2.0 Early vs. Delayed nutrient intake

January 31st, 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.

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.

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

2.0 Early vs. Delayed nutrient intake January 31st, 2009

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 14 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 8 studies comparing early vs. delayed EN whereas in 6 studies early EN was compared to no EN/IV fluids.

Mortality: When all the 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 0.68 95% CI 0.46,1.01, p =0.06, no heterogeneity present) (figure1). 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, no heterogeneity present), whereas early vs. delayed EN had no effect on mortality (RR = 0.77, 95% CI 0.43, 1.38, p = 0.39, no heterogeneity present) (figures 2, 3).

Infections: Nine studies reported on infections and of these only 7 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 0.76, 95 % confidence intervals 0.59, 0.98, p = 0.04) (figure 4). 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, moderate heterogeneity present), whereas early vs. delayed EN had no effect on infections (RR = 0.79, 95% CI 0.5, 1.25, p = 0.31, no heterogeneity present) (figures 5, 6).

LOS and Ventilator days: Thirteen studies looked at LOS (5 reported on ICU LOS only, 3 reported on hospital LOS only and 5 reported on both ICU and hospital LOS). When the results were meta-analyzed, early enteral nutrition had no effect on ICU stay (WMD -0.18, 95% CI -3.32, 2.96, p =0.91) (figure 7) or hospital length of stay (WMD – 0.18, 95%CI -8.15, 7.80 p = 0.97) (figure 8). A total of 7 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) (figure 9).

Other: All thirteen 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 Early vs Delayed intake or No EN	Mortality # (%)† Early EN	Mortality # (%)† Delayed	Infections # (%)‡ Early EN	Infections # (%)‡ 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 (10.5)	2/19 (10.5)	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	0/14 ICU 0/14	1/14 (7) ICU 0/14	NR	NR
7) Minard 2000	Closed head injuries N = 30	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

Study	Population	Methods (score)	Intervention Early vs Delayed intake	Mortality # (%)† Early EN	Mortality # (%)† Delayed	Infections # (%)‡ Early EN	Infections # (%)‡ Delayed
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 (3.3) 8/30 (26.7) Wound septic complications 10/30 (33) 8/30 (26.7)	
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	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	0/10	Infections per group 2.4 ± 1.5	Infections per group 1.7 ± 1.1
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	6/14 (43) ICU 4/14 (29)	6/14 (43) ICU 4/14 (29)	Pneumonia 3/14 (21)	Pneumonia 6/14 (43)

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

Study	LOS days Early EN	LOS days delayed	Ventilator days Early EN	Ventilator days delayed	Cost Early EN	Cost delayed	Other Early EN	Other delayed
1) Moore 1986	NR	NR	NR	NR	$ 16,280 ± 2146	$ 19,636 ± 3396	Complications 14/32 (44) 15/31 (48) Feed intolerance 12/32 (38) NR	
2) Chiarelli 1990	Hospital 69.2 ± 10.4 (10)	Hospital 89 ± 18.9 (10)	NR	NR	NR	NR	Days to + nitrogen balance 8.8 ± 4.1 24.1 ± 6.9 p < 0.05 intestinal complications 2/10 (20) 2/10 (20)	

Study	LOS days		Ventilator days		Cost		Other
	Early EN	delayed	Early EN	delayed	Early EN	delayed	Early EN delayed
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 19 ± 5 p < 0.001 Protein intake (gm/kg/day) 1.3 ± 0.3 0.9 ± 0.2 p < 0.001 Organ System Failure 2/19 (10.5) 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 ± 38.3 633.4 ± 83.7 Calories received in week 2 1850.3 ± 248.4 717.31 ± 142
5) Singh 1998	Hospital 14 ± 6.9 (19)	Hospital 13 ± 7.0 (18)	NR	NR	NR	NR	Complications 11/21 (52) 13/22 (59) Calorie intake by day 7 2610 ± 337 516 ± 156 Nitrogen balance by day 7 5.1 ± 0.7 - 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	Hospital 30 ± 14.7 (12) ICU 18.5 ± 8.8 (12)	Hospital 21.3 ± 13.7 (15) ICU 11.3 ± 6.1 (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	Hospital 45 ± 96 (11) ICU 7 ± 41 (11)	Hospital 29 ± 103 (18) ICU 6 ± 34 (18)	NR	NR	NR	NR	NR
9) Pupelis 2001	Hospital 35.3 ± 22.9 (30) ICU 13.9 ± 14.6 (30)	Hospital 35.8 ± 32.5 (30) ICU 16 ± 20.5 (30)	NR	NR	NR	NR	Total kcals received 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	Hospital 10.6 ICU 1.6	Hospital 10.7 ICU 2.10	NR	NR	NR	NR	% Patients receiving > 1500 calories post-op day 4 65% 0% p <0.001 % Patients receiving > 2500 calories post-op day 8 84% 0% p<0.001

