2.0 Early vs. Delayed Nutrient Intake May 2015

There were no new randomized controlled trials since the 2013 update and hence there are no changes to the following summary of evidence.

2013 Recommendation: *Based on 16 level 2 studies, we recommend early enteral nutrition (within 24-48 hours following admission to ICU) in critically ill patients.*

2013 Discussion: The committee noted the addition of 2 new small, level 2 RCTs (Moses 2009 and Chourdakis 2012), since the last update and despite the modest changes in the overall treatment effect of on mortality & infections, there were no other changes in the other overall scoring of values (confidence intervals, validity, reproducibility, adequacy of control group, etc. See table below). The committee noted the results of a large observational study of 1174 critically ill patients on vasopressors that demonstrated early enteral nutrition was associated with decreased hospital mortality and that the beneficial effect of early feeding was more evident in patients treated with multiple vasopressors [(1).] The committee agreed that based on the updated evidence and the unchanged scoring of values, the recommendation for early vs delayed enteral nutrition remain as "recommend".

(1) Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation Am J Crit Care. 2010 May;19(3):261-8.

2009 Recommendation: *Based on 14 level 2 studies, we recommend early enteral nutrition (within 24-48 hours following admission to ICU) in critically ill patients.*

2009 Discussion: The committee noted the inconsistent and variable definitions of early enteral nutrition and delayed nutrition, and the considerable heterogeneity in trial designs. Concern was expressed about the safety of early intragastric enteral nutrition given reports of increased harm (from non randomized trials) experienced by patients fed aggressive, early EN (1,2,3). However, given the potentially large treatment effect with respect to reduced mortality and infections, significant improvement in nutritional intake and the minimal cost and feasibility concerns of early enteral nutrition, the committee decided to put forward a recommendation for its use. It was postulated that the treatment effect would be larger in patients with a lower body mass index (BMI), however only 3 studies reported on BMI. Early enteral nutrition, like other interventions i.e. small bowel feeding (see section 5.3) and motility agents (see section 5.2) can be used as a strategy to optimize delivery of enteral nutrition. Based on the studies reviewed, the committee agreed that early enteral nutrition could be defined as "within 24-48 hrs from admission to ICU" and that it be applied to all mechanically ventilated patients presuming patients were adequately resuscitated and hemodynamically stable.

1) Mentec H, Dupont H, Bocchetti M, et al . Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. Crit Care Med 2001; 29(10):1955-1961.
2) Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V, Kollef M. Early versus late enteral feeding of mechanically ventilated patients: Results of a clinical trial. JPEN 2002;26:174-181.
3) Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest. 2006 Apr;129(4):960-7.

Semi Quantitative Scoring

Values	Definition	2009 Score	2013 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	3 (mortality) 2 (infection)	2 (mortality) 1 (infection)
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	1 (mortality) 2 (infection)	1 (mortality) 2 (infection)
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	3 (mortality) 1 (infection)	3 (mortality) 2 (infection)
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	2	2
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal inconsistencies=2, very consistent=3)	2	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre=1, moderate likelihood i.e. multicentre with limited patient population or practice setting=2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings=3	1	1
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2	2
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	2	2

2.0 Early vs. Delayed Nutrient Intake

Question: Does early enteral nutrition compared to delayed nutrient intake result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 16 randomized controlled trials (level 2 studies) comparing early enteral nutrition vs. delayed nutrient intake (i.e. delayed enteral nutrition, parenteral nutrition or oral diet). In all the trials, except one (started within 72 hrs of injury), enteral nutrition in the intervention group was started within 24-48 hours of admission/resuscitation. There were 10 studies comparing early vs. delayed EN whereas in 6 studies early EN was compared to no EN/IV fluids.

Mortality: When the data from the 16 studies that looked at the effect of early EN on mortality were aggregated, when compared to delayed nutrient intake, early enteral nutrition was associated with a trend towards a reduction in mortality (RR 0.72, 95% CI 0.50, 1.04, p=0.08, heterogeneity I^2=0%; figure 1). In a subgroup analysis, early EN vs. no EN/IV fluids was associated with a trend towards a reduction in mortality (RR 0.62, 95% CI 0.37, 1.05, p =0.08, heterogeneity I^2=0%; figure 1), whereas early vs. delayed EN had no effect on mortality (RR 0.83, 95% CI 0.49, 1.39, p=0.47, heterogeneity I^2=0%; figure 1). The difference between the two subgroups was not significant (p=0.44; figure 1).

