5.1a 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 3 cluster randomized controlled trials (RCTs) that examined the impact of a systematic effort to standardize and improve nutrition delivery including feeding protocols (defined as more than one strategy to enhance enteral nutrition) in the ICU setting. The protocol components studied in each study varied greatly (see Table 1) and given the cluster nature of the randomization, a meta-analysis was not done. Four patient-based RCTs evaluated the effect of feeding protocols were also included. Of these, two studies that were under section 3.2 Enhancing EN in 2018 (Pinilla 2001, Zavertailo 2010) have now also been included in this section. Pinilla 2001 compared a feeding protocol with mandatory prokinetics and a GRV threshold of 250 mLs to one with 150 mLs (Pinilla 2001) and this study also appears in the section 5.5a Gastric Residual Volume Threshold.

Mortality: One study that reported on mortality (Martin 2004) found a trend towards a reduction in hospital mortality in the ICUs that received the evidence-based protocols/education (p=0.058), whereas no such difference was observed in the other two cluster RCTs that reported on mortality. When the data from the patient based trials were aggregated, feeding protocols had no effect on mortality (RR 1.01. 95% CI 0.63, 1.60, p=0.98, test for heterogeneity I^2=0%, figure 1).

Infections: In the Heyland 2013 study, there were no differences in the incidence of pneumonia in the feeding protocol group (p=0.43), while the other two cluster RCTs did not report on infections. Feeding protocols had no effect on the rate of infections or ventilator associated pneumonia in the two patient based trials (Pinilla 2001 and Chinda 2020).

Length of Stay (LOS) and Ventilator days: Only one of the three cluster RCTs reported a significantly lower hospital LOS in the ICUs that received the evidence based protocols/education (p=0.003, Martin 2004) but no difference in ICU LOS. Two patient based RCTs reported ICU or hospital LOS as medians and ranges and found no differences between the groups that received feeding protocols or not (Yeh 2019, Chinda 2020). When the data from the other two patient based RCTs were aggregated, feeding protocols were associated with a trend towards a reduction in ICU LOS (WMD -4.49, 95% CI -9.90, 0.93, p=0.10, test for heterogeneity I^2 = 0%, figure 2). Heyland 2013 and Chinda 2020 reported on ventilator days and found no difference between the groups.

Other outcomes: The number of days that 100% of 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 intervention group in all three cluster RCTs (Martin 2004 p=0.17, Doig 2008 p<0.001, Heyland 2013 p=0.10). The use of a feeding protocol (PEP uP)

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 (Heyland 2013). In the Yeh 2019 study, the PEP uP feeding protocol was associated with significant increases in protein intake (grams protein p=0.02; grams protein/kg/day p=0.06) but not calorie intake (p=0.25) and was associated with higher rates of emesis (p=0.03). Pinilla 2001, Zavertailo 2010 and Chinda 2020 reported significant improvements in nutrition outcomes in the groups that were on feeding protocols, such as a shorter time to reach goal rate or a higher percentage of goal rate, amount of calories or protein received. As reported in the section 5.5a Gastric Residual Volume Threshold, in the Pinilla 2001 study there was a significantly lower number of patients with high GRV aspirations in the group with the higher 250 mL GRV threshold protocol compared to a 100 mL GRV threshold protocol (p<0.005). There no differences in overall intolerance, diarrhea or emesis between the two groups in this study.

Conclusions:
In the critical care setting, implementing a feeding protocol:

1) Does not affect mortality or infectious complications.
2) May reduce ICU length of stay
3) Results in an earlier start of EN and improved overall nutritional adequacy.

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 # (%) Intervention	Mortality # (%) Control	Infections # (%)‡ Intervention	Infections # (%)‡ Control
Cluster Randomized Controlled Trials							
1) 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	**Hospital** 72/269 (27)	**Hospital** 82/223 (37); p=0.058	NR	NR
2) 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), p=0.75 **ICU** 121/561 (21.5); p=0.43	NR	NR
3) 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); p=0.57 **60 Day** 63/267 (23.6); p=0.43	**ICU acquired pneumonia, by pt** 7/252 (2.8)	**ICU acquired pneumonia, by pt** 16/267 (6.0); p=0.43
Patient Based Randomized Controlled Trials							
4) 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	NR	1/44 (2)	. 0/36 (0)
5) Zavertailo 2010	Traumatic brain injury or hemorrhagic stroke 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 a hypercaloric. hyper nitrogenous 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.	**30 Day** 3/28 (10.7).	**30 Day** 3/28 (10.7)	NR	NR