Study	LOS days Early EN delayed	Ventilator days Early EN delayed	Cost Early EN delayed	Other Early EN delayed	Study	LOS days Early EN delayed	Ventilator days Early EN delayed
12) Peck 2004	Hospital 60 ± 44 (14) ICU 40 ± 32 (14)	Hospital 60 ± 38 (13) ICU 37 ± 33 (13)	32 ± 27 (14)	23 ± 26 (13)	NR	NR	Mean Calorie Intake 2234 2207 Mean calorie intake change per 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	13.7 ± 7.1	NR	NR	Mean Calorie Intake from day 0-4 2894 ± 198 0

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)

Figure 1

Review: Early Enteral Nutrition vs. delayed nutrient intake
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 01 Mortality

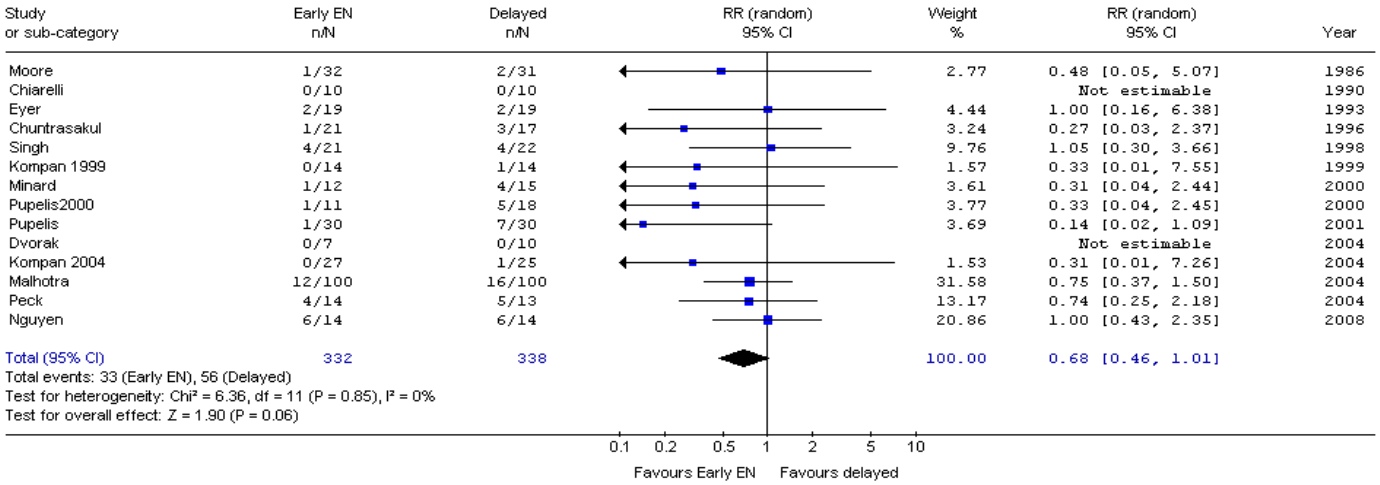


Figure 2. Subgroup analysis: Studies comparing early EN vs. IV fluids/no EN

Review: Early Enteral Nutrition vs. delayed nutrient intake
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 01 Mortality

