5.1 Strategies to Optimize Delivery and Minimize Risks of EN: Feeding Protocols May 2015

2015 Recommendation: *Based on 2 level 2 studies and 3 cluster randomized controlled trials, a feeding protocol should be considered that incorporates strategies to optimize delivery of enteral nutrition in critically ill adult patients.*

2015 Discussion: The committee noted the addition of 1 new trial in traumatic brain injury/hemorrhagic stroke patients (Zavetailo 2010) and 1 large cluster trial (Heyland 2012) to the existing studies of the implementation of a feeding protocol in critically ill patients. The components of the protocols varied slightly in the studies and some also utilized nursing education, however all resulted in an improvement in nutrition goals being met and earlier time to start of enteral nutrition. The committee noted the lack of an improvement in clinical outcomes other than the Martin 2004 trial. Given the improvement seen in enteral nutrition delivery in all the trials, the favourable safety, feasibility considerations and low cost, the committee decided that feeding protocols should be considered The following components of feeding protocols have been used in these trials and should be considered: early EN, EN over PN, higher target rates/volume based feeding, initial use of semi-elemental solutions then transitioning to polymeric, empiric use of protein supplements, initiating motility agents at the time of starting EN and tolerating a higher GRV threshold (300 mls vs 250 mls).

2013 and 2009 Recommendation: *Based on 1 level 2 study and 2 cluster randomized controlled trials, an evidence based feeding protocol that incorporates prokinetics at initiation and a higher gastric residual volume (250 mls) and the use of post pyloric feeding tubes, should be considered as a strategy to optimize delivery of enteral nutrition in critically ill adult patients.*

2013 and 2009 Discussion: There were 3 trials that demonstrated an improvement in nutritional outcomes (i.e. residual volumes, time to reach goal rate of EN, etc) with the use of a feeding protocol. It is uncertain whether this translates into an improvement in clinical outcomes since in one cluster trial, a moderately large reduction in mortality was observed, whereas a lack of treatment effect was observed in the other. Given the signals from several observational studies of protocols [1, 2, 3] of improving the delivery of enteral nutrition and the favourable safety, feasibility considerations and low cost, the committee decided that the use of a feeding protocol that incorporates prokinetics, higher gastric residual volumes and small bowel feeding, be considered as a strategy to optimize nutritional intake.

(1) Mackenzie SL et al. Implementation of a nutrition support protocol increases the proportion of mechanically ventilated patients reaching enteral nutrition targets in the adult intensive care unit. JPEN 2005 29(2):74-80.
(2) Barr J, Hecht M, Flavin KE et al. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. Chest. 2004 Apr;125(4):1446-57.
(3) Kozar RA, McQuiggan MM, Moore EE, Kudsk KA, Jurkovich GJ, Moore FA. Postinjury enteral tolerance is reliably achieved by a standardized protocol. J Surg Res. 2002 May 1;104(1):70-5.

Semi Quantitative Scoring

Values	Definition	Score 2013 (0,1,2,3)	Score 2015 (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	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	1	NA
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	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	0	0
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	1	1
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	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	3
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

5.1 Strategies to Optimize Delivery and Minimize Risks of EN: Feeding Protocols

Question: Does the use of a feeding protocol result in better outcomes in the critically ill adult patient?

Summary of evidence: There were two level two studies that looked at outcomes of implementing a feeding protocol. One study compared a higher gastric residual volume threshold (250 mls) plus mandatory prokinetics to a feeding protocol with a lower gastric residual volume threshold (150 mls) (Pinilla 2001), while the other compared a protocol with erythromycin, daily target feeding volumes and fibre containing hypercaloric formula to a protocol with fibre free, isotonic formula in traumatic brain injury/hemorrhagic stroke patients (Zavetailo 2010). In addition, two cluster randomized controlled trials evaluated the effect of a enhanced feeding protocol as one of several interventions geared towards optimizing nutrition (Martin 2004, Doig 2008). In both these 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 a more recent cluster trial implemented The PEP UP protocol which started at higher target rates, volume based goals, use of a semi-elemental formula, protein supplements, prophylactic use of motility agents and higher gastric residual volumes (300 mls) in mixed ICU patients coupled with nursing education (Heyland 2013). Given the disparate nature of the studies, a meta-analysis was not done.

Mortality: Only one study reported on mortality (Martin 2004) and 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 other trials.

Infections: The incidence of infections did not differ between groups in one study (Pinilla 2001) and in the other study that reported on infections, there were reduced incidences of pneumonia in the feeding protocol group [7/252 (2.8%) vs 16/267 (6%)], although this was not statistically different (p=0.43) (Heyland 2013).

LOS and Ventilator days: In all the randomized controlled trials, no differences in ICU/hospital 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 outcomes: In the study by Pinilla et al, there was a lower number of elevated gastric residual aspirations in the group that received the protocol with higher residual volume threshold + prokinetics ($p<0.005$). There was a trend towards less time taken to reach goal rate of feeding in the group that received the protocol with a higher gastric residual volume threshold + prokinetics ($p <0.09$). The time from ICU admission to start of enteral nutrition was lower in the ICUs that were randomized to the algorithm group (p=0.17) in the cluster randomized trial. The # days 100% goal calories were met was higher in the ICUs that were randomized to the practice change group in the Doig study (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). The use of a feeding protocol was associated with a significantly higher caloric intake in the Zavetailo 2010 study (p <0.01) while in the Heyland et al cluster trial, the PEP UP protocol was associated with a 12% (95% CI, 5–20%; *p* = 0.004), increase in calories and a 14% (95% CI, 5–23%; *p* = 0.005) increase in protein over the first 12 days of ICU. There was a significant decrease in the decrease in the average time from ICU admission to start of enteral nutrition with the use of the PEP UP protocol (40.7–29.7 hr vs 33.6–35.2 hr, *p* = 0.10).