6) Yeh 2019	Surgical ICU patients from 3 centres expected to be ventilated >48 hrs & stay in ICU >72 hrs N=36	C.Random: yes ITT: yes Blinding: no (10)	PEP uP protocol (initiation at goal rate, semi-elemental formula, prophylactic prokinetic agents, 24-hour volume-based goals, and modular protein supplementation) vs. standard of care (polymeric formula, rate based feeding, no compensatory feedings)	1/19 (5%)	2/17 (12%)	NR	NR
7) Chinda 2020	Surgical ICU patients expected stay >48 hours. High nutrition risk (Nutrition Risk Screening Tool score ≥3 in 90% patients) N=170	C.Random: no ITT: yes Blinding: no (6)	Feeding protocol (80% of 30 Kcal/kg started within 72 hrs vs. control (attending physician discretion)	**ICU** 10/85 (11.8%) **Hospital** 23/85 (27.1%)	**ICU** 15/85 (17.6%); p=0.28 **Hospital** 22/85 (25.9%); p=0.86	**Any infection** 28/85 (32.9%) **Pneumonia** 17/85 (20.0)	**Any infection** 29/85 (34.1%); p=0.59 **Pneumonia** 12/85 (14.1); p=0.59

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

Study	Nutritional and other Outcomes	
	Intervention vs. Control	Intervention vs. Control
Cluster Randomized Controlled Trials		
1) Martin 2004	**Hospital** 25 vs. 35; p=0.003 **ICU** 10.9 vs. 11.8; p=0.7	**Days from ICU admit to start of EN** 1.61 vs. 2.16; p=0.17 **Days to 80% goal rate of EN** 4.80 vs. 5.10; p=0.78 **Calorie intake per patient day (cals)** 1269 vs. 1002; p =0.31
2) Doig 2008	**ICU** 9.1 (8.2 - 10.1) vs. 9.9 (8.9 - 11.1); p=0.42 **Hospital** 24.2 (22.2 - 26.8) vs. 24.3 (22.3 - 26.4); p=0.97	**Time (days) from ICU admission to EN or PN (mean)** 0.75 (0.64 - 0.87) vs. 1.37 (1.17 - 1.60); p=0.04 **Energy (kcal) intake (mean)** 1241 (1121 - 1374) vs. 1065 (961 - 1179); p=0.62 **Protein (g) intake (mean)** 50.1 (45.4 - 55.3) vs. 44.2 (40.0 - 48.9); p=0.22 **100% Goal of kcal intake (days)** 6.1 (5.6 - 6.65) vs. 5.02 (4.61 - 5.48); p=0.03
3) Heyland 2013	**ICU** 7.2 (3.4-11.1) vs. 5.7 (2.8-11.8); p=0.35 **Hospital** 13.5 (8.1-28.4) vs. 13.8 (7.1-26.6); p=0.73	**Ventilator Days** 4.3 (1.1-9.9) vs. 3.0 (1.4-7.3); p=0.57 **% calories from total nutrition** 48.2 ± 32.5 vs. 37.9 ± 30.3; p=0.01 **% protein from total nutrition** 48.4 ± 34.3 vs. 34.4 ± 30; p=0.004 **% calories from EN** 43.6 ±32.1 vs. 33.6 ± 29.5; p=0.004 **% protein from EN** 47.4 ± 34.7 vs. 33.8 ± 29.9; p=0.005 **vomiting** (p=0.45) **regurgitation** (p=0.39) **macroaspiration** (p=0.11)
Patient Based Randomized Controlled Trials		
4) Pinilla 2001	**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<0.2 **Intolerances** 20/44 (45) vs. 21/36 (58); p=NS **High GRV aspirations** 10/44 (23) vs.19/36 (53); p<0.005