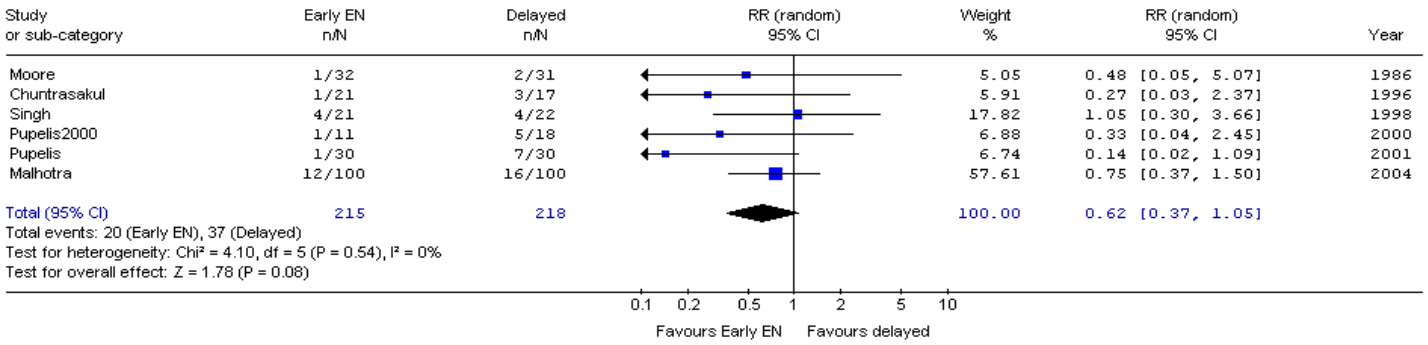


Figure 3. Subgroup analysis: Studies comparing early EN vs. delayed EN

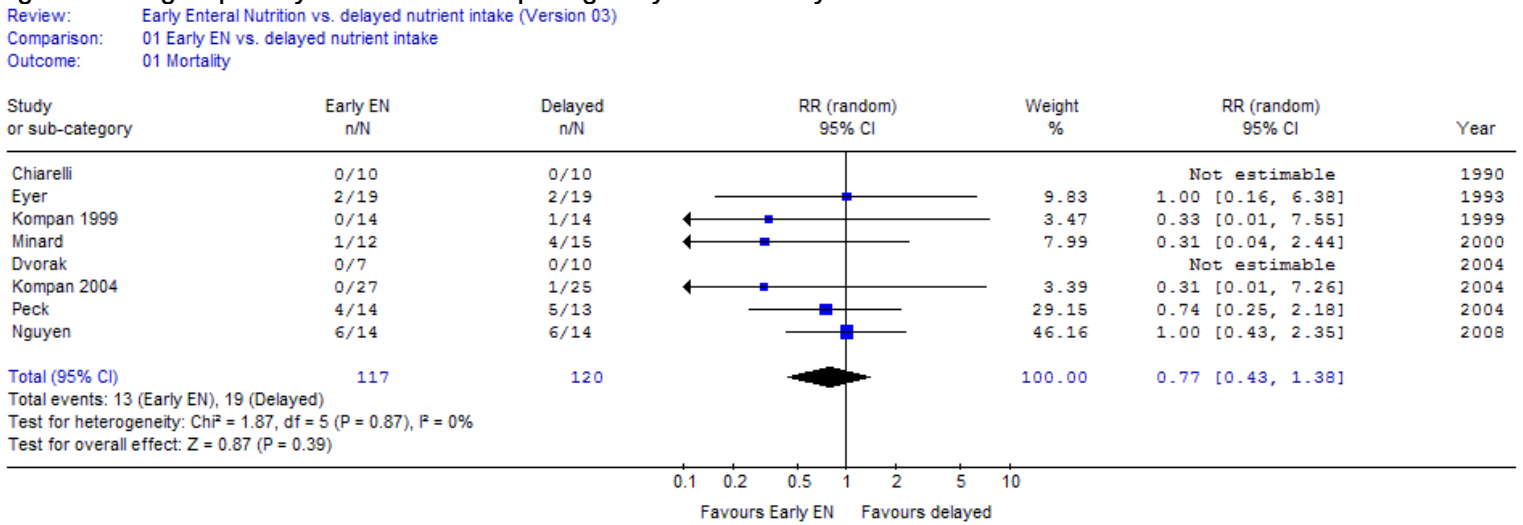


Figure 4.

