Nutrition in critically ill –recent update

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Route

- EN vs PN – summary of evidences
  - No benefit in mortality.
  - **Significant increase in number of infectious complication with use of PN.**
  - EN associated with **significant reduction in ICU days compared to PN.**
  - **But no difference in hospital length of stay or ventilator days**
  - EN associated with increased vomiting.

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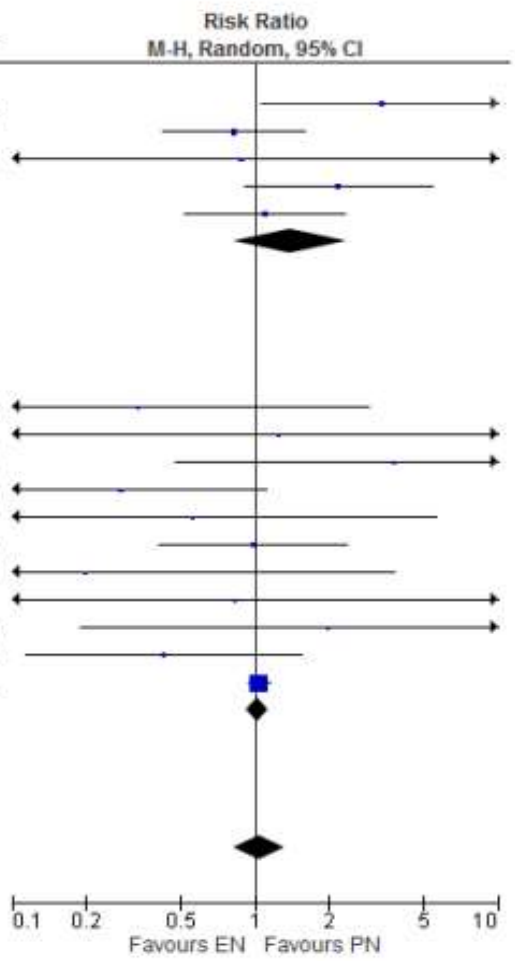
EN vs PN mortality

Figure 1. Studies comparing EN vs PN: Mortality

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Mortality (PN>EN kcal)							
Rapp	9	18	3	20	4.2%	3.33 [1.07, 10.43]	1983
Young	10	28	10	23	10.3%	0.82 [0.42, 1.62]	1987
Kudsk	1	51	1	45	0.8%	0.88 [0.06, 13.70]	1992
Woodcock	9	17	5	21	6.6%	2.22 [0.92, 5.40]	2001
Chen	11	49	10	49	8.6%	1.10 [0.51, 2.35]	2011
Subtotal (95% CI)		**163**		**158**	**30.4%**	**1.40 [0.82, 2.38]**	
Total events	40		29				
Heterogeneity: Tau² = 0.12; Chi² = 6.07, df = 4 (P = 0.19); I² = 34%							
Test for overall effect: Z = 1.24 (P = 0.22)							
1.2.2 Mortality (PN~EN kcal)							
Adams	1	23	3	23	1.2%	0.33 [0.04, 2.97]	1986
Dunham	1	12	1	15	0.8%	1.25 [0.09, 17.98]	1994
Borzotta	5	28	1	21	1.3%	3.75 [0.47, 29.75]	1994
Hadfield	2	13	6	11	2.9%	0.28 [0.07, 1.13]	1995
Kalfarentzos	1	18	2	20	1.1%	0.56 [0.05, 5.62]	1997
Cerra	7	31	8	35	6.5%	0.99 [0.40, 2.41]	1998
Casas	0	11	2	11	0.7%	0.20 [0.01, 3.74]	2007
Meirelles	1	12	1	10	0.8%	0.83 [0.06, 11.70]	2011
Sun	2	30	1	30	1.0%	2.00 [0.19, 20.90]	2013
Wang	3	61	7	60	3.2%	0.42 [0.11, 1.55]	2013
Harvey	450	1186	431	1185	50.0%	1.04 [0.94, 1.16]	2014
Subtotal (95% CI)		**1425**		**1421**	**69.6%**	**1.03 [0.93, 1.14]**	
Total events	473		463				
Heterogeneity: Tau² = 0.00; Chi² = 9.59, df = 10 (P = 0.48); I² = 0%							
Test for overall effect: Z = 0.52 (P = 0.60)							
Total (95% CI)		**1588**		**1579**	**100.0%**	**1.04 [0.82, 1.33]**	
Total events	513		492				
Heterogeneity: Tau² = 0.03; Chi² = 16.94, df = 15 (P = 0.32); I² = 11%							
Test for overall effect: Z = 0.32 (P = 0.75)							
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.5%							



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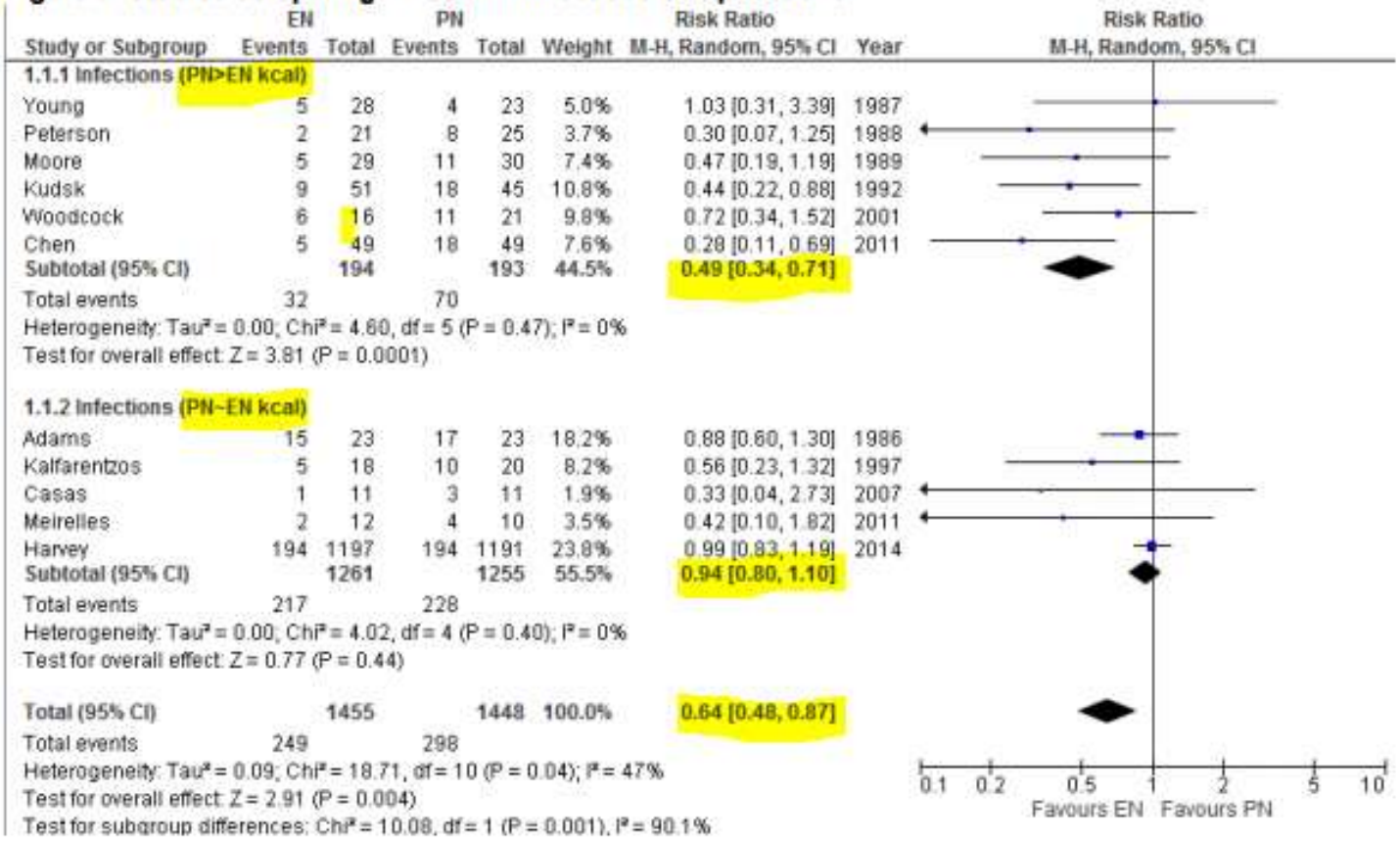
Infectious complication EN vs PN

Figure 3. Studies comparing EN vs PN: Infectious complications



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CALORIES trial –

[largest RCT on EN vs PN]

- Hypothesis -“parenteral route is superior to the enteral route for the delivery of early nutritional support in adults who had an unplanned admission to an intensive care unit (ICU) and who could be fed through either route.”
- Study design- pragmatic, open, multicenter, parallel-group, randomized, controlled trial.
- Method- patients who could be fed through either the parenteral or the enteral route were assigned to a delivery route, with nutritional support initiated within 36 hours after admission and continued for up to 5 days.
- Primary outcome- all cause mortality at day 30.
- Result -no significant difference in 30-day mortality associated with the route of delivery of early nutritional support in critically ill adults was found.

NEJM october 30 , 2014

Table 3. Primary and Secondary Outcomes.*

Outcome	Parenteral Group (N=1191)	Enteral Group (N=1197)	Absolute Difference between Groups (95% CI)	Relative Risk (95% CI)	P Value
Primary outcome: death within 30 days — no./total no. (%)	393/1188 (33.1)	409/1195 (34.2)	1.15 (−2.65 to 4.94)†	0.97 (0.86 to 1.08)‡	0.57§
Secondary outcomes					
No. of days alive and free of specified organ support up to 30 days¶					
Free of advanced respiratory support	14.3±12.1	14.3±12.2	0.04 (−0.94 to 1.01)		0.94
Free of advanced cardiovascular support	18.9±13.5	18.5±13.6	0.41 (−0.63 to 1.53)		0.44
Free of renal support	19.1±13.9	18.8±14.0	0.26 (−0.85 to 1.47)		0.66
Free of neurologic support	19.2±13.8	18.9±14.0	0.34 (−0.81 to 1.36)		0.57
Free of gastrointestinal support	13.0±11.7	13.2±11.8	−0.12 (−1.05 to 0.80)		0.81
No. of treated infectious complications per patient‖	0.22±0.60	0.21±0.56	0.01 (−0.04 to 0.06)		0.72
Noninfectious complications — no./total no. (%)					
Episodes of hypoglycemia	44/1191 (3.7)**	74/1197 (6.2)††	2.49 (0.75 to 4.22)†		0.006§
Elevated liver enzymes	212/1191 (17.8)	179/1197 (15.0)	−2.85 (−5.81 to 0.12)†		0.07§
Nausea requiring treatment	44/1191 (3.7)	53/1197 (4.4)	0.73 (−0.85 to 2.32)†		0.41§
Abdominal distention	78/1191 (6.5)	99/1197 (8.3)	1.72 (−0.38 to 3.82)†		0.12§
Vomiting	100/1191 (8.4)	194/1197 (16.2)	7.81 (5.20 to 10.43)†		<0.001§
New or substantially worsened pressure ulcers	181/1190 (15.2)	179/1195 (15.0)	−0.23 (−3.10 to 2.64)†		0.91§
Median no. of days in the ICU (IQR)‡‡	8.1 (4.0–15.8)	7.3 (3.9–14.3)			0.15
Median no. of days in acute care hospital (IQR)§§	17 (8–34)	16 (8–33)			0.32
Death — no./total no. (%)¶¶					
In the ICU	317/1190 (26.6)	352/1197 (29.4)		0.91 (0.80 to 1.03)	0.13§
In acute care hospital	431/1185 (36.4)	450/1186 (37.9)		0.96 (0.86 to 1.06)	0.44§
By 90 days	442/1184 (37.3)	464/1188 (39.1)		0.96 (0.86 to 1.06)	0.40§

NUTRIREA 2- ongoing RCT

- This is a multicenter, open-label, parallel-group, randomized controlled trial comparing early PN versus early EN in critically ill patients requiring IMV for an expected duration of at least 48 hours, combined with vasoactive drugs, for shock.
- It has completed recruitment but results are not published.

NCT01802099

Timing

- Early Enteral Nutrition when compared to delayed Enteral Nutrition:
  - no effect on mortality
  - no effect on ICU or hospital length of stay.
  - **But** improves overall nutritional intake
  - **And** associated with a significant reduction in infectious complications.