Infections: Eleven studies reported on infections and of these only 9 studies reported on the number of patients with infections and when these were aggregated, early enteral nutrition when compared to delayed nutrient intake was associated with a significant reduction in infectious complications (RR 0.81, 95% CI 0.68, 0.97, p=0.02, heterogeneity I^2=14%; figure 2). In a subgroup analysis, early EN vs. no EN/IV fluids was associated with a trend towards a reduction in infections (RR 0.70, 95% CI 0.48, 1.02, p= 0.06, heterogeneity I^2=26%; figure 2), whereas early vs. delayed EN had no effect on infections (RR 0.86, 95% CI 0.69, 1.08, p=0.20, heterogeneity I^2=12%; figure 2). The difference between the two subgroups was not significant (p=0.36; figure 2).

LOS and Ventilator days: Fifteen studies looked at LOS (6 reported on ICU LOS only, 3 reported on hospital LOS only and 6 reported on both ICU and hospital LOS). When the results were meta-analyzed, early enteral nutrition had no effect on ICU stay (WMD -0.78, 95% CI -3.56, 2.00, p=0.58, heterogeneity I^2=46%; figure 3) or hospital length of stay (WMD -0.18, 95% CI -8.15, 7.80 p = 0.97, heterogeneity I^2=51.7%; figure 4). A total of 8 studies reported on ventilator days and all showed no significant differences between the early vs. delayed fed groups (WMD 0.03, 95% CI -3.01, 3.06 p=0.99, heterogeneity I^2=42.6%; figure 5).

Other: All fifteen studies that reported nutritional endpoints showed a significant improvement in the groups receiving early enteral nutrition (calorie intake, protein intake, % goal achieved, faster nitrogen balance achieved). There were no differences in other complications between the groups.

Conclusions:

1) Early enteral nutrition, when compared to delayed nutrient intake is associated with a trend towards a reduction in mortality in critically ill patients.
2) Early enteral nutrition, when compared to delayed nutrient intake is associated with a significant reduction in infectious complications.

3) Early enteral nutrition, when compared to delayed nutrient intake has no effect on ICU or hospital length of stay.
4) Early enteral nutrition, when compared to delayed nutrient intake improves nutritional intake.

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 early EN vs. delayed nutrient intake in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				Early EN	Delayed	Early EN	Delayed
1) Moore 1986	Trauma with abdominal trauma index > 15 N=43	C.Random: not sure ITT: no Blinding: no (6)	Vivonex post op (< 24 hrs) via jejunostomy vs. D5W then progressed to parenteral nutrition if not on regular diet (both groups got PN)	1/32 (3)	2/31 (6)	3/32 (9)	9/31 (29)
2) Chiarelli 1990	Burns N=20	C.Random: not sure ITT: yes Blinding: no (6)	Immediate EN (4.4 ± 0.49 hrs) vs > 48 hrs (57.7 ± 2.6 hrs) (gastric feeding)	0/10 (0)	0/10 (0)	3/10 (30) +ve blood cultures	7/10 (70) +ve blood cultures
3) Eyer 1993	Trauma, ICU N=52	C.Random: not sure ITT: no Blinding: no (8)	EN < 24 hrs (31 ± 13 hrs from ICU admission) vs > 72 hrs (82 ± 11 hrs from ICU admission) (small bowel feeding)	2/19 (11)	2/19 (11)	29/19 per group	14/19 per group
4) Chuntrasakul 1996	Trauma patients with injury severity score 20-40 N=38	C.Random: not sure ITT: yes Blinding: no (6)	Traumacal via gastric route (early i.e. immediately after resuscitation) + PN if needed vs IV fluids and oral diet when bowel function detected	1/21 (5)	3/17 (18)	NR	NR
5) Singh 1998	Non traumatic intestinal perforation and peritonitis BMI 21-22 N=37	C.Random: no ITT: yes Blinding: no (8)	Low residue blenderized diet via jejunostomy 12-24 hrs post laporotomy vs. IV fluids/lytes, oral diet started once bowel activity resumed	4/21 (19)	4/22 (18)	7/21 (33)	12/22 (55)
6) Kompan 1999	Multiple trauma in shock N=28	C.Random: yes ITT: no Blinding: no (9)	EN ~4.4 hrs after admission to ICU, 9.2 hrs after trauma vs ~ 36.5 hrs from ICU admission, 41.4 hrs after trauma. Gastric feeding, both groups got PN	ICU 0/14 (0) Hospital 0/14 (0)	ICU 0/14 (0) Hospital 1/14 (7)	NR	NR
7) Minard 2000	Closed head injuries N=27	C.Random: not sure ITT: no Blinding: no (7)	EN < 60 hrs (33 ± 15 hrs) (small bowel) vs late (84 ± 41 hrs) (gastric)	1/12 (8)	4/15(27)	6/12 (50)	7/15 (47)