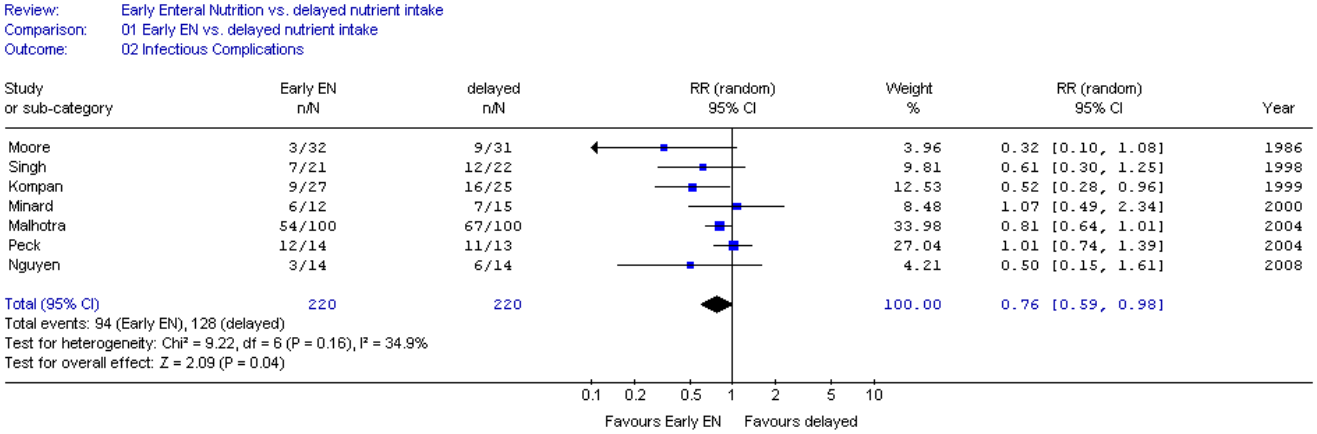
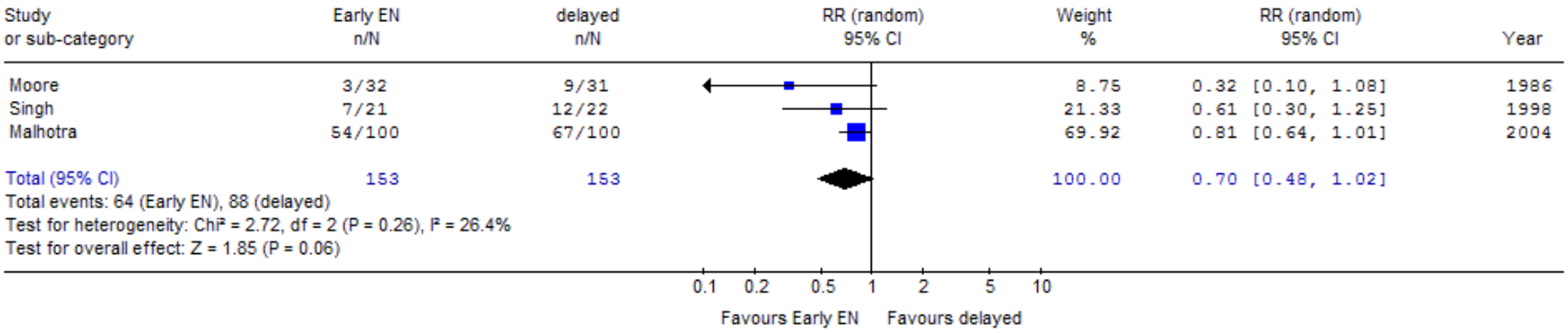


Figure 5. Subgroup analysis: Studies comparing early EN vs. IV fluids/no EN

Review: Early Enteral Nutrition vs. delayed nutrient intake (Version 03)
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 02 Infectious Complications



NEW Figure 6. Subgroup analysis: Studies comparing early EN vs. delayed EN

Review: Early Enteral Nutrition vs. delayed nutrient intake (Version 03)
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 02 Infectious Complications