Conclusions:

1) Feeding protocols/algorithms with prokinetics, post-pyloric tubes may be associated with a trend towards a reduction in hospital mortality and a significant reduction in hospital length of stay.
2) Feeding protocols with prokinetics and a higher gastric residual volume threshold (250 mls) are associated with a trend towards a reduction in gastric residual aspirations and less time taken to reach goal feeding rate in the critically ill.
3) Feeding protocols with higher target rates, volume based goals, use of a semi-elemental formula, protein supplements, prophylactic use of motility agents and higher gastric residual volumes (300 mls) are associated with a significantly higher calorie and protein intake and a decreased time to start of enteral nutrition in 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 feeding protocols in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
				High RV	Low RV	High RV	Low Rv
1) 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.	NR	NR	1/44 (2)	0/36 (0)
2) Martin 2004	Cluster RCT of 14 mixed ICU's N = 492	C.Random: no ITT: no Blinding:no (5)	Nutrition algorithms with prokinetics+post pyloric feeding+ supplemental parenteral nutrition to meet at least 80% caloric goal vs. none	Algorithms 72/269 (27)	No Algorithms 82/223 (37)	NR	NR
3) Doig 2008	Cluster RCT of 27 ICUs. Patients expected to remain in ICU >2 days N = 1118	C.Random: yes ITT: yes Blinding: no (8)	Development of evidence-based guideline + implementation of a practice-change strategy (including staff education, in-services) composed of 18 specific interventions vs. Site monitoring + data collection only	Hospital 172/561 (28.9) ICU 137/561 (24.5)	Hospital 153/557 (27.4) ICU 121/561 (21.5)	NR	NR
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.	30 Day 3/28 (10.7)	30 Day 3/28 (10.7)	NR	NR
5) Heyland 2013	Cluster RCT, Multicenter, ICUs previously demonstrating poor nutritional adequacy N=1059	C.Random: No ITT: yes Blinding: no (11)	PEP uP protocol – started feeds at higher target rate, volume-based goal, semi-elemental feeding, protein supplements starting day 1, metoclopramide starting day 1 prophylactically, GRV threshold of 300 ml. Nursing education of protocol, plus bedside tools available.	ICU 35/252 (13.9) 60 Day 68/252 (27)	ICU 42/267 (15.7) 60 Day 63/267 (23.6)	ICU acquired pneumonia, by pt 7/252 (2.8)	ICU acquired pneumonia, by pt 16/267 (6.0)

Table 1. Randomized studies evaluating feeding protocols in critically ill patients (continued)

Study	LOS (days)		Nutritional and other Outcomes	
	High RV	Low RV	High RV	Low RV
1) Pinilla 2001	ICU 9.5 ± 6.4 (44)	ICU 13.2 ± 18.3 (36)	Hours to reach goal rate 15 ± 10	22 ± 22 % nutritional needs met 76 ± 18 70 ± 25 intolerances 20/44 (45) 21/36 (58) High GRV aspirations 10/44 (23) 19/36 (53)
2) Martin 2004	Algorithms Hospital 25 ICU 10.9	No algorithms 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	No algorithms 2.16 5.10 1002
3) Doig 2008	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) 1.37 (1.17 - 1.60) Energy (kcal) intake (mean) 1241 (1121 - 1374) 1065 (961 - 1179) Protein (g) intake (mean) 50.1 (45.4 - 55.3) 44.2 (40.0 - 48.9) 100% Goal of kcal intake (days) 6.1 (5.6 - 6.65)	5.02 (4.61 - 5.48)
4) Zavetailo 2010	ICU 25.8±14	ICU 32.6±25.4	Calories received per kg/d 31.8±10.5 kcal/kg/d	20.6±10.1 kcal/kg/d

5) Heyland 2013	ICU 7.2 (3.4-11.1) Hospital 13.5 (8.1-28.4)	ICU 5.7 (2.8-11.8) Hospital 13.8 (7.1-26.6)	Ventilator Days 4.3 (1.1-9.9) 3.0 (1.4-7.3) % calories from total nutrition 48.2 ± 32.5 37.9 ± 30.3 % protein from total nutrition 48.4 ± 34.3 34.4 ± 30 % calories from EN 43.6 ±32.1 33.6 ± 29.5 % protein from EN 47.4 ± 34.7 33.8 ± 29.9 vomiting (p=.45) regurgitation (p=.39) macroaspiration (p=.11)

C.Random: concealed randomization
ITT: intent to treat
RV: residual volume
GRV: gastric residual volume
Ventilator days: not reported

± ( ) : mean ± Standard deviation (number)
‡ refers to the # of patients with infections unless specified
NA: not available
** RR= relative risk, CI= Confidence intervals