8) Pupelis 2000	Severe pancreatitis patients undergoing emergency surgery N=29	C.Random: not sure ITT: yes Blinding: no (6)	EN < 24 hrs post-op via jejunum + IV fluids vs. IV fluids until reintroduction of normal diet	1/11 (9)	5/18 (28)	NR	NR
9) Pupelis 2001	Post laporotomy for severe pancreatitis and peritonitis N=60	C.Random: not sure ITT: yes Blinding: no (6)	EN < 12 hrs post-op via jejunum + IV fluids vs. IV fluids until reintroduction of normal diet	1/30 (3)	7/30 (23)	Unresolved Peritonitis 1/30 (3) Wound Septic Complications 10/30 (33)	8/30 (27) 8/30 (27)
10) Kompan 2004	Multiple trauma patients, ICU N=52	C.Random: not sure ITT: yes Blinding: no (6)	EN ~10.6 hrs after injury vs ~ 36.5 hrs from ICU admission. Gastric feeding, both groups got PN	0/27 (0)	1/25 (4)	9/27 (33)	16/25 (64)
11) Malhotra 2004	Post-op for peritonitis N=200	C.Random: not sure ITT: yes Blinding: no (6)	EN post-op < 48 hrs via nasoogastric+ IV fluids (oral feeds if ready by day 8 post-op) vs. IV fluids for 7 days (oral feeds if ready on day 5 post-op)	12/100 (12)	16/100 (16)	54/100 (54)	67/100 (67)
12) Peck 2004	Burns N=27	C.Random: not sure ITT: no Blinding: no (6)	Crucial < 24 hrs from burn injury vs. 7 days. Both groups received oral diet as tolerated (4-9% calories) (gastric feeding)	4/14 (28)	5/13 (38)	12/14 (86)	11/13 (85)
13) Dvorak 2004	Acute spinal cord injury patients BMI=26-29 N=17	C.Random: yes ITT: yes Blinding: no (10)	Continuous enteral feeding via nasogastric route within 72 hours of injury vs. after 120 hrs of injury. Both groups followed feeding protocol (head of bed, starting rate 25 ml/hr, gastric residual volumes checked, etc).	0/7 (0)	0/10 (0)	2.4 ± 1.5 per group	1.7 ± 1.1 per group
14) Nguyen 2008	Mixed ICU BMI=27-28 N=28	C.Random: no ITT: yes Blinding: no (9)	EN < 24 hrs of ICU admission vs. after day 4. No motility agents given	ICU 4/14 (29) Hospital 6/14 (43)	ICU 4/14 (29) Hospital 6/14 (43)	Pneumonia 3/14 (21)	Pneumonia 6/14 (43)
15) Moses 2009	Organophosphate poisoned, mechanically ventilated ICU patients N=59	C.Random: No ITT: No Blinding: No (5)	Hypocaloric EN within 48hr of intubation + IV glucose (Day 1 20 ml/hr (0.5 kcal/ml), day 2 20 ml/hr (1 kcal/ml) day 3 40 ml/hr (1 kcal/ml) feeds), max 1000 kcals/day vs.EN post tracheostomy placement + IV glucose	3/29 (10)	3/30 (10)	14/29 (48)	15/30 (50)