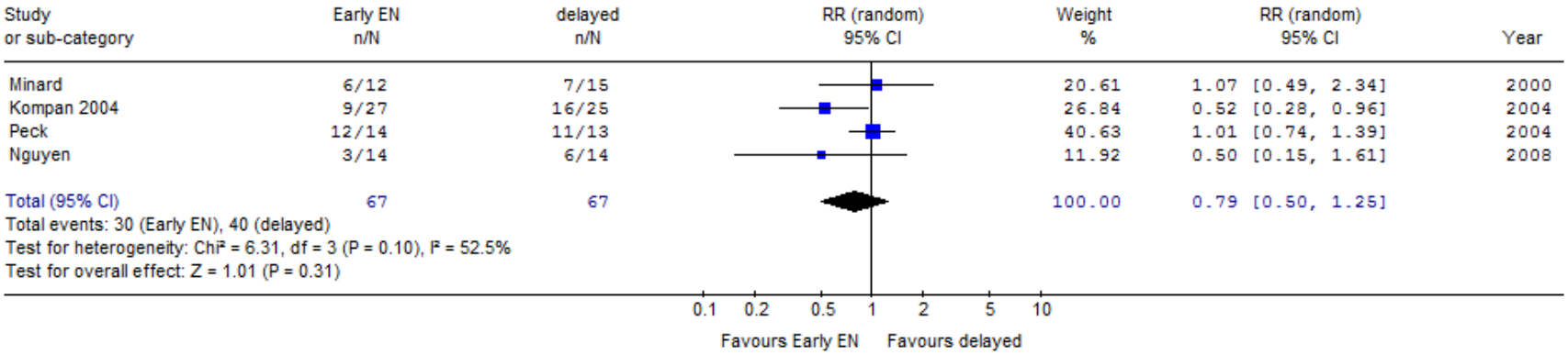


Figure 7

Review: Early Enteral Nutrition vs. delayed nutrient intake
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 03 ICU LOS

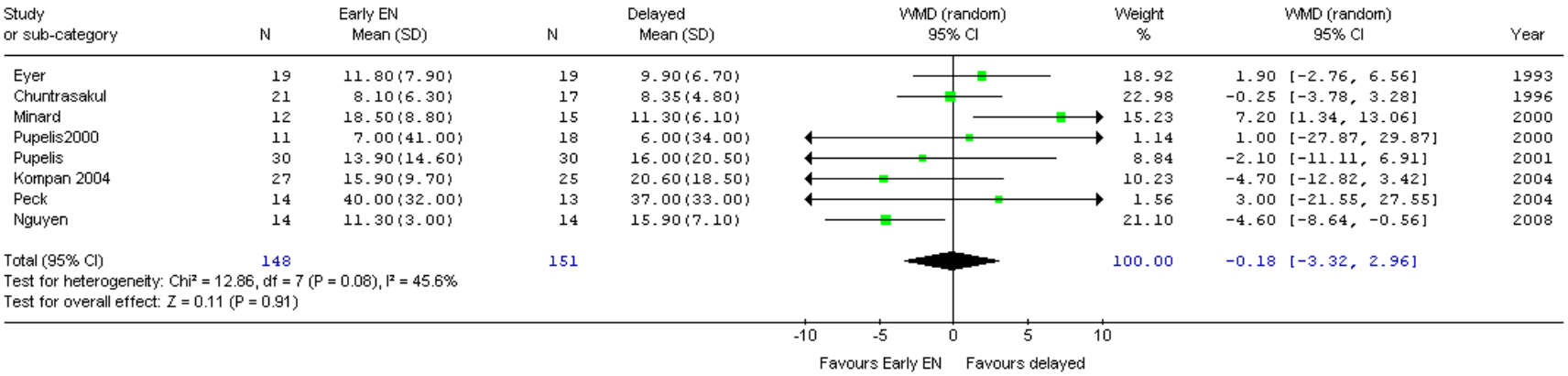


Figure 8.

Review: Early Enteral Nutrition vs. delayed nutrient intake
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 04 Hospital LOS

