation could not be made at this time.

1) Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. Crit Care Med 2001; 29(10):1955-61.

2) Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V, Kollef M. Early versus late enteral feeding of mechanically ventilated patients: Results of a clinical trial. JPEN 2002;26:174-181.

3) Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest* 2003;124:297-305

4) Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr* 2005;24:502-9

Semi Quantitative Scoring

Values	Definition	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
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	2
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
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	3
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
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
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2
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	1

3.2 Nutritional Prescription of Enteral Nutrition: Achieving Target Dose of Enteral Nutrition March 2013

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

Summary of evidence: There were 2 level 2 studies that compared the use of early enhanced enteral nutrition to standard early enteral nutrition and two cluster randomized controlled trials that evaluated the effect of a enhanced feeding protocol as one of several interventions geared towards optimizing nutrition (Martin 2004, Doig 2008). In both the cluster randomized controlled trials, the effect of evidence based nutrition algorithms (plus an educational intervention) geared at improving nutrition on patient outcomes was tested. These algorithms assessed gastrointestinal tolerance and promoted the use of prokinetics, post pyloric feeding tubes and supplemental parenteral nutrition to meet at least 80% caloric goal. In two of the randomized trials, enteral nutrition was started at 15ml/hour to 25ml/hr on day 1 and increased gradually. Gastric residual volume thresholds varied from 200 mls (Taylor 1999) to 300 mls (Desachy 2008) and other strategies such as HOB elevation and prokinetics were employed. In the Taylor study, 34% patients received small bowel feedings. The Taylor 1999 study included patients > 10 years of age but was not excluded from this review as the median age was 28 (95% C.I. 22-37) for the control and 34 (95% C.I. 24-43) for the experimental group.

Mortality: Three studies reported on ICU and hospital mortality while the other study reported on 6 month mortality. In the ACCEPT trial (Martin 2004), there was a trend towards a reduction in hospital mortality in the ICUs that received the evidence based algorithms/education (p=0.058) whereas no such difference was observed in the Doig 2008 cluster randomized trial. There were no differences in mortality between the two groups in the other two studies. Given the disparate nature of the studies, a meta-analysis was not done.

Infections: Only one study reported on infectious complications and the goal rate fed group had significantly less infections (p 0.02).

LOS: In the Desachy 2008 study, there were no differences in ICU and hospital length of stay between the two groups. In one study, length of stay was only reported on a sub group of patients and hence was not included. In the twocluster randomized controlled trials, no differences in ICU length of stay was observed, however, the hospital length of stay was significantly lower in the ICUs that received the evidence based algorithms/education in one trial (p=0.003, Martin 2004).

Other complications and nutritional outcomes: In one study, early enhanced enteral nutrition was associated with a trend towards fewer major complications and better neurological outcome at 3 months (p =0.08). The early-enhanced fed group also received significantly more calories in two studies and had a significantly lower cumulative caloric deficit than the slowly fed group in one study (Desachy 2008 p < 0.0001). The # days 100% goal calories were met was higher in the ICUs that were randomized to the practice change group in the Doig cluster trial (p=0.03). The time from

ICU admission to start of enteral nutrition was lower in the ICUs that were randomized to the algorithm group/practice change group in both cluster trials (Martin 2004 $p=0.17$, Doig 2008 $p<0.001$).

Conclusions:

1) Early enhanced EN compared to slower rate of advancement of EN may be associated with a reduction in mortality in the critically ill patient
2) Early enhanced EN compared to slower rate of advancement of EN may be associated with a reduction in hospital lengths of stay in the critically ill patient
3) Early enhanced EN compared to a slower rate of advancement of EN is associated with a trend towards a reduction in the # infections and complications in head injured patients.
4) Early enhanced EN compared to a slower rate of advancement of EN results in a significantly higher calorie intake/lower calorie deficit in head injured patients and 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 # (%)		Infections # (%)‡		LOS days		Other outcomes	
				Goal rate	Standard	Goal rate	Standard	Goal rate	Standard	Goal rate	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	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%	36.8 37.9 61% 39% 61%
2)Martin 2004	Cluster RCT of 14 mixed ICU's N = 492	C.Random: no ITT: no Blinding:no (NA)**	Nutrition algorithms with prokinetics+post pyloric feeding+ supplemental parenteral nutrition to meet at least 80% caloric goal vs. none	Algorithms 72/269 (27)	No ne 82/223 (37)	Algorithms NR	No ne NR	Algorithms Hospital 25 ICU 10.9	None Hospital 35 ICU 11.8	Algorithms Days from ICU admit to start of EN 1.61 Days to 80% goal rate of EN 4.80 Calorie intake per patient day (cals) 1269	None 2.16 5.10 1002
3) Desachy 2008	Patients from two mixed ICUs N =100	C.Random: not sure ITT: yes Blinding: no (8)	Goal rate EN on day 1vs. 25 ml/hr day 1 and gradual increase. Both on standard formula, goal rate 25 kcal/kg	Hospital 14/50 (28) ICU 6/50 (12)	Hospital 11/50 (22) ICU 8/50 (16)	NR	NR	ICU 15 ± 11 Hospital 56 ± 59	ICU 15 ± 11 Hospital 51 ± 75	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
4) Doig 2008	Cluster RCT of 27 ICUs. Patients expected to remain in ICU >2 days N = 1118	C.Random: No ITT: yes Blinding: no (NA)**	Guideline development and practice change strategy of 18 guideline interventions vs. standard	Hospital 172/561 (28.9) ICU 137/561 (24.5)	Hospital 153/557 (27.4) ICU 121/561 (21.5)	NR	NR	ICU 9.1 (8.2 – 10.1) Hospital 24.2 (22.2 – 26.8)	ICU 9.9 (8.9 – 11.1) Hospital 24.3 (22.3 – 26.4)	Time (days) from ICU admission to EN or PN (mean) 0.75 (0.64 – 0.87) Energy (kcal) intake (mean) 1241 (1121 – 1374) Protein (g) intake (mean) 50.1 (45.4 – 55.3) 100% Goal of kcal intake (days) 6.1 (5.6 – 6.65)	1.37 (1.17 – 1.60) 1065 (961 – 1179) 44.2 (40.0 – 48.9) 5.02 (4.61 – 5.48)

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