16) Chourdakis 2012	Traumatic brain injury requiring mechanical ventilation in ICU N=59	C.Random: No ITT: Yes Blinding: No (6)	Early enteral feed within 24-48 hrs post ICU admission (hrs in ICU prior to first feeding: 31.2 ± 11.2 hrs) vs.delayed enteral feed within 48-120hrs post ICU admission (hrs in ICU prior to first feeding: 76.5 ± 22.6 hrs)	3/34 (9)	2/25 (8)	VAP 13/34 (38)	VAP 12/25 (43)

Table 1. Randomized studies evaluating early EN vs. delayed nutrient intake in critically ill patients (continued)

Study	LOS days		Ventilator days		Cost		Other	
	Early EN	Delayed	Early EN	Delayed	Early EN	Delayed	Early EN	Delayed
1) Moore 1986	NR	NR	NR	NR	$16,280 ± 2146	$19,636 ± 3396	Complications 14/32 (44) Feed Intolerance 12/32 (38)	15/31 (48) NR
2) Chiarelli 1990	Hospital 69.2 ± 10.4 (10)	Hospital 89 ± 18.9 (10)	NR	NR	NR	NR	Days to +ve Nitrogen Balance 8.8 ± 4.1 p<0.05 Intestinal Complications 2/10 (20)	24.1 ± 6.9 2/10 (20)
3) Eyer 1993	ICU 11.8 ± 7.9 (19)	ICU 9.9 ± 6.7 (19)	10.2 ± 8.1 (19)	8.1 ± 6.8 (19)	NR	NR	Calorie Intake (kcal/kg/day) 30 ± 6 p<0.001 Protein Intake (gm/kg/day) 1.3 ± 0.3 p<0.001 Organ System Failure 2/19 (10.5)	19 ± 5 0.9 ± 0.2 2/19 (10.5)
4) Chuntrasakul 1996	ICU 8.1 ± 6.3 (21)	ICU 8.35 ± 4.8 (17)	5.29 ± 6.3 (21)	6.12 ± 5.3 (17)	NR	NR	Calories Received in Week 1 1885.2 ± 38.3 Calories Received in Week 2 1850.3 ± 248.4	633.4 ± 83.7 717.31 ± 142
5) Singh 1998	Hospital 14 ± 6.9 (19)	Hospital 13 ± 7.0 (18)	NR	NR	NR	NR	Complications 11/21 (52) Calorie Intake by Day 7 2610 ± 337 Nitrogen Balance by Day 7 5.1 ± 0.7	13/22 (59) 516 ± 156 10.8 ± 3.1

6) Kompan 1999	ICU 11 (10.5-24.7)	ICU 14 (10.5-24.7)	13 (6.7-18)	11.9 (6-7.7)	NR	NR	EN Received on Day 4 (mls) 1340 ± 473 703 ± 701 p=0.009
7) Minard 2000	ICU 18.5 ± 8.8 (12) Hospital 30 ± 14.7 (12)	ICU 11.3 ± 6.1 (15) Hospital 21.3 ± 13.7 (15)	15.1 ± 7.5 (12)	10.4 ± 6.1 (15)	NR	NR	Calorie Intake 1509 ± 45 1174 ± 425 p< 0.02 Feed Infusion Complications 22/12 28/15
8) Pupelis 2000	ICU 7 ± 41 (11) Hospital 45 ± 96 (11)	ICU 6 ± 34 (18) Hospital 29 ± 103 (18)	NR	NR	NR	NR	NR
9) Pupelis 2001	ICU 13.9 ± 14.6 (30) Hospital 35.3 ± 22.9 (30)	ICU 16 ± 20.5 (30) Hospital 35.8 ± 32.5 (30)	NR	NR	NR	NR	Total kcals After Surgery 1295 ± 327 473 ± 156
10) Kompan 2004	ICU 15.9 ± 9.7 (27)	ICU 20.6 ± 18.5 (25)	12.9 ± 8.1 (27)	15.6 ± 16.1 (25)	NR	NR	EN Received on Day 4 (mls) 1175 ± 485 803 ± 545 p=0.012
11) Malhotra 2004	ICU 1.59 (mean) Hospital 10.59 (mean)	ICU 2.10 (mean) Hospital 10.70 (mean)	NR	NR	NR	NR	Patients Receiving > 1500 cals Post-op Day 4 65% 0% p<0.001 Patients Receiving > 2500 cals Post-op Day 8 84% 0% p<0.001
12) Peck 2004	ICU 40 ± 32 (14) Hospital 60 ± 44 (14)	ICU 37 ± 33 (13) Hospital 60 ± 38 (13)	32 ± 27 (14)	23 ± 26 (13)	NR	NR	Mean Calorie Intake 2234 2207 Mean Calorie Intake Change/Week 156 166