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Figure 1. Studies comparing early EN vs delayed nutrient intake: Mortality

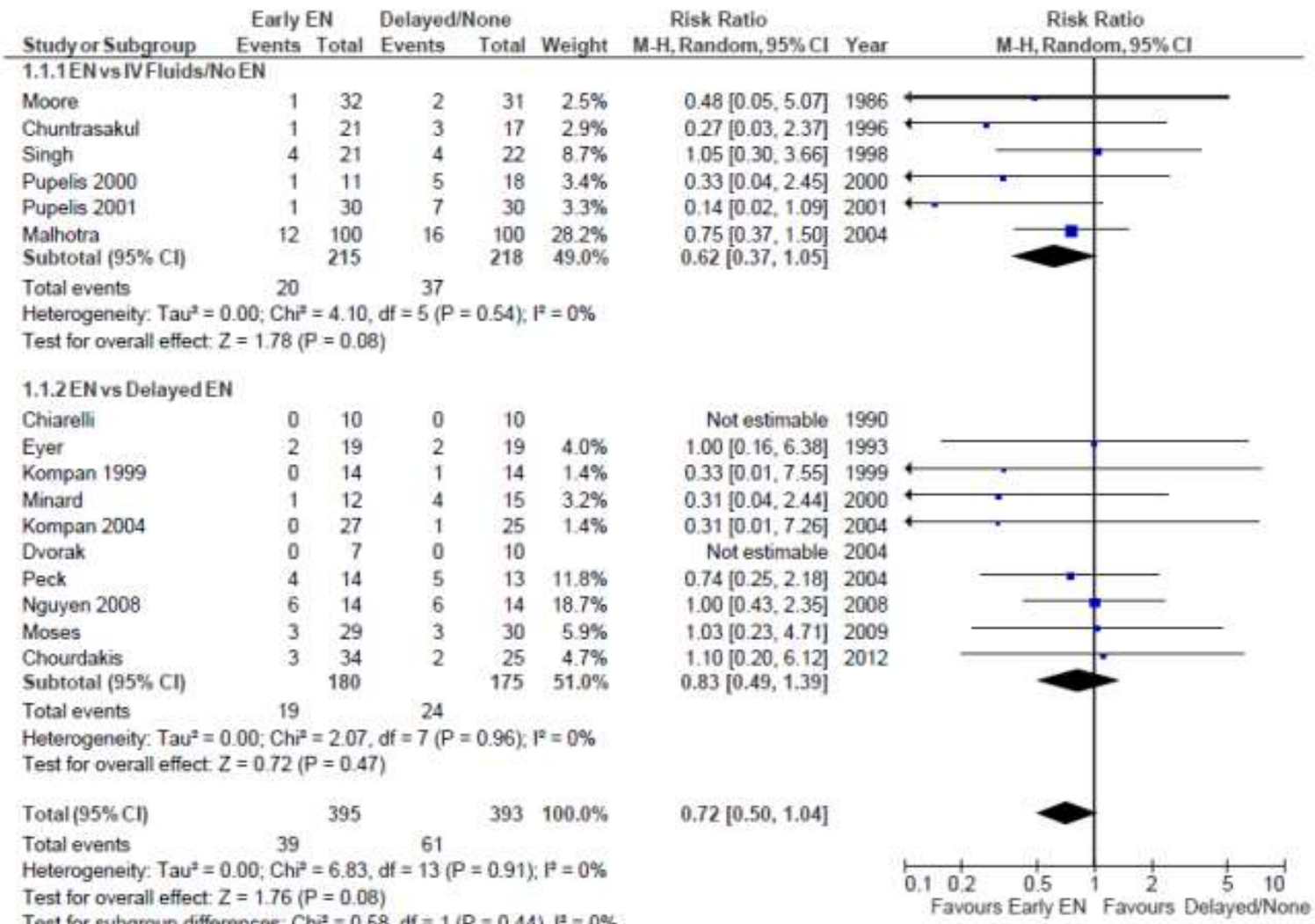
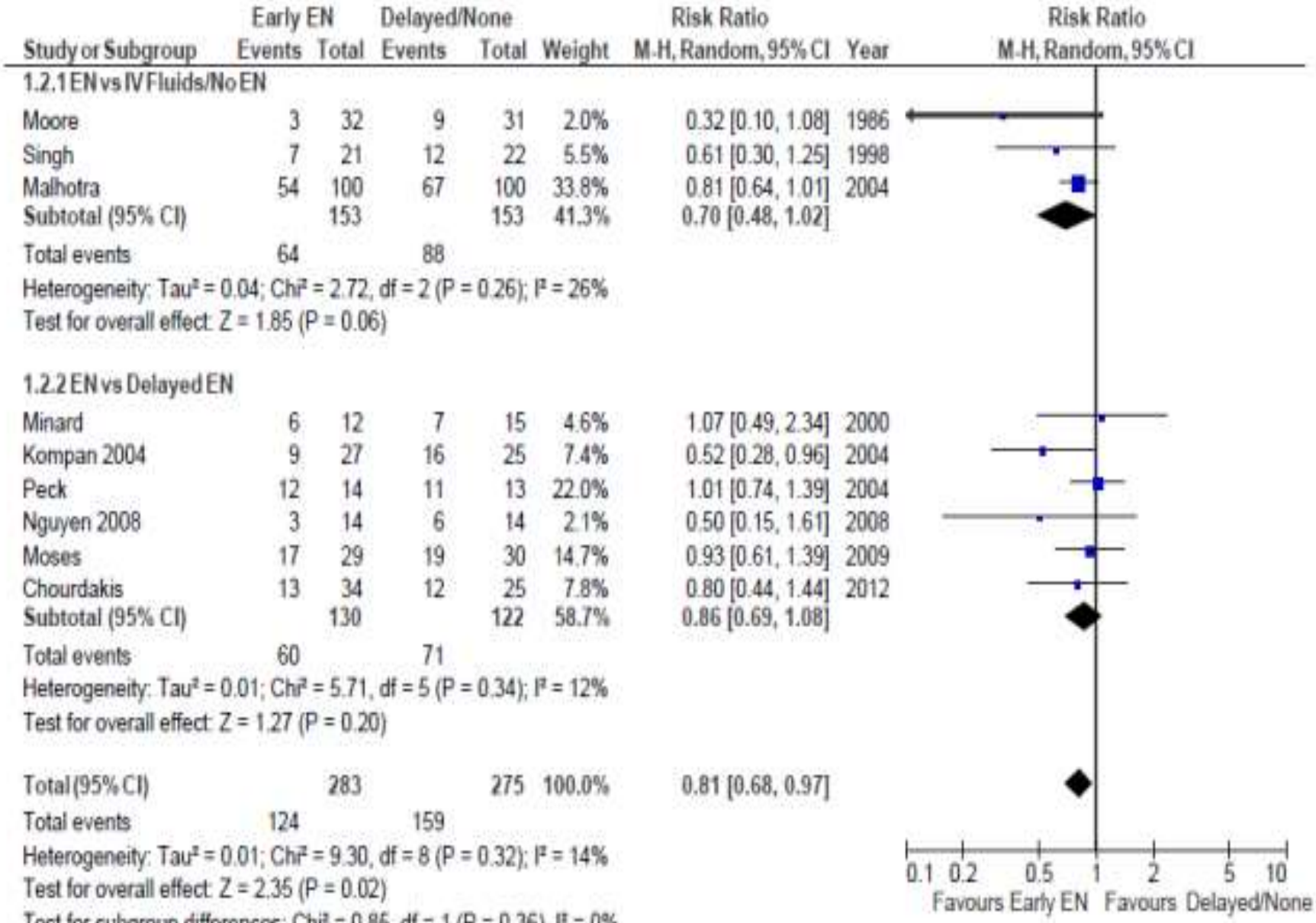


Figure 2. Studies comparing early EN vs delayed nutrient intake: Infectious complications



Initiation of enteral feeding

- Trophic vs full feeding –
    - had no effect on mortality in critically ill patient.
    - had no effect on the incidence of VAP.
    - may be associated with significant underfeeding but better gastrointestinal tolerance.
    - may be associated with poorer functional outcome at 12 months

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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)

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EDEN study -2012

- **Objective** To determine if initial lower-volume trophic enteral feeding would increase ventilator-free days and decrease gastrointestinal intolerances compared with initial full enteral feeding in patients with ALI
- **Design -**randomized, open-label, multicenter trial conducted from January 2, 2008, through April 12, 2011
- **Participants** were adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition
- **Interventions** Participants were randomized to receive either trophic or full enteral feeding for the first 6 days. After day 6, the care of all patients who were still receiving mechanical ventilation was managed according to the full feeding protocol.
- **Main Outcome Measures** Ventilator-free days to study day 28.
- **Conclusion** In patients with acute lung injury, compared with full enteral feeding, a strategy of initial trophic enteral feeding for up to 6 days did not improve ventilator free days, 60-day mortality, or infectious complications but was associated with less gastrointestinal intolerance.

JAMA. 2012;307(8):795-803

Figure 2. Full-Feeding Protocol

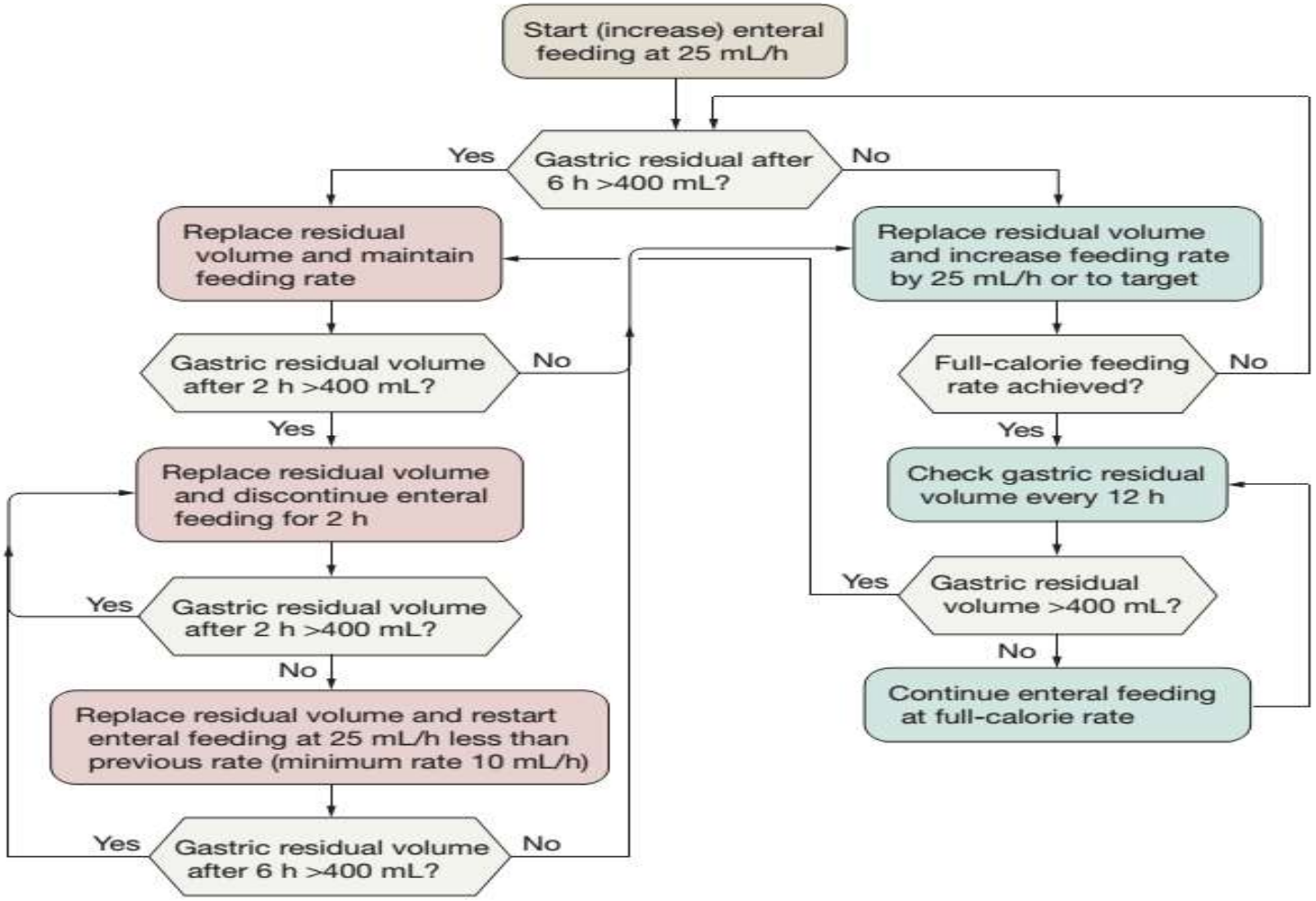

Table 2. Clinical Outcomes

Outcome	Trophic Feeding (n = 508)	Full Feeding (n = 492)	*P* Value
Ventilator-free days, No. (95% CI)	14.9 (13.9-15.8)	15.0 (14.1-15.9)	.89
Failure-free days, No. (95% CI)			
Cardiovascular	19.1 (18.2-20.0)	18.9 (18.1-19.8)	.75
Renal	20.0 (19.0-20/9)	19.4 (18.4-20.5)	.43
Hepatic	22.0 (21.2-22.9)	22.6 (21.8-23.5)	.37
Coagulation	22.3 (21.4-23.1)	23.1 (22.3-23.9)	.16
ICU-free days, No. (95% CI)	14.4 (13.5-15.3)	14.7 (13.8-15.6)	.67
60-d mortality, No. (%) [95% CI]	118 (23.2) [19.6-26.9]	109 (22.2) [18.5-25.8]	.77
Development of infections, No. (%) [95% CI]			
VAP	37 (7.3) [5.0-9.5]	33 (6.7) [4.5-8.9]	.72
Clostridium difficile colitis	15 (3.0) [1.5-4.4]	13 (2.6) [1.2-4.1]	.77
Bacteremia, No. (%)	59 (11.6) [8.8-14.4]	46 (9.3) [6.8-11.9]	.24

Abbreviations: ICU, intensive care unit; VAP, ventilator-associated pneumonia.

- Hypocaloric enteral nutrition:
    - Hypocaloric enteral nutrition vs full feeds not associated with any significant difference in mortality, ICU LOS, Hospital LOS
    - but associated with significantly less days on ventilator.