5) Zavertailo 2010	**ICU** 25.8±14 (28) vs. 32.6±25.4 (28); p=0.22	**Calories received per kg/d** 31.8±10.5 vs. 20.6±10.1; p<0.01
6) Yeh 2019	**ICU** 12.0 (6.0-41.7) vs. 12.5 (10.6-15.9); p=NS **Hospital** 21.4 (14.9-60.0) vs. 16.6 (13.9-21.1); p=NS	**Energy, kcal** 1409.9±409.5 vs. 1237.9±459.1; p= 0.25 **Energy, kcal/kg** 15.9±5.5 vs. 14.8±5.7; p= 0.57 **Protein, g** 106.8±37.0 vs. 78.5±30.3; p=0.02 **Protein, g/kg** 1.2±0.4 vs. 0.9±0.4; p=0.06 **Energy adequacy from EN,%** 49.4±23.7 vs. 60.3±22.8; p=0.17 **Protein adequacy from EN, %** 55.1±24.4 vs. 52.9±23.2; p=0.78 **Vomiting, % in 12 hrs period** 4.9% vs. 1.7%; p=0.10 **Emesis, %** 32% vs. 12%; p=0.03
7) Chinda 2020	**ICU** 6.2 (4.3-13.3) vs. 6.3 (3.6-13.1); p=0.57 **Hospital** 27.3 (15.2-44.4) vs. 27.1 (12.2-44.2); p=0.62	**Length of Ventilation, days, mean and SD** 4.6 (2.7-12.2) vs. 4.9 (2.4-10.7); p=0.83 **Energy, kcal/day** 775.4±342.2 vs. 773±391.9; p=0.936 **Energy, kcal/kg/day** 13.5±6.3 vs. 13.5±7.6; p=0.136 **Protein, g/day** 40.3±19.7 vs. 47.4±22.7; p=0.045 **Protein, g/kg/day** 0.7±0.3 vs. 0.8±0.4; p= 0.039

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

Figure 1. Overall Mortality

Study or Subgroup	Feeding Protocols Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Zavertailo	3	28	3	28	9.5%	1.00 [0.22, 4.54]	2010
Yeh	1	19	2	17	4.1%	0.45 [0.04, 4.50]	2019
Chinda	23	85	22	85	86.4%	1.05 [0.63, 1.73]	2020
Total (95% CI)		**132**		**130**	**100.0%**	**1.01 [0.63, 1.60]**	
Total events	27		27				

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

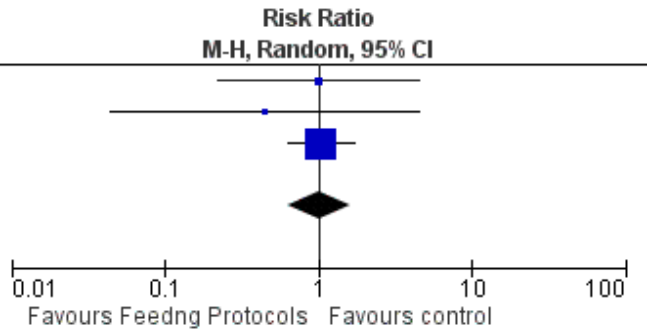
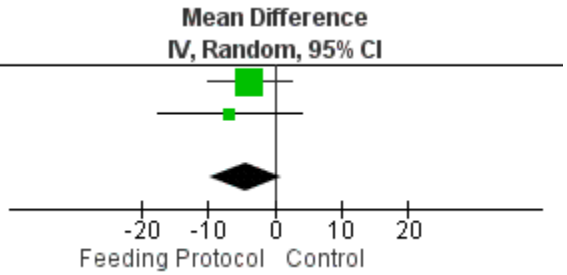


Figure 2. ICU Length of Stay

Study or Subgroup	Feeding Protocol Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Pinilla	9.5	6.4	44	13.2	18.3	36	74.6%	-3.70 [-9.97, 2.57]	2001
Zavertailo	25.8	14	28	32.6	25.4	28	25.4%	-6.80 [-17.54, 3.94]	2010
Total (95% CI)			**72**			**64**	**100.0%**	**-4.49 [-9.90, 0.93]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.62 (P = 0.10)



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7. Chinda P, Poomthong P, Toadithep P, Thanakiattiwibun C, Chaiwat O. The implementation of a nutrition protocol in a surgical intensive care unit; a randomized controlled trial at a tertiary care hospital. PLoS One. 2020 Apr 16;15(4):e0231777. doi: 10.1371/journal.pone.0231777. PMID: 32298381; PMCID: PMC7162472.