13) Dvorak 2004	Hospital 53 ± 34.4	Hospital 37.9 ± 14.6	31.8 ± 35	20.9 ± 14.4	NR	NR	Number of Feeding Complications 39 59 Hours to Reach Energy Goals 113 166 Energy Intake 1938 ± 1100 1588 ± 983 Protein Intake 86.8 ± 59 67.6 ± 54
14) Nguyen 2008	ICU 11.3 ± 3.0	ICU 15.9 ± 7.1	9.2 ± 3.4 (14)	13.7 ± 7.1 (14)	NR	NR	Mean Calorie Intake from Day 0-4 2894 ± 198 0
15) Moses 2009	ICU 10.6 (6-13) Hospital 15 (9.5-20)	ICU 8 (5-17.5) Hospital 12 (7.5-15)	12 (5.5-14)	10 (4-12)	NR	NR	Total Calories 604 (500-713) 447 (424-484) p<0.0001
16) Chourdakis 2012	ICU 24.8 ± 7.6 (34)	ICU 28.5 ± 8.9 (25)	NR	NR	NR	NR	Hyperglycemia 5/34 (15) 4/25 (16) Feed Intolerance 3/34 (9) 3/25 (12) Diarrhea 4/34 (12) 3/25 (12) Constipation 1/34 (3) 1/25 (4) Day 10 of Intake (kcal/day) 1432.0 ± 156.3 813.0 ± 235.1

C.Random: Concealed randomization
ITT: Intent to treat
NR: Not reported
‡ Refers to the # of patients with infections unless specified
† Presumed hospital mortality unless otherwise specified
± ( ) : Mean ± SD =Standard deviation (number); (-) : mean (range) * SEM converted to SD

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

Study or Subgroup	Early EN Events	Early EN Total	Delayed/None Events	Delayed/None Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 EN vs IV Fluids/No EN							
Moore	1	32	2	31	2.5%	0.48 [0.05, 5.07]	1986
Chuntrasakul	1	21	3	17	2.9%	0.27 [0.03, 2.37]	1996
Singh	4	21	4	22	8.7%	1.05 [0.30, 3.66]	1998
Pupelis 2000	1	11	5	18	3.4%	0.33 [0.04, 2.45]	2000
Pupelis 2001	1	30	7	30	3.3%	0.14 [0.02, 1.09]	2001
Malhotra	12	100	16	100	28.2%	0.75 [0.37, 1.50]	2004
Subtotal (95% CI)		**215**		**218**	**49.0%**	**0.62 [0.37, 1.05]**	
Total events	20		37				
Heterogeneity: Tau² = 0.00; Chi² = 4.10, df = 5 (P = 0.54); I² = 0%							
Test for overall effect: Z = 1.78 (P = 0.08)							
1.1.2 EN vs Delayed EN							
Chiarelli	0	10	0	10		Not estimable	1990
Eyer	2	19	2	19	4.0%	1.00 [0.16, 6.38]	1993
Kompan 1999	0	14	1	14	1.4%	0.33 [0.01, 7.55]	1999
Minard	1	12	4	15	3.2%	0.31 [0.04, 2.44]	2000
Kompan 2004	0	27	1	25	1.4%	0.31 [0.01, 7.26]	2004
Dvorak	0	7	0	10		Not estimable	2004
Peck	4	14	5	13	11.8%	0.74 [0.25, 2.18]	2004
Nguyen 2008	6	14	6	14	18.7%	1.00 [0.43, 2.35]	2008
Moses	3	29	3	30	5.9%	1.03 [0.23, 4.71]	2009
Chourdakis	3	34	2	25	4.7%	1.10 [0.20, 6.12]	2012
Subtotal (95% CI)		**180**		**175**	**51.0%**	**0.83 [0.49, 1.39]**	
Total events	19		24				
Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 7 (P = 0.96); I² = 0%							
Test for overall effect: Z = 0.72 (P = 0.47)							
Total (95% CI)		**395**		**393**	**100.0%**	**0.72 [0.50, 1.04]**	
Total events	39		61				
Heterogeneity: Tau² = 0.00; Chi² = 6.83, df = 13 (P = 0.91); I² = 0%							
Test for overall effect: Z = 1.76 (P = 0.08)							
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.44), I² = 0%							