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Table 1. Randomized studies evaluating hypocaloric vs. full feeding in critically ill patients

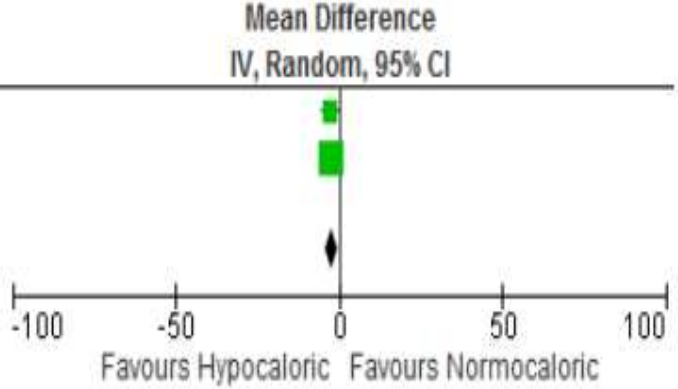
Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Hypocaloric Feeds	Full Feeds	HypocaloricFeeds	Full Feeds
1) Arabi 2011*	ICU patients ~30% brain trauma 40% Type 2 diabetes N=240 **BMI (kg/m²)** Trophic feeds pts: 28.5±7.4 Full feeds pts: 28.5±8.4 **Age** Trophic 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 19.7 kcal/kg/d Non-isocaloric, non-isonitrogenous.	**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)
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)

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: $Tau^2 = 0.00$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$

Test for overall effect: Z = 2.54 (P = 0.01)



PermiT trial –Arabi 2015

- **Hypothesis** : permissive-underfeeding strategy that restricts nonprotein calories but preserves protein intake, as compared with a standard feeding strategy, would reduce 90-day mortality among critically ill adults.
- **Study design** -The Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients(PermiT) trial was an unblinded, pragmatic, randomized, controlled trial conducted at seven tertiary care centers in Saudi Arabia and Canada between November 2009 and September 2014.
- **Method:** At seven centers, 894 critically ill adults with a medical, surgical, or trauma admission category were randomly assigned to permissive underfeeding (40 to 60% of calculated caloric requirements) or standard enteral feeding (70 to 100%) for upto 14 days while maintaining a similar protein intake in the two groups.
- **The primary outcome** was 90-day mortality.
- **RESULTS -** Enteral feeding to deliver a moderate amount of nonprotein calories to critically ill adults was not associated with lower mortality than that associated with planned delivery of a full amount of nonprotein calories.

N Engl J Med June 18, 2015DOI: 10.1056/NEJMoa1502826

- Early enhanced nutrition compared to slower rate of advancement of EN :
    - has no effect on mortality in the critically ill patient
    - has no effect on ICU LOS but is associated with a significant increase in hospital lengths of stay in the critically ill patient
    - associated with a significant reduction in the infection
    - results in a significantly higher calorie and protein intake/lower calorie deficit in head injured patients and other critically ill patients.

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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)	1.37 (1.17 – 1.60) 1065 (961 – 1179) 44.2 (40.0 – 48.9)

										6.1 (5.6 – 6.65) 5.02 (4.61 – 5.48)
5) Braunschweig 2014	Acute lung injury, single center ICU N= 78	C. Random: yes ITT: yes Blinding: No (7)	Intensive Medical Nutrition Therapy >75% of energy and protein goal (continuous feed), vs standard nutrition support (bolus, intermittent or continuous feed). Goal 30 kcal/kg/d, 1.5g/kg/d protein	**Hospital** 16/40 (40)	**Hospital** 6/38 (15.8)	S/40 (12)	8/38 (21)	**ICU** 15.5 ± 12.8 **Hospital** 27.2 ± 18.2	**ICU** **16.1** ± 11.5' **Hospital** 22.8 ± 14.3	**Ventilator days (mean)** 6 (4-10) 7 (3-14) p<0.25 **Caloric adequacy** 84.7 ± 22 55.4 ± 19 **Protein adequacy** 76.1 ± 18 54.4 ± 21
6) Peake 2014	Emergency operative and non-operative and elective operative admissions N=112	C. Random: yes ITT: yes Blinding: yes (9)	Fresubin 2250 Complete 1.5kcal/ml vs Fresubin 1000 Complete 1.0kcal/ml. Goal rate of 1 ml/kg IBW/hr to a max of 100ml/hour to be achieved within 48 hours of feeding start in both groups. Comparable protein between formulas.	**ICU** 6/57 (11) **Hospital** 10/57 (19) **28 day** 11/57 (20) **90 day** 11/57 (20)	**ICU** 9/55 (16) **Hospital** 14/55 (27) **28 day** 18/55 (33) **90 day** 20/55 (27)	NR	NR	**ICU** 12.8 ± 11.3 **Hospital** 33.3 ± 25.3	**ICU** 12.2 ± 8.3 **Hospital** 24 ± 17.6	**% Energy adequacy** 110.8 ± 26.8 83.2 ± 29 **% Protein adequacy** 82 ± 23.6 88.2 ± 39.1 **Ventilator days** 8.6 ± 8.5 6.8 ± 6

Figure 1: ICU Mortality

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Desachy 2008	6	50	8	50	49.0%	0.75 [0.28, 2.00]	2008
Peake 2014	6	57	9	55	51.0%	0.64 [0.25, 1.69]	2014
Total (95% CI)		**107**		**105**	**100.0%**	**0.69 [0.35, 1.38]**	
Total events	12		17				

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)

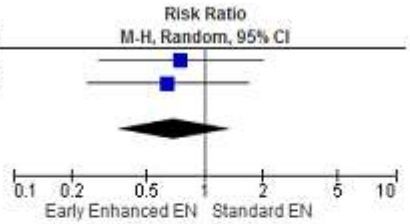


Figure 2: Hospital Mortality

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Desachy 2008	14	50	11	50	35.3%	1.27 [0.64, 2.53]	2008
Peake 2014	10	57	14	55	34.1%	0.69 [0.33, 1.42]	2014
Braunschweig 2014	16	40	6	38	30.7%	2.53 [1.11, 5.79]	2014
Total (95% CI)		**147**		**143**	**100.0%**	**1.28 [0.63, 2.58]**	
Total events	40		31				

Heterogeneity: Tau² = 0.25; Chi² = 5.42, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 0.68 (P = 0.50)

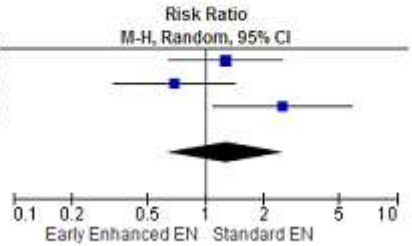


Figure 3: Infectious complications

Study or Subgroup	Early Enhanced EN Events	Total	Standard EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Taylor 1999	25	41	35	41	93.3%	0.71 [0.54, 0.94]	1999
Braunschweig 2014	5	40	8	38	6.7%	0.59 [0.21, 1.66]	2014
Total (95% CI)		81		79	100.0%	**0.71 [0.54, 0.92]**	
Total events	30		43				

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)

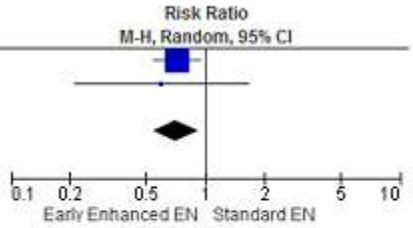


Figure 4 ICU LOS

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	4	3.6	41	5.8	5.6	41	59.7%	-1.80 [-3.84, 0.24]	1999
Desachy 2008	15	11	50	15	11	50	13.3%	0.00 [-4.31, 4.31]	2008
Peake 2014	12.8	11.3	57	12.2	8.3	55	18.5%	0.60 [-3.06, 4.26]	2014
Braunschweig 2014	15.5	12.8	40	16.1	11.5	38	8.5%	-0.60 [-5.99, 4.79]	2014
Total (95% CI)			188			184	100.0%	**-1.01 [-2.59, 0.56]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

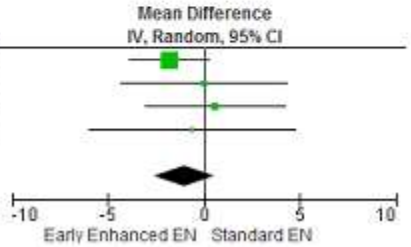


Figure 5 Hospital LOS

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	56.3	59.5	41	60.8	55.7	41	4.3%	-4.50 [-29.45, 20.45]	1999
Desachy 2008	56	59	50	51	75	50	3.8%	5.00 [-21.45, 31.45]	2008
Peake 2014	33.3	25.3	57	24	17.6	55	41.1%	9.30 [1.25, 17.35]	2014
Braunschweig 2014	27.2	18.2	40	22.8	14.3	38	50.8%	4.40 [-2.84, 11.64]	2014
Total (95% CI)			188			184	100.0%	**6.06 [0.90, 11.22]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)

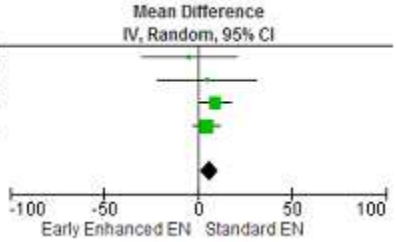
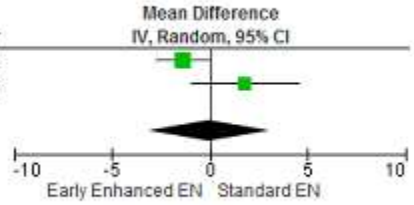


Figure 6 Ventilator Days

Study or Subgroup	Early Enhanced EN Mean	SD	Total	Standard EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Taylor 1999	3.8	2.4	41	5.2	3.8	41	57.0%	-1.40 [-2.78, -0.02]	1999
Peake 2014	8.6	8.5	57	6.8	6	55	43.0%	1.80 [-0.92, 4.52]	2014
Total (95% CI)			98			96	100.0%	-0.02 [-3.13, 3.08]	

Heterogeneity: Tau² = 3.91; Chi² = 4.24, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 0.01 (P = 0.99)



ACCEPT trial –Martin 2004

- Hypothesis -evidence-based algorithm for nutritional support in critically ill patients, accompanied by a multifaceted implementation strategy, would improve the provision of nutritional support and patient outcomes.
- Study design -prospective, cluster-randomized clinical trial.
- Method -Hospital ICUs were stratified by hospital type and randomized to the intervention or control arm. Patients at least 16 years of age with an expected ICU stay of at least 48 hours were enrolled in the study (n = 499). Evidence-based recommendations were introduced in the 7 intervention hospitals by means of in-service education sessions, reminders (local dietitian, posters) and academic detailing that stressed early institution of nutritional support, preferably enteral.
- Result -Two hospitals crossed over and were excluded from the primary analysis. Compared with the patients in the control hospitals (n = 214), the patients in the intervention hospitals (n = 248) received significantly more days of enteral nutrition (6.7 v. 5.4 per 10 patient-days; p = 0.042), had a significantly shorter mean stay in hospital (25 v. 35 days; p = 0.003) and showed a trend toward reduced mortality (27% v. 37%; p = 0.058). The mean stay in the ICU did not differ between the control and intervention groups (10.9 v. 11.8 days; p = 0.7).

CMAJ • JAN. 20, 2004; 170(2)

Table 4: Primary outcomes in the randomized phase

	Appropriately randomized hospitals							
	Actual values			Design effect*		All 14 hospitals; actual values		
Outcome	Control	Intervention	*p* value	C_1	C_2	Control	Intervention	*p* value
Hospital mortality rate, %	37	27	0.058	1.79	1.65	37	24	0.047
Mean hospital stay, d	35	25	0.003	20.33	63.29	34.3	25.4	0.006
Mean ICU stay, d	11.8	10.9	0.7	9.16	86.63	11.7	10.8	0.65

*The design effect is the ratio of the total number of subjects required with cluster randomization to the number required with simple randomization. For example, if 100 patients were required per group to obtain statistical significance in a mortality-rate difference in a simple randomized trial, 179 and 165 patients per group would be required in a cluster-randomized trial. The design effects for hospital and ICU stay were obtained with the method of Rao and Scott[22] for the appropriately randomized hospitals.

INTACT trial – Braunschweig 2015

- **Hypothesis:** patients randomized to receive the intensive medical nutrition intervention (IMNT) would have fewer infections, shorter hospital and ICU lengths of stay (LOS) and lower mortality than those randomized to standard care (SC).
- **Method** - A prospective randomized trial was conducted evaluate the impact on outcomes of intensive medical nutrition therapy (IMNT; provision of >75% of estimated energy and protein needs per day via EN and adequate oral diet) from diagnosis of acute lung injury (ALI) to hospital discharge compared with standard nutrition support care (SNSC; standard EN and ad lib feeding). The primary outcome was infections; secondary outcomes included number of days on mechanical ventilation, in the ICU, and in the hospital and mortality.
- **RESULTS:** Overall, 78 patients (40 IMNT and 38 SNSC) were recruited. No significant differences between groups for age, body mass index, disease severity, white blood cell count, glucose, C-reactive protein, energy or protein needs occurred. The IMNT group received significantly higher percentage of estimated energy (84.7% vs 55.4%, $P < .0001$) and protein needs (76.1 vs 54.4%, $P < .0001$) per day compared with SNSC. No differences occurred in length of mechanical ventilation, hospital or ICU stay, or infections. The trial was stopped early because of significantly greater hospital mortality in IMNT vs SNSC (40% vs 16%, $P = .02$). Cox proportional hazards models indicated the hazard of death in the IMNT group was 5.67 times higher ($P = .001$) than in the SNSC group.
- **CONCLUSIONS:** Provision of IMNT from ALI diagnosis to hospital discharge increases mortality.