Excluded Articles

#	Reason excluded	Citation
1	Unclear if critically ill, no clinically important outcomes	Yan Z, Chen H, Ni Y, Gu J, Yu W, Gao J. Observation of clinical effects of care bundle on patients with traumatic brain injury during nasal feeding. Int J Clin Exp Med. 2017;10(9):13790-13795
2	Before-After Study	Brierley-Hobson S, Clarke G, O'Keeffe V. Safety and efficacy of volume-based feeding in critically ill, mechanically ventilated adults using the 'Protein & Energy Requirements Fed for Every Critically ill patient every Time' (PERFECT) protocol: a before-and-after study. Crit Care. 2019;23(1):105. Published 2019 Apr 2. doi:10.1186/s13054-019-2388-7
3	Before-After Study	Jiang L, Huang X, Wu C, et al. The effects of an enteral nutrition feeding protocol on critically ill patients: A prospective multi-center, before-after study. J Crit Care. 2020;56:249-256. doi:10.1016/j.jcrc.2020.01.018
4	Observational study	Bharal M, Morgan S, Husain T, et al. Volume based feeding versus rate based feeding in the critically ill: A UK study. J Intensive Care Soc. 2019;20(4):299-308. doi:10.1177/1751143719847321
5	Quasi-experimental study	Holyk A, Belden V, Sirimaturos M, et al. Volume-Based Feeding Enhances Enteral Delivery by Maximizing the Optimal Rate of Enteral Feeding (FEED MORE). JPEN J Parenter Enteral Nutr. 2020;44(6):1038-1046. doi:10.1002/jpen.1727

6	Preprints (will update after publication)	Ke, Lu and Lin, Jiajia and Doig, Gordon S. and van Zanten, Arthur R.H. and Wang, Yang and Xing, Juang and Zhang, Zhongheng and Chen, Tao and Zhou, Lixin and Jiang, Dongpo and Shi, Qindong and Lin, Jiandong and Liu, Jun and Cheng, Aibin and Liang, Yafeng and Gao, Peiyang and Sun, Junli and Liu, Wenming and Yang, Zhenyu and Zhang, Rumin and Xing, Wei and Zhang, An and Zhou, Zhigang and Zhou, Tingfa and Liu, Yang and Tong, Fei and Wang, Qiuhui and Pan, Aijun and Huang, Xiaobo and Fan, Chuming and Lu, Weihua and Shi, Dongwu and Wang, Lei and Li, Wei and Gu, Liming and Xie, Yingguang and Sun, Rongqing and Guo, Feng and Han, Lin and Zhou, Lihua and Zheng, Xiangde and Shan, Feng and Liu, Jianbo and Ai, Yuhang and Qu, Yan and Li, Liandi and Li, Hailing and Pan, Zhiguo and Xu, Donglin and Zou, Zhiqiang and Gao, Yan and Yang, Chunli and Kou, Qiuye and Zhang, Xijing and Wu, Jinglan and Qian, Chuanyun and Zhang, Weixing and Zhang, Minjie and Zong, Yuan and Qin, Bingyu and Zhang, Fusen and Zhai, Zhe and Sun, Yun and Chang, Ping and Yu, Bo and Yu, Min and Yuan, Shiying and Deng, YiJun and Zhao, Liyun and Zang, Bin and Li, Yuanfei and Zhou, Fachun and Chen, Xiaomei and Shao, Min and Wu, Weidong and Wu, Ming and Zhang, Zhaohui and Li, Yimin and Guo, Qiang and Wang, Zhiyong and Gong, Yuanqi and Song, Yunlin and Qian, Kejian and Feng, Yongjian and Fu, Baocai and Liu, Xueyan and Li, Zhiping and Gong, Chuanyong and Sun, Cheng and Yu, Jian and Tang, Zhongzhi and Huang, Linxi and Ma, Biao and He, Zhijie and Zhou, Qingshan and Yu, Rongguo and Tong, Zhihui and Li, Weiqin, Active Implementation of an Evidence-Based Nutrition Guideline for Critically Ill Patients Versus Standard Care: A Cluster Randomised, Multicentre, Controlled Trial. Available at SSRN: https://ssrn.com/abstract=3792190 or http://dx.doi.org/10.2139/ssrn.3792190