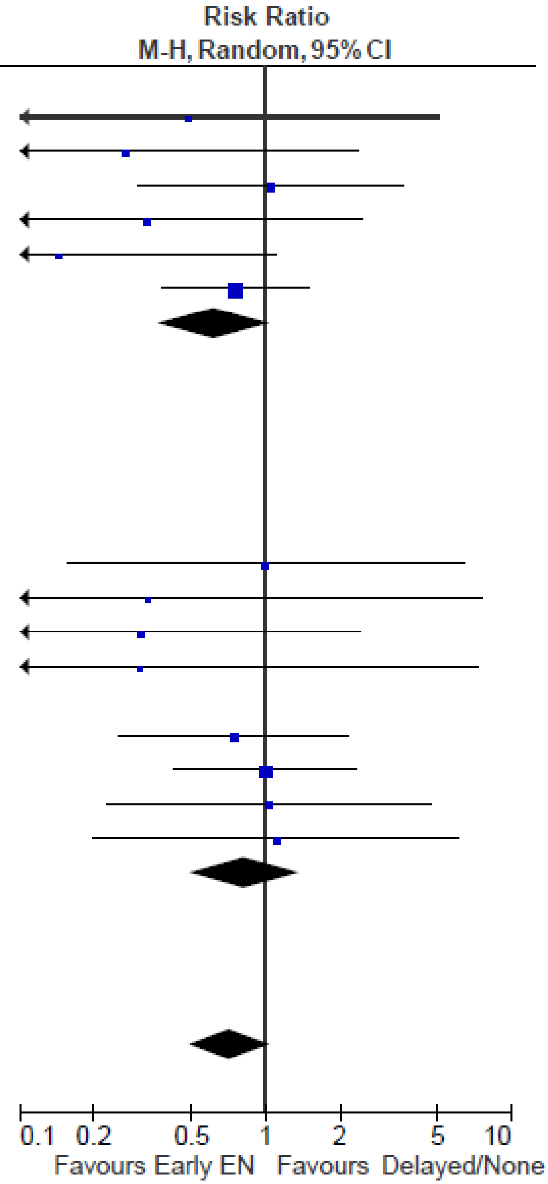

Figure 2. Studies comparing early EN vs delayed nutrient intake: Infectious complications

Study or Subgroup	Early EN Events	Early EN Total	Delayed/None Events	Delayed/None Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 EN vs IV Fluids/No EN							
Moore	3	32	9	31	2.0%	0.32 [0.10, 1.08]	1986
Singh	7	21	12	22	5.5%	0.61 [0.30, 1.25]	1998
Malhotra	54	100	67	100	33.8%	0.81 [0.64, 1.01]	2004
Subtotal (95% CI)		**153**		**153**	**41.3%**	**0.70 [0.48, 1.02]**	
Total events	64		88				
Heterogeneity: Tau² = 0.04; Chi² = 2.72, df = 2 (P = 0.26); I² = 26%							
Test for overall effect: Z = 1.85 (P = 0.06)							
1.2.2 EN vs Delayed EN							
Minard	6	12	7	15	4.6%	1.07 [0.49, 2.34]	2000
Kompan 2004	9	27	16	25	7.4%	0.52 [0.28, 0.96]	2004
Peck	12	14	11	13	22.0%	1.01 [0.74, 1.39]	2004
Nguyen 2008	3	14	6	14	2.1%	0.50 [0.15, 1.61]	2008
Moses	17	29	19	30	14.7%	0.93 [0.61, 1.39]	2009
Chourdakis	13	34	12	25	7.8%	0.80 [0.44, 1.44]	2012
Subtotal (95% CI)		**130**		**122**	**58.7%**	**0.86 [0.69, 1.08]**	
Total events	60		71				
Heterogeneity: Tau² = 0.01; Chi² = 5.71, df = 5 (P = 0.34); I² = 12%							
Test for overall effect: Z = 1.27 (P = 0.20)							
Total (95% CI)		**283**		**275**	**100.0%**	**0.81 [0.68, 0.97]**	
Total events	124		159				
Heterogeneity: Tau² = 0.01; Chi² = 9.30, df = 8 (P = 0.32); I² = 14%							
Test for overall effect: Z = 2.35 (P = 0.02)							
Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0%							