***JPEN J Parenter Enteral Nutr*. 2015 January ;. doi:10.1177/0148607114528541**.

Table 3

Clinical Outcomes in IMNT vs SNSC Participants (N = 78).

Variable	IMNT (n = 40)	SNSC (n= 38)	*P* Value
Hospital LOS, d	27.2 (18.2)	22.8 (14.3)	.33
ICU LOS, d	15.5 (12.8)	16.1 (11.5)	.83
Number of days between hospital admission and enrollment	8.8 (8.7)	6.4 (6.6)	.17
Days on ventilator (median, IQR)	6 (4–10)	7 (3–14)	.85
Number of infections, n (%)	5 (12)	8 (21)	.29
Any hyperglycemic event, n (%)[a]	30 (73)	26 (68)	.64
Number of days with hyperglycemia	2.2 (3.0)	2.4 (4.0)	.85
Any hypoglycemic event, n (%)[a]	12 (29.3)	11 (28.9)	.98
Number of days with hypoglycemia	0.3 (0.6)	0.9 (0.7)	.08
Insulin received per day, U	23.6 (47.6)	14 (23.6)	.25
Insulin received per day on days insulin was received in participants who were given insulin, U	77.7 (70.4)	35.9 (27.9)	.03
Died	16 (40.0)	6 (15.8)	.017

All values are mean (SD) unless otherwise indicated. ICU, intensive care unit; IMNT, intensive medical nutrition therapy; IQR, interquartile range; LOS, length of stay; SNSC, standard nutrition support care.

[a]

- Optimizing en:

  Gastric residual volume

  - Not checking GRV vs checking GRV with 250ml as threshold have no effect on mortality, infection or hospital/ICU stay but associated with significantly better calorie delivery.
  - Monitoring GRV every 4 hrs vs every 8hrs have no effect on mortality, infection, or hospital or ICU stay but associated with less vomiting or regurgitation
  - GRV 500 ml vs > 250ml has no effect on mortality, infection or LOS (ICU/Hospital) or gastrointestinal tolerance but associated with significantly better calorie delivery.

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Study	Population	Methods (score)	Intervention	Mortality # (%)†	Infections # (%)‡
1) Montejo 2010	Mechanically ventilated patients from 28 ICUs requiring EN for at least 5 days N = 329	C.Random: No ITT: No Blinding: No (5)	GRV limit of 500mL vs. GRV limit of 200mL Both groups: nasogastric EN, prophylactic prokinetics X 3 days & PN, if needed	**GRV 500mL** **ICU** 31/157 (20) **GRV 200mL** **ICU** 26/165 (16) RR 1.25, 95% CI 0.78, 2.01, p=0.35 **Hospital** 53/157 (34) **Hospital** 55/165 (34) RR 1.01, 95% CI 0.74, 1.38, p=0.94	**GRV 500mL** **GRV 200mL** **Pneumonia** 44/157 (28) 45/165 (27) RR 1.03, 95% CI 0.72, 1.46, p=0.88
2) Reignier 2013	Mechanically ventilated patients from 9 ICUs requiring EN via NG within 36 hrs after intubation N= 452	C.Random: Yes ITT: Yes Blinding: No (11)	Not monitoring GRV vs. GRV limit of 250 ml Vomiting considered an intolerance to EN in both groups	**No GRV** **ICU** 63/227 (28) **GRV 250mL** **ICU** 61/222 (28) **Hospital** 82/227 (36) **Hospital** 76/222 (34)	**No GRV** **GRV 250mL** **VAP** 38/227 (17) 35/222(16) **ICU acquired** 60/227 (26) 60/222 (27)
3) Williams 2014	Critically ill pts, single centre, LOS expected >48 hrs, EN expected >72 hrs N=357	C.Random: Yes ITT: Yes Blinding: No (9)	Monitoring GRVs for gastric feeds up to every 8 hrs vs every 4 hrs. For both groups, GRVs were returned if the volume was ≤300 mL and for GRV exceeding 300 mL, the first 300 mL was returned to the stomach and the remainder discarded.	**GRVs q8hr** **GRVs q4hr** **ICU** 32/178 (18) 25/179 (14) **Hospital** 39/178 (22) 34/179 (19)	**Pts with VAP** (p=0.81) 13.2% 14.1%

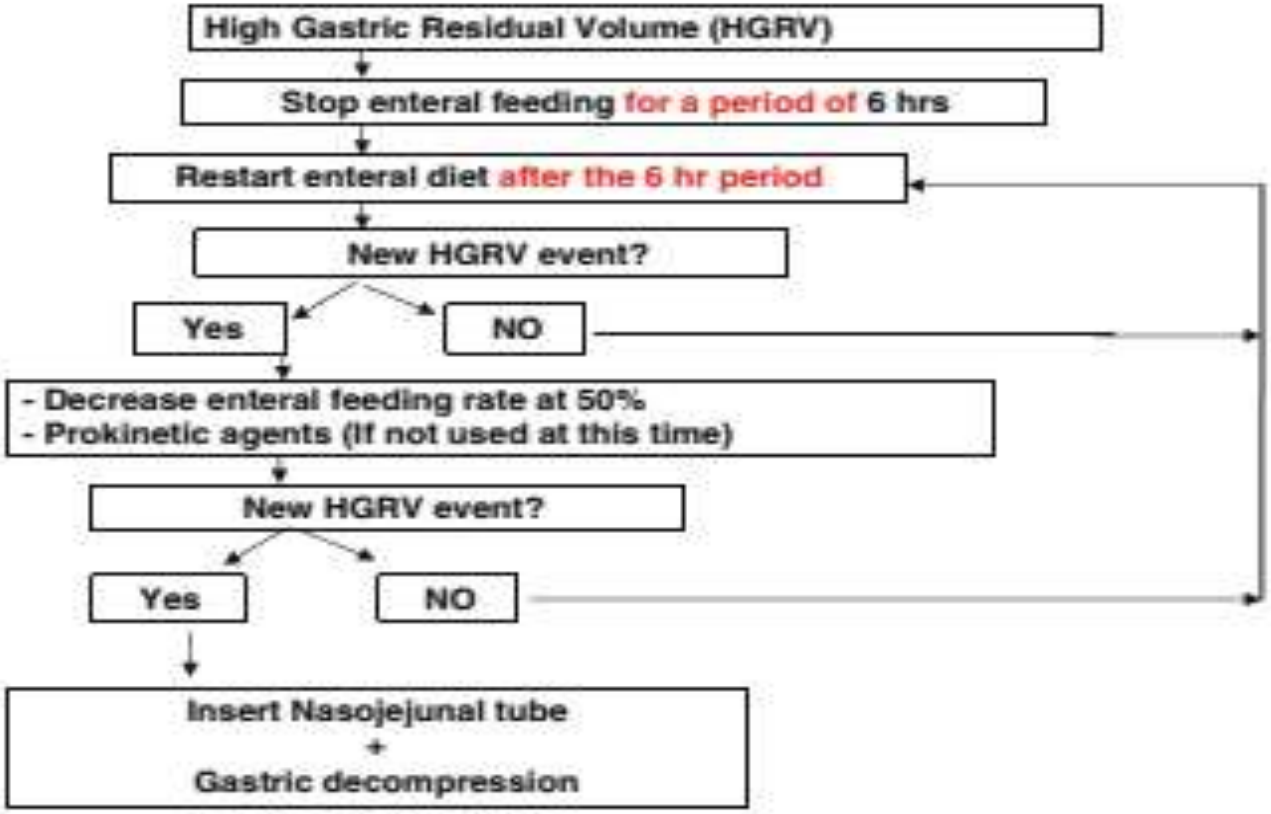
Gastric residual volume during enteral nutrition in ICU patients: the REGANE study

J. C. Montejo

REGANE study –Montejo 2010

- **Hypothesis -**if a higher limit is used to define ‘‘normal GRV,’’ the frequency of ‘‘HGRV’’ is lessened and also the number of episodes of stopping the diet. So,as a consequence of this, patients could receive more diet and, consequently, the energy deficit would be prevented.
- **Design** –open prospective randomized study.
- **Method** -329 patients across 28 intensive care unit in Spain were recruited and randomly assigned to a study group (GRV 500ml) and control group (GRV 200ml). EN was administered through naso gastric tube and a protocol for management of EN related gastrointestinal management was used.
- **outcome variables-** Diet volume ratio (diet received/diet prescribed), incidence of gastrointestinal complications, ICU acquired pneumonia, days on mechanical ventilation and ICU length of stay were the study variables.
- **Result and conclusion** -Diet volume ratio of mechanically ventilated patients treated with enteral nutrition is not affected by increasing the limit in GRV. A limit of 500 ml is not associated with adverse effects in gastrointestinal complications or in outcome variables

Intensive Care Med (2010) 36:1386–1393


High Gastric Residual Volume (HGRV)
Stop enteral feeding for a period of 6 hrs
Restart enteral diet after the 6 hr period
New HGRV event?
Yes
NO
- Decrease enteral feeding rate at 50%
- Prokinetic agents (If not used at this time)
New HGRV event?
Yes
NO
Insert Nasojejunal tube
+
Gastric decompression

- Hypothesis –variable gastric tube aspiration regimen would reduce frequency of gastric tube aspiration with no increase in the incidence of feed regurgitation or VAP (or pneumonia in nonventilated patients).
- Study design- nonblinded RCT using computer generated randomization
- Method -This randomized controlled trial (RCT) enrolled patients who stayed in the intensive care unit (ICU) for >48 hours, had a gastric tube, and were likely to receive EN for 3 or more days. Patients were randomized (computer generated randomization) to either the control (every 4 hours) or intervention group (variable regimen).
- Outcome – primary - number of gastric tube aspirations per day from randomization until EN was ceased or up to 2 weeks post randomization.

  secondary -Secondary outcomes included incidence of

  1. vomiting or regurgitation, defined as the presence of feed in the mouth or flowing out of the mouth;
  2. VAP or pneumonia in nonventilated patients (up to 16 days after enteral feeding commenced);
  3. attainment of target feeding volume each day.
- Result and conclusion -In the intention-to-treat analysis, the intervention group had fewer tube aspirations per day (3.4 versus 5.4 in the control group, $P < .001$). Vomiting/regurgitation was increased in the intervention group (2.1% versus 3.6%, $P = .02$). There were no other differences in complications noted.

journal of enteral and parenteral nutrition September 2014

Table 2. Patient outcomes.

Outcome	Control Group (n = 179)	Intervention Group (n = 178)	*P* Value
Mean number of tube aspirations per enteral feeding days	5.4 (1.3)	3.4 (1.3)	<.001
Patients with ventilator-associated pneumonia, %	14.1	13.2	.81
Vomiting/regurgitation, %	2.1	3.6	.02
Interruptions to enteral feeding due to vomiting, %	1.5	2.1	.24
Median ICU length of stay, d	9 (5–15)	9 (6–14)	.57
Median hospital length of stay, d	25 (13–41)	23 (12–38)	.19
Intensive care unit survival, %	86	82	.24
Hospital survival, %	81	78	.36

- Discarding GRV:

Refeeding GRV not associated with more gastrointestinal complication when compared to discarding GRV.

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Table 1. Randomized studies evaluating gastric residual volume in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				GRV return	GRV discard	GRV return	GRV discard
1) Juve-Udina 2009	ICU patients fed via EN or PN N=125	C.Random: no ITT: No Blinding: No (5)	GRV>250 mL discard excess, reefed 250mL vs. if GRV>250 mL discard entire feed	NR	NR	NR	NR

- Motility agent
  - Motility agent have no effect on mortality or infectious complication in critically ill patient.
  - Motility agent may decrease feeding intolerance and increase total calorie intake.

Table 1. Randomized Studies Motility Agents in Critically Ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)† Experimental	Mortality # (%)† Control	Infections # (%)‡ Experimental	Infections # (%)‡ Control	Nutritional Indices Experimental	Nutritional Indices Control
Placebo-controlled Trials									
1) Chapman 2000	Mixed ICU patient with GRV>250ml N=20	C.Random: Yes ITT: yes Blinding: Yes (12)	Erythro 200 mg IV vs placebo x 1 dose	NR	NR	NR	NR	**Successful feeding defined as GRV <250 mo and continuing with feeds.** Erythro 9/10 vs placebo 5/10, p=0.05	
2) Yavagal 2000	Mixed ICU N=305	C.Random: not sure ITT: yes Blinding: yes (10)	Metoclopramide 10 mg NG q 6 h vs. placebo	73/ 131 (56)	92/174 (53)	**Pneumonia** 22/131 (17)	**Pneumonia** 24/174 (14)	NR	
3) Berne 2002	Critically injured patients n=48	C.Random: not sure ITT: no Blinding: no (6)	Erythromycin 250 mg IV q 6 hrs vs. placebo	2/32 (6)	2/36 (6)	**Pneumonia** 13/32 per group*	**Pneumonia** 18/36 per group*	**Feeds tolerated at 48 hrs** 58% 44 % p=0.001 **Feeds tolerated for the study** 65% 59% p=0.06	
4) Reignier 2002	Mixed ICU patients N=48	C.Random: not sure ITT: yes Blinding: no (6)	Erythro 250 mg q 6h IV vs placebo x 5 days	6/20 (30)	8/20 (40)	NR	NR	**EN discontinued if GRV>250 or vomited:** Erythro 35% vs Placebo 70 p<0.001	
5) Meissner 2003**	ICU patients N=84	C.Random: yes ITT: no Blinding: double (11)	Naloxone 8 mg q 6 hrs via NG vs. placebo	6/38 (16)	7/43 (16)	**Pneumonia** 13/38 (34)	**Pneumonia** 24/43 (56)	**Feeding volumes after day 3** Higher in naloxone group (trend) **Amount of Reflux (mls)** 54 129	
6) Nursal 2007	Traumatic Brain Injured patients N=19	C.Random: no ITT: no Blinding: double (10)	Metoclopramide 10 mg IV TID vs. saline IV TID	**Hospital** 3/10 (30)	**Hospital** 3/9 (33)	NR	NR	**Patients with high GRV** 5/10 (50) 2/9 (22) **Days to target calories** 5.8 ± 5.2 3.4 ± 1.4 **Calorie intake/total calories** 61.3% 92.2%	

Head to Head Comparisons								
7) MacLaren 2008	Mixed ICU patient with GRV>150ml N=20	C.Random: not sure ITT: yes Blinding: no (9)	Erythro 250 mg q6h vs Meto 10 mg IV q 6h for 4 doses	NR	NR	NR	NR	**Both agents resulted in significant reduction in GRV and increase in feeding rate**
Combo vs Mono								
8) Nguyen 2007	Mixed ICU patients N=75	C.Random: yes ITT: yes Blinding: double (11)	Combination of Erythromycin 200 mg IV bid + Metoclopramide 10 mg IV qid vs. Erythromycin 200 mg IV bid alone	**Hospital** 8/37 (22)	**Hospital** 10/38 (26)	NR	NR	**Failure of feeding (days)** 6.5 ± 0.5 4.5 ± 0.5 **Caloric intake % prescribed 7 days** Higher in combination group (p=0.02) **Gastric residual volumes** Lower in combination group (p<0.05) **Need for post-pyloric feeds** 2/37 (5) 8/38 (21)
Motility Agent vs Small Bowel Tubes								
9) Boivin 2001	Mixed ICU patients N=80	C.Random: not sure ITT: no Blinding: no (5)	Erythro 200 mg q 8 hrs x 96 hrs vs transpyloric feeding	7/39 (18)	7/39 (18)	NR	NR	**No difference in time to goal rate or overall adequacy.**

RCT comparing between motility agents

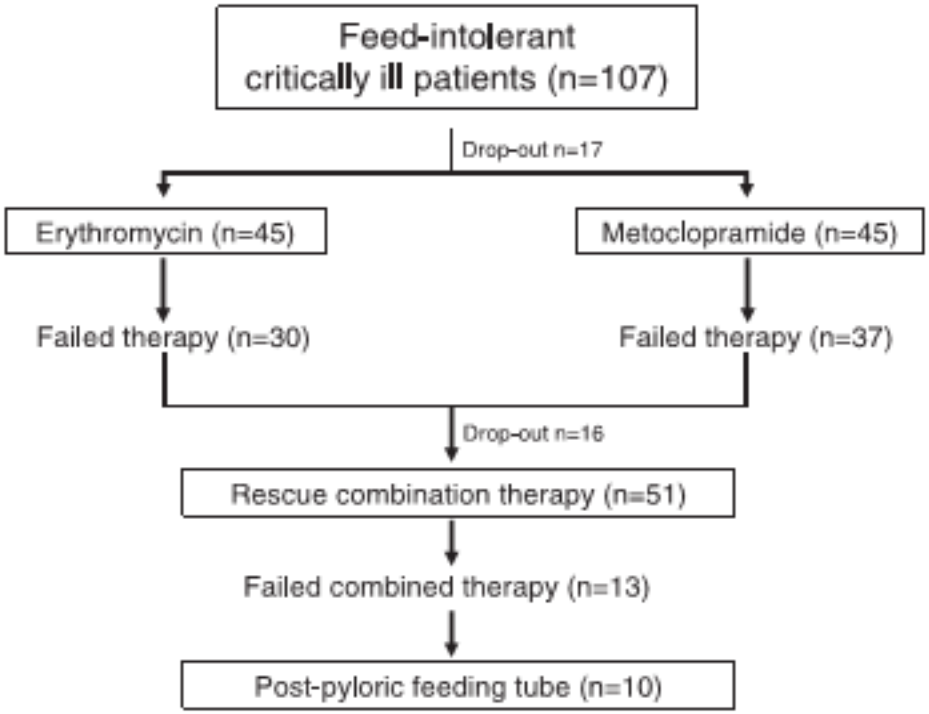
- Objective:
  - to compare chronic administration of metoclopramide and erythromycin in the management of feed intolerance;
  - to determine the effectiveness of “rescue” combination therapy in patients who fail monotherapy

- Design : The study was conducted as a two-way randomized, double-blind, parallel group study.

- Participants :
  - One-hundred and seven consecutive mechanically ventilated patients who failed NG feeding were enrolled into the study over a 12-month period (August 2004 to August 2005).
  - Failure of feeding was defined clinically as a 6-hourly gastric residual volume (GRV) 250 mL 6 hrs after commencing enteral feeding at a rate of 40 mi/hr.

Crit Care Med 2007; 35:483–489

- Material and method:
  - Patients received either metoclopramide 10 mg intravenously four times daily or erythromycin 200 mg intravenously twice a day in a double-blind, randomized fashion.
  - After the first dose, nasogastric feeding was commenced and 6-hourly nasogastric aspirates were performed. If a gastric residual volume >250 mL recurred on treatment, open-label, combination therapy was given. Patients were studied for 7 days. Successful feeding was defined as 6-hourly gastric residual volume <250 mL with a feeding rate >40 mL/hr


Feed-intolerant critically ill patients (n=107)
Drop-out n=17
Erythromycin (n=45)
Metoclopramide (n=45)
Failed therapy (n=30)
Failed therapy (n=37)
Drop-out n=16
Rescue combination therapy (n=51)
Failed combined therapy (n=13)
Post-pyloric feeding tube (n=10)

- Result
  - Monotherapies reduced the mean gastric residual volume (metoclopramide, 830 +/- 32 mL to 435 +/- 30 mL, $p < .0001$; erythromycin, 798 +/- 33 mL to 201 +/- 19 mL, $p < .0001$) and improved the proportion of patients with successful feeding (metoclopramide 62% and erythromycin 87%).
  - Treatment with erythromycin was more effective than metoclopramide, but the effectiveness of both treatments declined rapidly over time.
  - In patients who failed monotherapy, rescue combination therapy was highly effective (day 1 92%) and maintained its effectiveness for the study duration (day 6 67%).
  - High pretreatment gastric residual volume was associated with poor response to prokinetic therapy.

- Small bowel vs intragastric feeding:
  - Small bowel feeding in comparison to intragastric feeding was associated with significant reduction in incidence of pneumonia.
  - No difference in mortality or ventilator days between small bowel and intragastric feeding.
  - Small bowel feeding associated with higher calorie and protein intake and is associated with less time taken to reach target rate of enteral nutrition.

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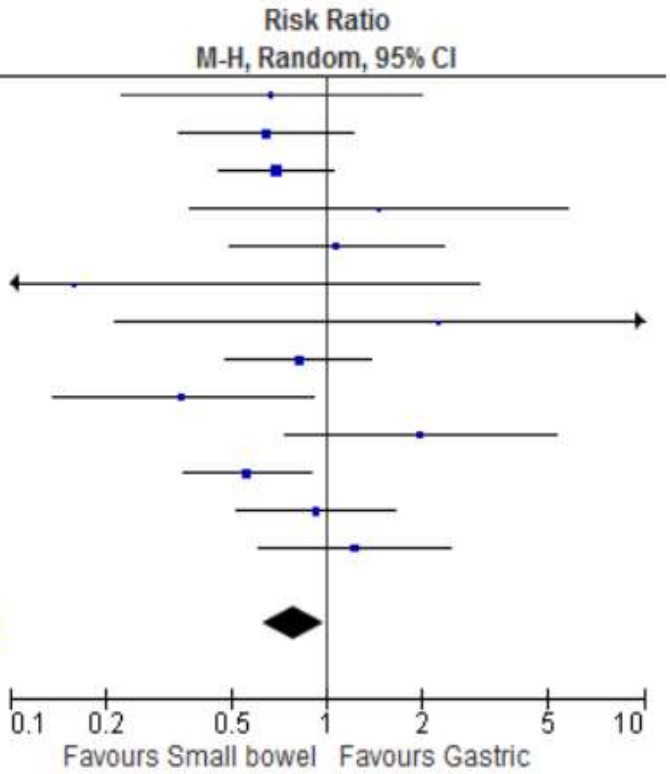
Figure 3. Pneumonia

Study or Subgroup	Small Bowel Events	Small Bowel Total	Gastric Events	Gastric Total	Weight	Risk Ratio M-H, Random, 95% CI
Montecalvo	4	19	6	19	3.7%	0.67 [0.22, 1.99]
Kortbeek	10	37	18	43	9.7%	0.65 [0.34, 1.22]
Taylor	18	41	26	41	18.1%	0.69 [0.46, 1.05]
Kearns	4	21	3	23	2.4%	1.46 [0.37, 5.78]
Minard	6	12	7	15	6.8%	1.07 [0.49, 2.34]
Day	0	14	2	11	0.6%	0.16 [0.01, 3.03]
Davies 2002	2	31	1	35	0.9%	2.26 [0.22, 23.71]
Montejo	16	50	20	51	12.9%	0.82 [0.48, 1.39]
Hsu	5	59	15	62	4.9%	0.35 [0.14, 0.90]
White	11	57	5	51	4.5%	1.97 [0.73, 5.28]
Acosta-Escribano	16	50	31	54	15.6%	0.56 [0.35, 0.89]
Davies 2012	18	91	19	89	11.4%	0.93 [0.52, 1.65]
Friedman	13	54	12	61	8.4%	1.22 [0.61, 2.45]
Total (95% CI)		**536**		**555**	**100.0%**	**0.78 [0.63, 0.98]**
Total events	123		165			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.19$, $df = 12$ ($P = 0.29$); $I^2 = 15\%$

Test for overall effect: $Z = 2.17$ ($P = 0.03$)



- **Hypothesis** –the use of a jejunal tube does not reduce the incidence of nosocomial pneumonia.
- **Design** – pragmatic open randomized control trial.
- **Method** –Patients were randomly assigned to receive enteral feed via a gastric or jejunal tube. Jejunal tubes were inserted at bedside and placement was confirmed radiographically
- **Outcome** –The primary objective of this study is to evaluate the incidence of pneumonia throughout the stay in Intensive Care Unit (ICU) comparing gastric with jejunal nutrition. Secondarily, we evaluated the mortality rate in the ICU until the 28th day and other complications potentially related to enteral feeding
- **Result** - A total of 115 patients were enrolled, with 61 patients into the gastric tube group and 54 patients into the jejunal group tube. Baseline characteristics were similar. There was no difference in pneumonia or ICU mortality rates, ICU length of stay and ventilator days. Complications rates were similar.
- **Conclusion** - We conclude that the enteral nutrition through a jejunal tube does not reduce the rate of pneumonia in comparison to a gastric tube. In addition, we did not observe differences in rates of gastrointestinal complications or ICU mortality. The routine placement of a jejunal tube in critically ill patients cannot be recommended.

IJCCM February 2015

Table 2: Groups outcomes

Variables	Nasogastric tube (*n*=61)	Nasojejunal tube (*n*=54)	*P*
MV-*n* (%)	51 (84)	44 (82)	0.957
MV duration (days)-median (CI 25-75)	7 (3-13)	4 (2-11)	0.241
ICU stay (days)-median (CI 25-75)	12 (8-20)	10 (7-21)	0.444
ICU mortality-*n* (%)	22 (36)	20 (37)	1.000
Pneumonia-*n* (%)	12 (20)	13 (24)	0.730
Diarrhea-*n* (%)	11 (18)	15 (28)	0.306
Vomiting-*n* (%)	18 (30)	14 (26)	0.826
Constipation-*n* (%)	14 (23)	9 (17)	0.544
Total cost (US$)	467	1163	-

- Bolus vs. continuous feeding:
  - There are no differences in mortality, frequency of interrupted feeds, % goal feeds achieved or diarrhea between patients receiving enteral feeds via continuous vs. other methods of administration.

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Bolus vs continuous feeding

- **Hypothesis** -intermittent enteral feeding route would optimize caloric intake in the first 7 days of critical illness as compared with continuous tube feedings,.
- **Design** – prospective randomized trial.
- Method -A total of 164 trauma patients, were randomized to receive enteral nutrition via an intermittent feeding regimen versus a continuous feeding regimen. A single nutritionist calculated caloric and protein goals.
- **Result** - A total of 164 patients were randomized and 139 reached their calculated nutritional goal within 7 days. There were no statistical differences in complications of tube feeding. The patients intermittently fed reached the goal faster and by day 7 had a higher probability of being at goal than did the patients fed continuously Intermittent patients maintained 100% of goal for 4 of 10 days per patient (95% CI 3.5–4.4) as compared with the drip arm goal for only 3 of 10 days per patient (95% CI 2.7–3.6).
- **Conclusion** - In a critically ill trauma population, patients fed an intermittent regimen received goal enteral nutrition more quickly and were more likely to remain at goal enteral caloric intake than were patients fed with continuous feeding regimens

J Trauma. 2007;63:57–61.