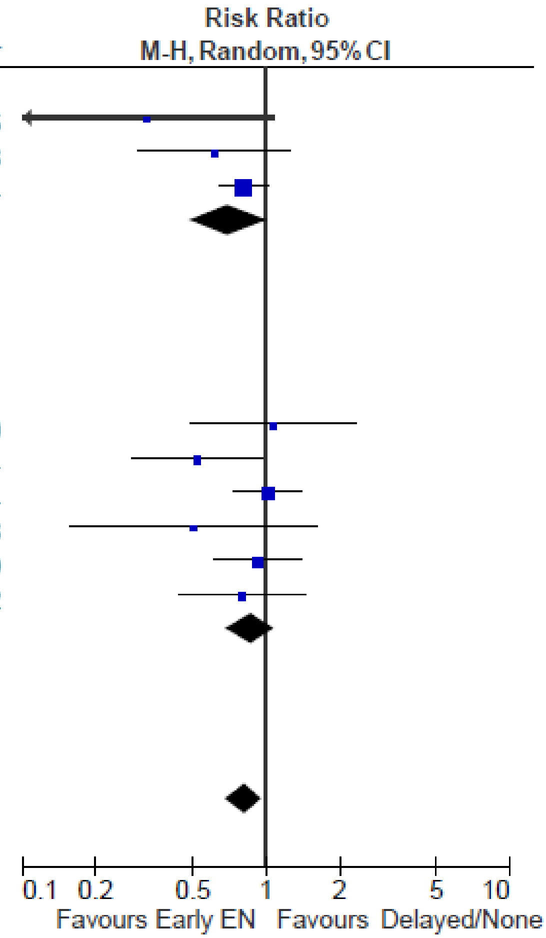

Figure 3. Studies comparing early EN vs delayed nutrient intake: ICU LOS

	Early EN			Delayed/None				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Eyer	11.8	7.9	19	9.9	6.7	19	15.8%	1.90 [-2.76, 6.56]	1993
Chuntrasakul	8.1	6.3	21	8.35	4.8	17	19.5%	-0.25 [-3.78, 3.28]	1996
Pupelis 2000	7	41	11	6	34	18	0.9%	1.00 [-27.87, 29.87]	2000
Minard	18.5	8.8	12	11.3	6.1	15	12.6%	7.20 [1.34, 13.06]	2000
Pupelis 2001	13.9	14.6	30	16	20.5	30	7.1%	-2.10 [-11.11, 6.91]	2001
Kompan 2004	15.9	9.7	27	20.6	18.5	25	8.3%	-4.70 [-12.82, 3.42]	2004
Peck	40	32	14	37	33	13	1.2%	3.00 [-21.55, 27.55]	2004
Nguyen 2008	11.3	3	14	15.9	7.1	14	17.8%	-4.60 [-8.64, -0.56]	2008
Chourdakis	24.8	7.6	34	28.5	8.9	25	16.8%	-3.70 [-8.02, 0.62]	2012
Total (95% CI)			**182**			**176**	**100.0%**	**-0.78 [-3.56, 2.00]**	

Heterogeneity: Tau² = 7.11; Chi² = 14.71, df = 8 (P = 0.06); I² = 46%
Test for overall effect: Z = 0.55 (P = 0.58)