Table 3 Nutritional Outcomes and Adverse Events by Randomized Intervention Group

	Intermittent Feeding Regimen (N = 79)	Continuous Feeding Regimen (N = 81)	*p* Value for a Difference Between Groups
Onset of diarrhea, n (%)	5 (6.3)	3 (3.7)	0.45
ICU mortality rate, n (%)	11 (13.9)	6 (7.4)	0.18
Patients extubated prior to day 7 of study, n (%)	5 (6.3)	7 (8.6)	0.58
New onset pneumonia, n (%)	38 (48)	33 (41)	0.45

drip arm patients, which maintained goal for only 3 days

ered between the two groups was not statistically different

- Combined EN and PN in comparison to EN alone:
  - has no effect on mortality in critically ill patient
  - has no effect on infectious complications in critically ill patients
  - is associated with a significant reduction in hospital length of stay and a trend towards a reduction in ICU LOS in critically ill patients.
  - has no effect on duration of ventilation in critically ill patients.
  - is associated with a higher cost.

Table 1. Randomized studies evaluating combined EN + PN in critically ill patients

Study	Population	Methods (score)	Intervention (both interventions started at same time)	Mortality # (%)†		Infections # (%)‡	
				EN + PN	EN	EN + PN	EN
1) Herndon 1987	Burns > 50 % TBSA N = 28	C.Random: not sure ITT: yes Blinding: no (6)	EN + PN vs EN EN + PN group received significantly more calories than EN group	8/13 (62)	8/15 (53)	NR	NR
2) Herndon 1989	Burn patients N = 39	C.Randomization: not sure ITT: yes Blinding: no (7)	EN+ PN vs EN EN + PN group received significantly more calories than EN group	**> Day 14** 10/16 (63)	**> Day 14** 6/23 (26)	NR	NR
3) Dunham 1994*	Blunt trauma N = 37	C.Random: not sure ITT: no Blinding: no (8)	EN+ PN vs EN EN + PN group given same calories as EN	3/10 (30)	1/12 (8.3)	NR	NR
4) Chiarelli 1996	ICU patients medical and surgical N = 24	C.Random: not sure ITT: yes Blinding: no (8)	EN+ PN vs EN EN + PN were given 33 kcal/kg/day, EN were given 31 kcals/kg/day	3/12 (25)	4/12 (33)	6/12 (50)	3/12 (25)
5) Bauer 2000	Patients from 2 ICUs N =120 (all degrees of malnutrition)	C.Random: not sure ITT: yes Blinding: double (12)	EN+ PN vs EN + placebo. EN + PN received 24.6 ± 4.9 kcal/kg/day vs. EN group 14.2 ± 6.5 kcal/kg/day (p< 0.0001)	**< Day 4** 3/60 (5) **90-day** 17/60 (28)	**< Day 4** 4/60 (6.7) **90-day** 18/60 (30)	39/60 (65)	39/60 (65)
6) Abrishami 2010	SIRS patients with APACHE II > 10 N=20	C.Random: not sure ITT: yes Blinding: no (7)	EN vs.EN + PN Metoclopramide if GRV >300ml. Non isocaloric/isonitrogenous	2/10 (20)	1/10 (10)	NR	NR

7) Chen 2011*	Elderly Patients in respiratory intensive care unit N=147	C.Random: yes ITT: yes Blinding: no (7)	**EN + PN**: EN as above + PN to make up kcal and nitrogen deficit vs **EN**: 100ml/hr=goal rate; metoclopramide if GRV >200mL, NJ if not tolerating NG Non-isocaloric/isonitrogenous	**20-day** 3/49 (6)	**20-day** 11/49 (22)	6/49 (12)	5/49 (10)
8) Heidegger 2012	ICU patients requiring at least 5 days of treatment with no contraindication to EN, not achieving 60% of energy target (equation based) by end of D3 N=305	C.Random yes ITT: yes Blinding: single (13)	EN vs EN+PN to make up energy target verified by indirect calorimetry in 65% of patients. EN progression encouraged in both groups. Non-isocaloric/isonitrogenous	**ICU** 8/153 (5) **28-day** 20/153 (13)	**ICU** 11/152 (7) **28-day** 28/152 (18)	**Day 4 to 28**** 77/153 (50)	**Day 4 to 28**** 85/152 (56)

*Pertains to EN+PN vs EN comparison; for the Chen EN+PN vs PN comparison see section 1.0
** Date obtained from authors

Figure 2. Infectious complications

Study or Subgroup	EN +PN Events	Total	EN Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Chiarelli	6	12	3	12	2.0%	2.00 [0.65, 6.20]	1996
Bauer	39	60	39	60	37.7%	1.00 [0.77, 1.30]	2000
Chen	6	49	5	49	2.1%	1.20 [0.39, 3.67]	2011
Heidegger	77	153	85	152	58.2%	0.90 [0.73, 1.11]	2012
Total (95% CI)		**274**		**273**	**100.0%**	**0.96 [0.81, 1.13]**	
Total events	128		132				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.23$, $df = 3$ ($P = 0.53$); $I^2 = 0\%$

Test for overall effect: $Z = 0.53$ ($P = 0.60$)

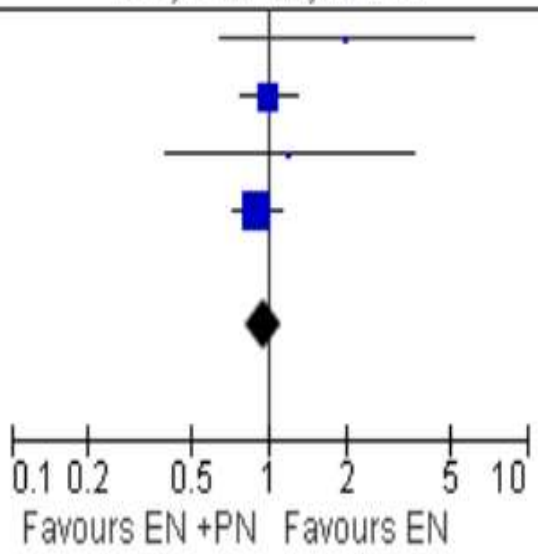
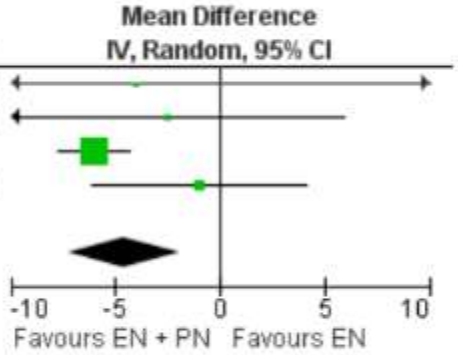


Figure 3. Hospital LOS

Study or Subgroup	EN + PN Mean	EN + PN SD	EN + PN Total	EN Mean	EN SD	EN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Chiarelli	37	13	12	41	23	12	3.1%	-4.00 [-18.95, 10.95]	1996
Bauer	31.2	18.5	60	33.7	27.7	60	9.1%	-2.50 [-10.93, 5.93]	2000
Chen	17.3	2.47	49	23.32	5.6	49	66.9%	-6.02 [-7.73, -4.31]	2011
Heidegger	31	23	153	32	23	152	20.9%	-1.00 [-6.16, 4.16]	2012
Total (95% CI)			**274**			**273**	**100.0%**	**-4.59 [-7.27, -1.91]**	

Heterogeneity: Tau² = 2.03; Chi² = 3.78, df = 3 (P = 0.29); I² = 21%

Test for overall effect: Z = 3.35 (P = 0.0008)



RCT – Heidegger 2012

- **Hypothesis** - Delivery of 100% of the energy target from days 4 to 8 in the ICU with EN plus supplemental parenteral nutrition (SPN) could optimise clinical outcome.
- **Participants** patients on day 3 of admission to the ICU who had received less than 60% of their energy target from EN, were expected to stay for longer than 5 days, and to survive for longer than 7 days were enrolled.
- **Method** Patients were randomized to receive either EN or SPN. 153 patients receive EN and 152 received PN.
- **The primary outcome** was occurrence of nosocomial infection after cessation of intervention (day 8), measured until end of follow-up (day 28), analysed by intention to treat.
- Result SPN group had a statistically significant reduction in nosocomial infection .[p=0.0248]

Lancet 2013; 381: 385–93

- Timing of supplemental PN
  - Early vs late PN to supplement EN has no effect on mortality in critically ill patients.
  - Early supplemental PN is associated with an increase in infectious complications in critically ill patients compared to late supplemental PN.
  - Early supplemental PN is associated with significantly longer ICU and hospital length of stay in critically ill patients compared to late supplemental PN.
  - Early supplemental PN is associated with an increase in duration of ventilation in critically ill patients compared to late supplemental PN.

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Table 1. Randomized studies evaluating early vs delayed supplemental PN in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				EN + PN	EN	EN + PN	EN
1) Casaer 2011	Critically ill from 7 ICUs Admitted with a nutrition risk ≥3 based on Nutrition Risk Screening (NRS) N=4640	C.Random: Yes ITT: Yes Blinding: No (11)	EN + early PN (20% IV glucose; kcal target day 1=400kcal, day 2=800 kcal, Day 3 initiate PN with goal of 100% caloric goal with EN+PN; caloric needs based on IBW, PN d/c if kcal via EN ≥80% requirements, restarted if EN ≤50%) vs EN + late PN (Late initiation; 5% glucose IV equal to PN group to match hydration) If EN sufficient >7 days, PN added on day 8 to reach kcal requirements) Non-isocaloric/isonitrogenous	**ICU** 146/2312 (6)	**ICU** 141/2328 (6)	**Total** 605/2312 (26)	**Total** 531/2328 (23)
				RR 1.04, 95% CI 0.83, 1.30 p=0.72		RR 1.15, 95% CI 1.04, 1.27 p=0.008	
				Hospital 251/2312 (11)	**Hospital** 242/2328 (10)		
				RR 1.04, 95% CI 0.88, 1.23 p=0.61			
				90-day 255/2312 (11)	**90-day** 257/2328 (11)		
				RR 1.00, 95% CI 0.85, 1.18 p=0.99			

EPaNIC trial

- **Hypothesis: whether preventing a caloric deficit during critical illness by providing parenteral nutrition to supplement enteral nutrition early in the** disease course would reduce the rate of complications or whether withholding parenteral nutrition for 1 week would be clinically superior
- Design –multicentric parallel group, randomized controlled trial.
- Method - 4640 patients with NRS score >/=3 were recruited and randomly assigned to one of the two categories of early (within 48 hrs) and late (not before day 8) initiation of supplemental parenteral nutrition. A protocol for the early initiation of enteral nutrition was applied to both groups, and insulin was infused to achieve normoglycemia
- Outcome – primary -ICU stay

  secondary
  - ❑ number of patients with new infections;
  - ❑ the infection site the duration of antibiotic therapy;
  - ❑ the time to final weaning from mechanical ventilatory support and the need for tracheostomy;
  - ❑ the rate of incident acute kidney injury,
  - ❑ need for and duration of pharmacologic or mechanical hemodynamic support
  - ❑ status according to the distance walked in 6 minutes
  - ❑ and the proportion of patients who were independent in all activities of daily living. with respect to the total incremental health care costs from randomization to hospital discharge

Table 2. Outcomes.*

Variable	Late-Initiation Group (N=2328)	Early-Initiation Group (N=2312)	P Value
Safety outcome			
Vital status — no. (%)			
Discharged live from ICU within 8 days	1750 (75.2)	1658 (71.7)	0.007
Death			
In ICU	141 (6.1)	146 (6.3)	0.76
In hospital	242 (10.4)	251 (10.9)	0.63
Within 90 days after enrollment†	257 (11.2)	255 (11.2)	1.00
Nutrition-related complication — no. (%)	423 (18.2)	434 (18.8)	0.62
Hypoglycemia during intervention — no. (%)‡	81 (3.5)	45 (1.9)	0.001
Primary outcome			
Duration of stay in ICU§			
Median (interquartile range) — days	3 (2–7)	4 (2–9)	0.02
Duration >3 days — no. (%)	1117 (48.0)	1185 (51.3)	0.02
Hazard ratio (95% CI) for time to discharge alive from ICU	1.06 (1.00–1.13)		0.04
Secondary outcome			
New infection — no. (%)			
Any	531 (22.8)	605 (26.2)	0.008
Airway or lung	381 (16.4)	447 (19.3)	0.009
Bloodstream	142 (6.1)	174 (7.5)	0.05
Wound	64 (2.7)	98 (4.2)	0.006
Urinary tract	60 (2.6)	72 (3.1)	0.28
Inflammation			
Median peak C-reactive protein level during ICU stay (interquartile range) — mg/liter	190.6 (100.8–263.2)	159.7 (84.3–243.5)	<0.001
Mechanical ventilation			
Median duration (interquartile range) — days	2 (1–5)	2 (1–5)	0.02
Duration >2 days — no. (%)	846 (36.3)	930 (40.2)	0.006
Hazard ratio (95% CI) for time to definitive weaning from ventilation	1.06 (0.99–1.12)		0.07
Tracheostomy — no. (%)	134 (5.8)	162 (7.0)	0.08

Table 2. (Continued.)

Variable	Late-Initiation Group (N = 2328)	Early-Initiation Group (N = 2312)	P Value
Kidney failure			
Modified RIFLE category — no. (%)¶	104 (4.6)	131 (5.8)	0.06
Renal-replacement therapy — no. (%)	201 (8.6)	205 (8.9)	0.77
Median duration of renal-replacement therapy (interquartile range) — days	7 (3–16)	10 (5–23)	0.008
Duration of hospital stay			
Median (interquartile range) — days	14 (9–27)	16 (9–29)	0.004
Duration >15 days — no. (%)	1060 (45.5)	1159 (50.1)	0.001
Hazard ratio (95% CI) for time to discharge alive from hospital	1.06 (1.00–1.13)		0.04
Functional status at hospital discharge			
Distance on 6-min walk test			
No. of patients evaluated	624	603	
Distance (interquartile range) — m	277 (210–345)	283 (205–336)	0.57
Activities of daily living			
No. of patients evaluated	1060	996	
Independent in all activities — no. (%)	779 (73.5)	752 (75.5)	0.31
Mean total incremental health care cost (interquartile range) — €	16,863 (8,793–17,774)	17,973 (8,749–18,677)	0.04

- Conclusion :

  Late initiation of parenteral nutrition was associated with faster recovery and fewer complications, as compared with early initiation.

NEJM August 11, 2011

- Indirect calorimetry vs predictive equation.
  - has no effect on mortality.
  - but associated with a significant reduction in hospital mortality.
  - When used to supplement EN with PN may be associated with a higher incidence of infections.
  - When used as a guide to supplement EN with PN may be associated with a longer ICU length of stay, and duration of ventilation.
  - The use of indirect calorimetry compared to predictive equations may result in improved nutritional intake

Table 1. Randomized studies evaluating indirect calorimetry vs. predictive equation in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)	
				Indirect Calorimetry	Predictive Equation	Indirect Calorimetry	Predictive Equation
1) Saffle 1990	Burns 47 % TSBA N=49	C.Random: not sure ITT: yes Blinding: no (7)	EN via Indirect calorimetry (IC) vs. Curreri formula	3/26 (12)	2/23 (9)	NR	NR
2) Singer 2011*	Mechanically ventilated critically ill patients (Mixed medical, surgical, trauma) N=130	C.Random: Yes ITT: No Blinding: No (8)	EN via indirect calorimetry with measurements Q48H supplemented with PN and energy delivery adjusted accordingly vs. EN (using 25kcal/kg/day and not readjusted for 14 days). PN attempted to make up shortfall Non isocaloric/isonitrogenous	**ICU** 16/56 (29) **Hospital** 16/56 (29) **60-day** 24/56 (58)	**ICU** 17/56 (30) **Hospital** 27/56 (48) **60-day** 29/56 (48)	**VAP** 18/56 (32) **Total** 37/56 (66)	**VAP** 9/56 (16) **Total** 20/56 (36)

- High fat/low carbohydrate:
  - A high fat, low CHO enteral formula ay be associated with a reduction in ventilator days in medical ICU patients with respiratoy failure and better glycemic control in patients with hyperglycemia.
  - No difference in mortality, infections or LOS found between the critically ill patient receiving high fat/ low carbohydrate formula or standard.

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Table 1. Randomized Studies Evaluating High Fat/Low CHO Enteral Nutrition In Critically ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		RR (CI)**	Infections # (%)		RR (CI)**
1. van den Berg 1994	Medical ICU patients with COPD Chronically ventilated N=32	C.Random: not sure ITT: yes Blinding: no (5)	55% fat, 28 % CHO (Pulmocare) vs 30 % fat, 53 % CHO (standard, Ensure Plus)	**High fat/low CHO** NR	**Standard** NR	NR	**High fat/low CHO** NR	**Standard** NR	NR
2. Al Saady 1994	Ventilated patients Acute respiratory failure N=40	C.Random: not sure ITT: no Blinding: double (9)	55% fat, 28 % CHO (Pulmocare) vs 30 % fat, 53 % CHO (standard, Ensure Plus)	3/9 (33)	3/11 (27)	1.22 (0.32-4.65)	NR	NR	NR
3. Mesejo 2003	Critically ill pts with Diabetes or hyperglycemia from 2 different centers N=50	C.Random: not sure ITT: yes Blinding: single (9)	40% fat, 40 % CHO (Novasource Diab Plus) vs. 29 % fat, 49 % CHO (Standard, Isosource Protein)	8/26 (31)	7/24 (29)	1.05 (0.45, 2.47)	10/26 (38.5)	8/24 (33)	1.15 (0.55, 2.43)

- Low fat/high carbohydrate:
    - low fat enteral feeding may be associated with lower incidence of pneumonia and trend towards a reduction in LOS in burn patients.

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- High protein vs low protein
  - High protein vs low protein has no effect on mortality in critically ill patient on CRRT.
  - High protein vs low protein has no effect on ICU length of stay or duration of mechanical ventilation.
  - Higher protein formula has no effect on mortality and infectious complications in head injured patients

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Table 1. Randomized Studies Evaluating Higher Protein vs. Low Protein Enteral Formula in Critically ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		RR (CI)**	Infections # (%)		RR (CI)**
1) Clifton 1985	Head injured patients Comatose for 24 hrs N=20	C.Random: not sure ITT: yes Blinding: no (8)	22% pro, 38 % CHO, 41 % fat, 1.5 Kcal/ml (Traumacal vs. 14 % pro, 50 % CHO, 36 % fat, 2.0 Kcal/ml (Magnacal) Isocaloric, 29 gm Nitrogen vs.17.6 gms Nitrogen	**High protein** 1/10 (10)	**Low protein** 1/10 (10)	1.00 (0.07-13.9)	**High protein** 3/10 (30)	**Low protein** 2/10 (20)	1.50 (0.32, 7.1)
2) Scheinkestel 2003	Critically ill ventilated pts on 6 days CRRT for renal failure N=50	C.Random: yes ITT: yes Blinding: no (9)	1.5 g/kg/d protein x2 days, 2.0 g/kg/d protein x2 days and 2.5 g/kg/d protein x2 days while receiving CRRT vs 2.0 g/kg/d protein x6 days while receiving CRRT	**High protein** ICU: 9/40 (23)	**Low protein** ICU: 4/10 (40)	0.56 (0.22-1.46)	NA	NA	NA
3) Rugeles 2013	Medical adult ICU patients N=80	C.Random: yes ITT: no Blinding: double (7)	hypocaloric hyperproteic (15 kcal/kg, 1.7 g/kg/d) x 7 days vs standard (25 kcal/kg, 20% calories from protein).	NR	NA	NA	NR	NR	NA

C.Random: concealed randomization ± : mean ± standard deviation

- Peptide vs polymeric protein
  - No difference between mortality, infection or length of stay.
  - No difference in incidence of diarrhea
  - No difference in protein or energy intake.

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Table 1. Randomized studies evaluating enteral PROTEIN vs. PEPTIDES in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)	
				Peptide	Whole Protein	Peptide	Whole Protein
1. Brinson 1988	Mixed ICU's patients with MOF, hypoalbuminemia, malnutrition from 2 ICUs N=12	C.Random: no ITT: yes Blinding: nsingle (5)	Peptide based formula (vital HN) vs whole protein formula (Osmolite HN)	0/7 (0)	2/5 (40)	NR	NR
2. Meredith 1990	ICU patients, trauma, N=18	C.Random: yes ITT: yes Blinding: no (8)	Peptide based formula (Reabilan HN) vs whole protein formula (Osmolite HN)	1/9 (11)	1/9 (11)	NR	NR
3. Mowatt-Larsen 1992	Critically ill, acutely injured patients, albumin < 30 N=41	C.Random: not sure ITT: no Blinding: no (6)	Peptide based formula (Reabilan HN) vs whole protein formula (Isocal)	NR	NR	12/21 (60)	14/20 (70)
4. Heimburger 1997	ICU patients from 2 ICUs N=50	C.Random: not sure ITT: no Blinding: no (7)	Small peptide formula vs whole protein formula	NR	NR	17/26 (65)	18/24 (75)
5. de Aguilar-Nascimento 2011	Elderly patients with acute ischemic stroke in ICU N=31	C.Random: Yes ITT: No Blinding: No (7)	Hydrolyzed whey protein feed (Peptamin 1.5) vs. Hydrolyzed casein protein feed (Hiper Diet Energy Plus)	3/10 (30)	4/15 (27)	NR	NR

- Probiotics with enteral nutrition
  - The addition of probiotics to enteral nutrition has no effect on ICU mortality.
  - Overall probiotic with EN showed a significant reduction of infectious complication.
  - Probiotics when added to enteral nutrition showed no significant reduction in hospital LOS, or ICU LOS.

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Intensive Care Med (2009) 35:854–861
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ORIGINAL

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Effect of synbiotic therapy on the incidence of ventilator associated pneumonia in critically ill patients: a randomised, double-blind, placebo-controlled trial

- Hypothesis: administration of enteral synbiotics would significantly decrease the incidence of VAP in mechanically ventilated (MV) critically ill patients when compared to placebo.
- Design: Prospective, randomised, double blind, placebo controlled trial.
- Method: 259 enterally fed patients requiring mechanical ventilation for 48 h or more were enrolled. All patients were enterally fed as per a standard protocol and randomly assigned to receive either synbiotic 2000 FORTE (twice a day) or a cellulose based placebo for a maximum of 28 days.
- Outcome –primary –incidence of VAP.

  Secondary -variables were oropharyngeal flora, ventilator days, and VAP rates per 1,000 ventilator days, ICU length of stay, ICU mortality and hospital mortality

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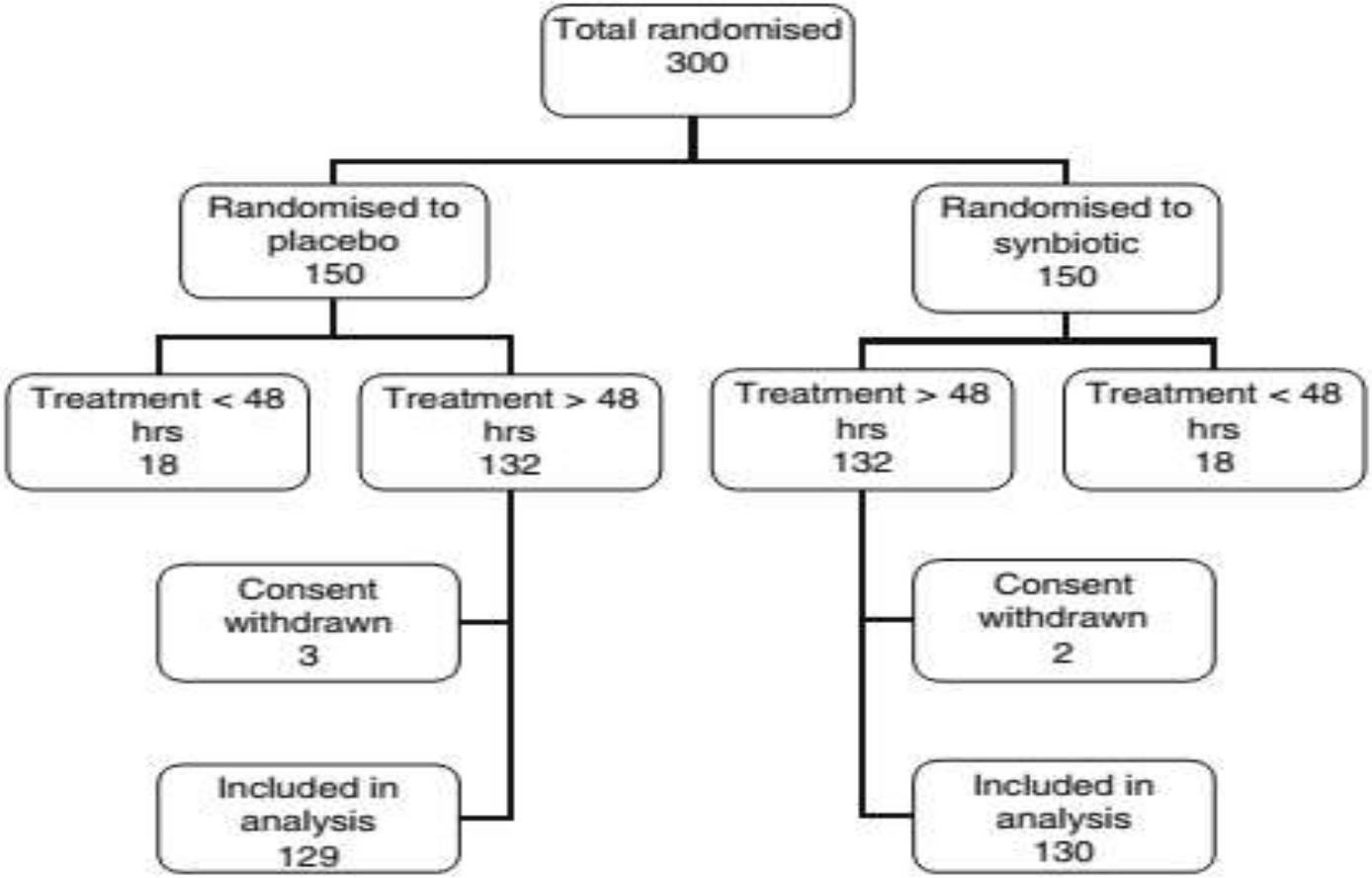