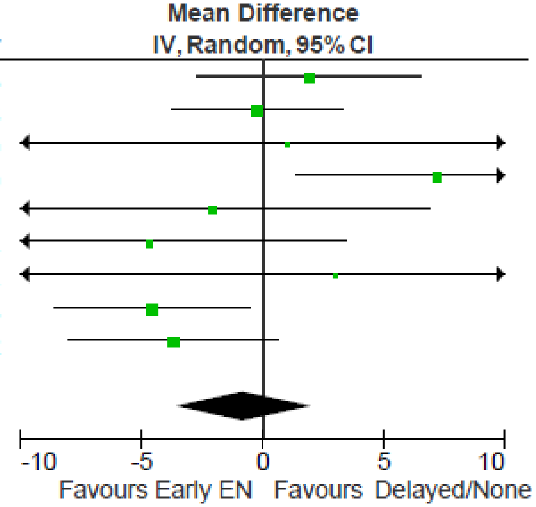

Figure 4. Studies comparing early EN vs delayed nutrient intake: Hospital LOS

	Early EN			Delayed/None				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Chiarelli	69.2	10.4	10	89	18.9	10	17.5%	-19.80 [-33.17, -6.43]	1990
Singh	14	6.9	19	13	7	18	31.2%	1.00 [-3.48, 5.48]	1998
Minard	30	14.7	12	21.3	13.7	15	21.1%	8.70 [-2.13, 19.53]	2000
Pupelis 2000	45	96	11	29	103	18	1.1%	16.00 [-58.04, 90.04]	2000
Pupelis 2001	35.3	22.9	30	35.8	32.5	30	16.5%	-0.50 [-14.73, 13.73]	2001
Peck	60	44	14	60	38	13	5.6%	0.00 [-30.95, 30.95]	2004
Dvorak	53	34.4	7	37.9	14.6	10	7.0%	15.10 [-11.94, 42.14]	2004
Total (95% CI)			**103**			**114**	**100.0%**	**-0.18 [-8.15, 7.80]**	

Heterogeneity: Tau² = 47.83; Chi² = 12.41, df = 6 (P = 0.05); I² = 52%
Test for overall effect: Z = 0.04 (P = 0.97)

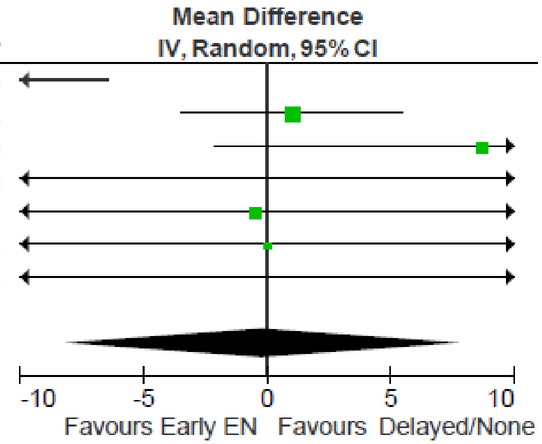

Figure 5. Studies comparing early EN vs delayed nutrient intake: Ventilator days

	Early EN			Delayed/None				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Eyer	10.2	8.1	19	8.1	6.8	19	19.7%	2.10 [-2.66, 6.86]	1993
Chuntrasakul	5.29	6.3	21	6.12	5.3	17	24.3%	-0.83 [-4.52, 2.86]	1996
Minard	15.1	7.5	12	10.4	6.1	15	17.8%	4.70 [-0.55, 9.95]	2000
Kompan 2004	12.9	8.1	27	15.6	16.1	25	12.5%	-2.70 [-9.71, 4.31]	2004
Peck	32	27	14	23	26	13	2.2%	9.00 [-10.99, 28.99]	2004
Dvorak	31.8	35	7	20.9	14.4	10	1.2%	10.90 [-16.52, 38.32]	2004
Nguyen 2008	9.2	3.4	14	13.7	7.1	14	22.3%	-4.50 [-8.62, -0.38]	2008
Total (95% CI)			**114**			**113**	**100.0%**	**0.03 [-3.01, 3.06]**	

Heterogeneity: Tau² = 6.30; Chi² = 10.45, df = 6 (P = 0.11); I² = 43%
Test for overall effect: Z = 0.02 (P = 0.99)

Mean Difference
IV, Random, 95% CI