Fig. 1 CONSORT flow diagram of trial

Table 3 VAP diagnosis

Variable	Synbiotic	Placebo	*P*	Relative risk (95% Confidence Interval)
Number of patients	130	129		
VAP (% of total)	12 (9)	17 (13)	0.42	0.70 (0.35–1.41)
Polymicrobial VAP	3	5		
Individual pathogens				
Enterobacteriaceae	6	7		
Pseudomonas aeruginosa		1		
MRSA		1		
Haemophilus influenzae		1		
Acinetobacter baumannii	3	1		
Stenotrophomonas maltophilia		1		
VAP episodes per 1,000 ventilator days	13	14.6	0.91	0.89 (0.42–1.87)
Number of ventilator days, median (IQR)	5 (2–9)	5 (3–11)	0.82	

Table 5 Secondary outcome results

Variable	Synbiotic	Placebo	*P*	Relative risk (95% CI)
Number of patients	130	129		
ICU length of stay in days, median (IQR)	6.0 (3–11)	7.0 (3–14)	0.45	
Hospital length of stay in days, median (IQR)	19 (8–36)	18 (7–32)	0.85	
Mortality				
ICU total (%)	28 (21.5)	34 (26.3)	0.44	0.82 (0.53–1.26)
Hospital total (%)	35 (26.9)	42 (32.5)	0.39	0.83 (0.57–1.20)

Importance of feeding protocol in ICU

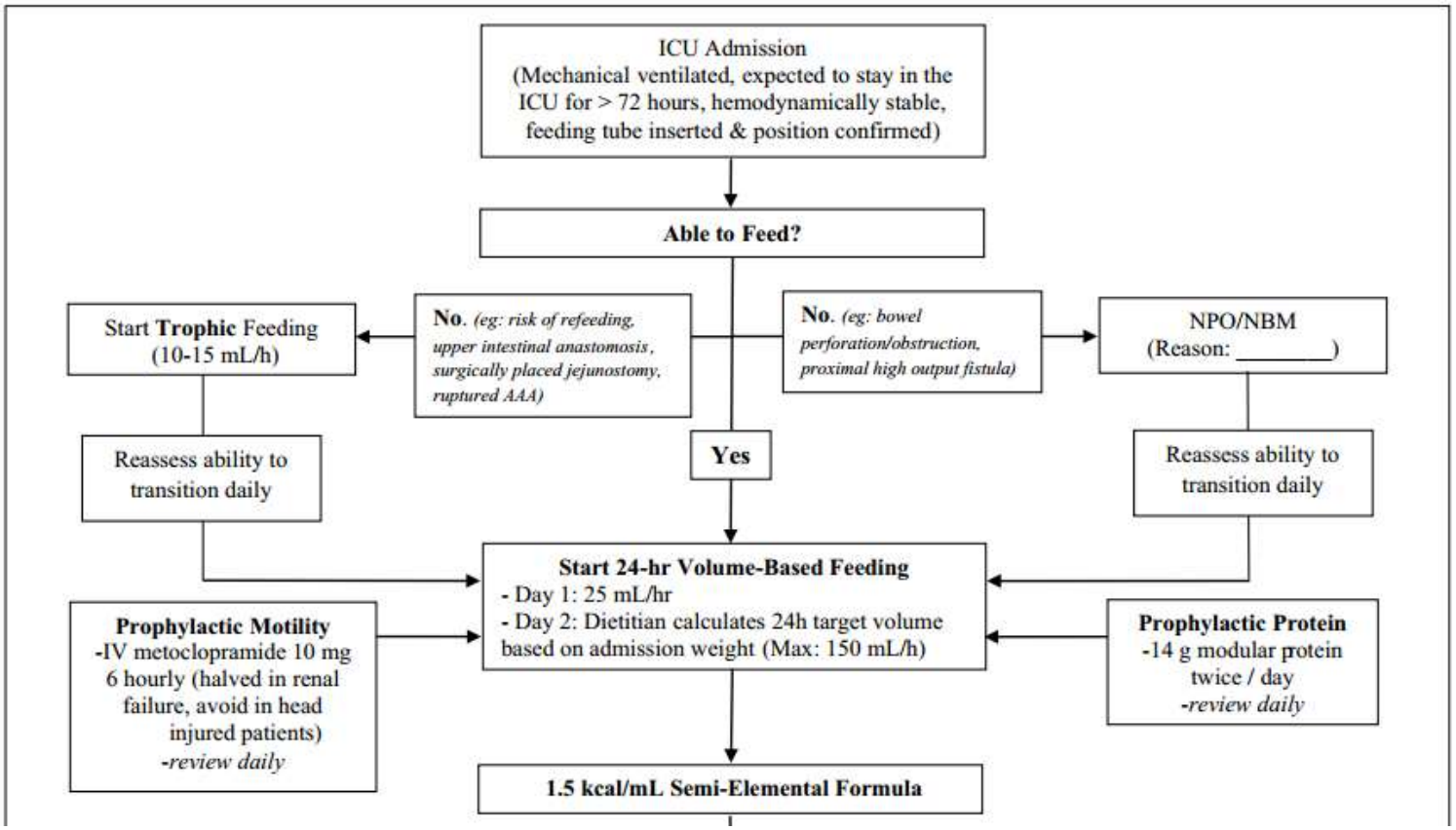
- Feeding protocols/algorithms with prokinetics, post-pyloric tubes may be associated with a trend towards a reduction in hospital mortality and a significant reduction in hospital length of stay.
- Feeding protocols with prokinetics and a higher gastric residual volume threshold (250 mls) are associated with a trend towards a reduction in gastric residual aspirations and less time taken to reach goal feeding rate in the critically ill.
- 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.

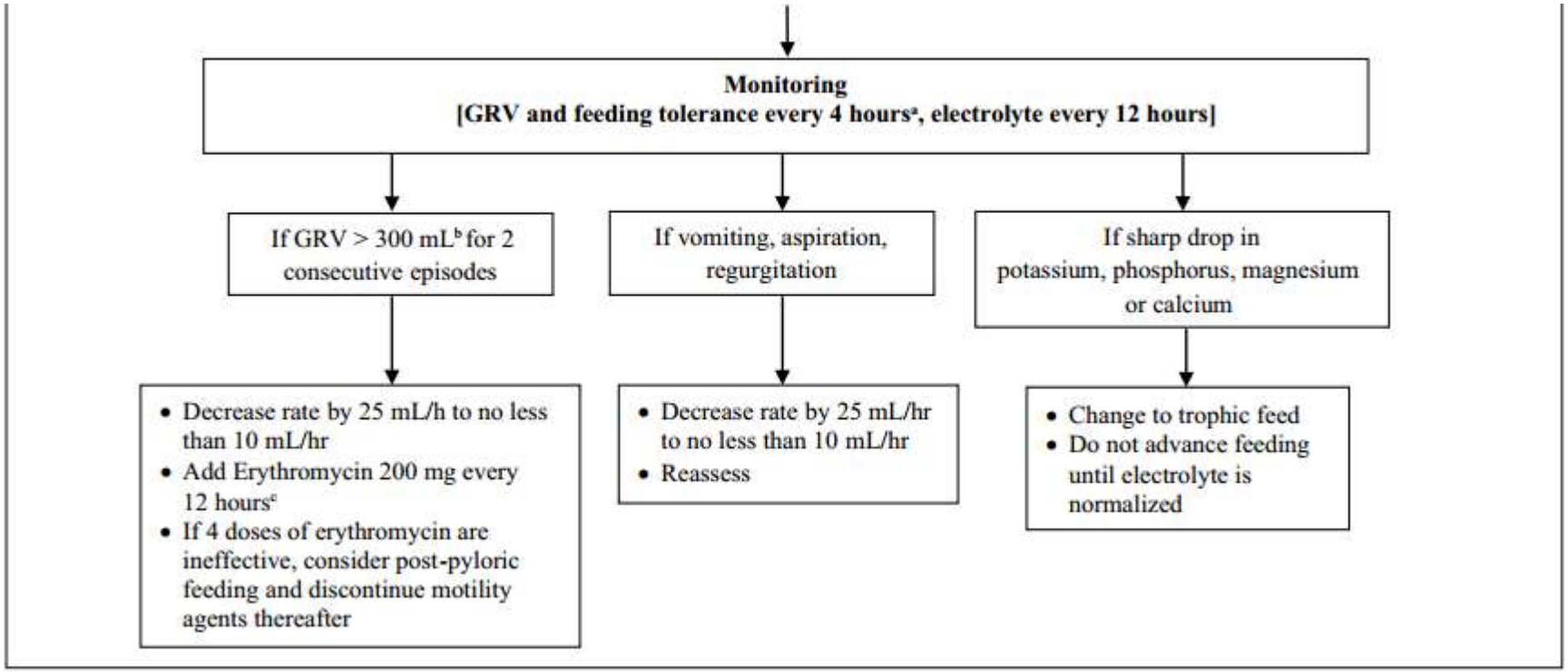
Canadian clinical practice guideline 2015

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	**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)

PEP UP feeding algorithm chart




Monitoring
[GRV and feeding tolerance every 4 hours[a], electrolyte every 12 hours]
If GRV > 300 mL[b] for 2 consecutive episodes
If vomiting, aspiration, regurgitation
If sharp drop in potassium, phosphorus, magnesium or calcium
• Decrease rate by 25 mL/h to no less than 10 mL/hr
• Add Erythromycin 200 mg every 12 hours[c]
• If 4 doses of erythromycin are ineffective, consider post-pyloric feeding and discontinue motility agents thereafter
• Decrease rate by 25 mL/hr to no less than 10 mL/hr
• Reassess
• Change to trophic feed
• Do not advance feeding until electrolyte is normalized

PEP u P studies

Table 2. Summary of Nutrition, Safety, and Clinical Outcomes of the PEP uP Studies.

PEP uP Studies	N	Nutrition Outcome	Safety Outcome	Clinical Outcome
Pilot Study (2010)	Before group: 20 After group: 30	Adequacy of calories EN: 58.8% (before) vs 70.2% (after); $P = .23$ Total nutrition[a]: 71.7% (before) vs 80.3% (after); $P = .23$ Adequacy of protein EN: 61.2% (before) vs 76.1% (after); $P = .08$ Total nutrition[a]: 61.2% (before) vs 73.6% (after); $P = .13$ Time of initiation of EN (hours): 16.0 (before) vs 17.7 (after); $P = .72$	Vomiting: 15.0% (before) vs 6.7% (after); $P = .38$ Regurgitation: 10.0% (before) vs 0 (after); $P = .16$ Macroaspiration: 10.0% (before) vs 0 (after); $P = .16$ Pneumonia (48 hours after ICU admission): 25.0% (before) vs 13.3% (after); $P = .45$	Length of ICU stay (days): 17.9 (before) vs 8.5 (after); $P = .14$ Length of hospital stay (days): 57.4 (before) vs 22.9 (after); $P = .02$ Length of mechanical ventilation (days): 11.8 (before) vs 5.8 (after); $P = .06$ 60-day mortality: 10.0% (before) vs 30.0% (after); $P = .16$
Clustered Randomized Controlled Trial (2013)	Site • Control: 9 • Intervention: 9 Patient • Control o Baseline: 270 o Follow-up: 267 • Intervention o Baseline: 270 o Follow-up: 252	Adequacy of calories (% difference) EN: −0.6% (control) vs 11.6% (intervention); $P = .004$ Total nutrition[a]: 0.2% (control) vs 12.3% (Intervention); $P = .01$ Adequacy of protein (% difference) EN: −0.2%% (control) vs 13.6% (intervention); $P = .005$ Total nutrition[a]: −1.2% (control) vs 14.4% (intervention); $P = .004$ Time of initiation of EN (hours difference): 1.6 (control) vs −11.0 (intervention); $P = .10$	Vomiting (% difference): −2.9% (control) vs 1.2 % (intervention); $P = .45$ Regurgitation (% difference): −0.4% (control) vs −1.2% (intervention); $P = .39$ Macroaspiration (% difference): −0.4% (control) vs 1.3% (intervention); $P = .11$ ICU-acquired pneumonia (% difference): 1.9% (control) vs 0.6% (intervention); $P = .43$	Length of ICU stay (days difference): −0.7 (control) vs 1.1 (intervention); $P = .35$ Length of hospital stay (days difference): −2.9 (control) vs −0.7 (intervention); $P = .73$ Length of mechanical ventilation (days difference): −0.1 (control) vs 0.6 (intervention); $P = .57$ ICU mortality (% difference): −7% (control) vs −12% (intervention); $P = .57$ 60-day mortality (% difference): −2% (control) vs −2% (intervention); $P = .53$

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Nutrition in ICU –PGI experience

- In a prospective cohort study conducted in RICU , PGIMER found that
  - Calorie delivery increased from 55.1% (35.4–81.3%) of the recommended value on day 1 to 92.0% (35.7–124.6%) on day 28. Protein delivery improved from 46.7% (31.6–72.1%) of the recommended value on day 1 to 75.3% (54.3–85.5%) on day 28. but none of them reached the goal.
  - Risk factors for hospital mortality identified were admission Sequential Organ-Failure Assessment score(odds ratio 1.30, 95% confidence interval 1.03–1.63) and mean daily calorie delivery of < 50% of the recommended value

Respir Care 2009;54(12):1688–1696.

Take home message

- All ICUs should have feeding protocol.
- Early initiation of enteral feeding [preferably full] should be the first step in all such protocol.
- Volume based feeding and compensation for missed calories are something new and worth trying.
- Supplemental PN may be beneficial in selected patients.