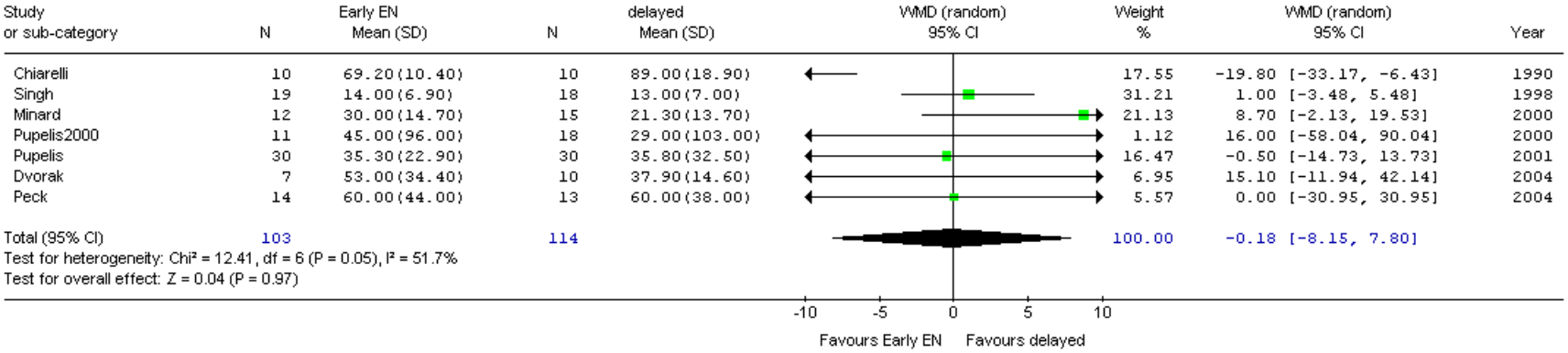
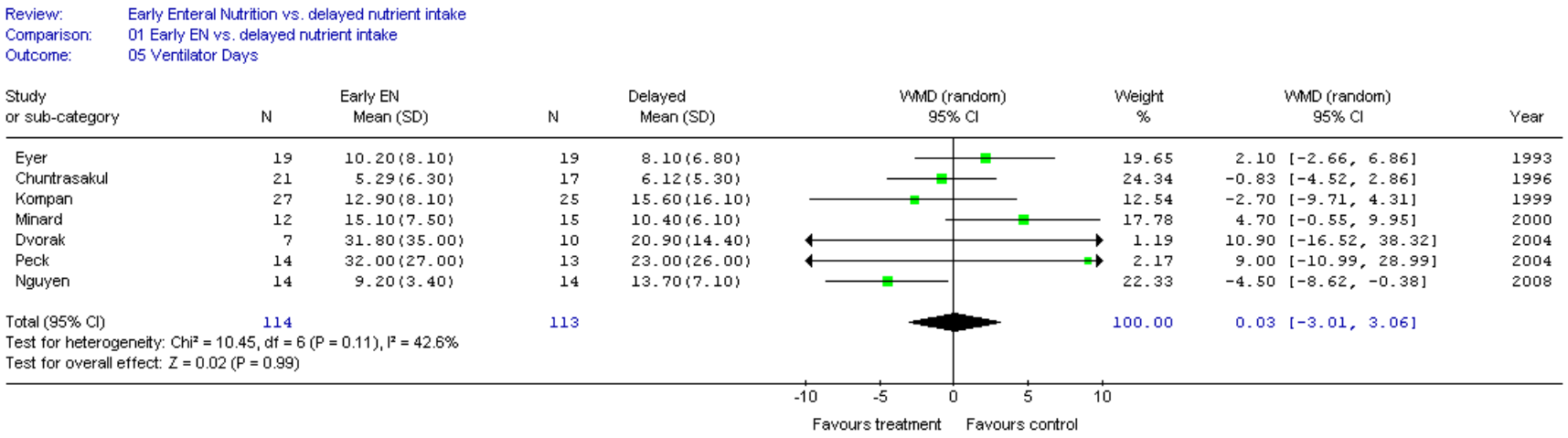


Figure 9.


Review: Early Enteral Nutrition vs. delayed nutrient intake
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 05 Ventilator Days
Study or sub-category
N
Early EN Mean (SD)
N
Delayed Mean (SD)
WMD (random) 95% CI
Weight %
WMD (random) 95% CI
Year
Eyer 19 10.20(8.10) 19 8.10(6.80) 19.65 2.10 [-2.66, 6.86] 1993
Chuntrasakul 21 5.29(6.30) 17 6.12(5.30) 24.34 -0.83 [-4.52, 2.86] 1996
Kompan 27 12.90(8.10) 25 15.60(16.10) 12.54 -2.70 [-9.71, 4.31] 1999
Minard 12 15.10(7.50) 15 10.40(6.10) 17.78 4.70 [-0.55, 9.95] 2000
Dvorak 7 31.80(35.00) 10 20.90(14.40) 1.19 10.90 [-16.52, 38.32] 2004
Peck 14 32.00(27.00) 13 23.00(26.00) 2.17 9.00 [-10.99, 28.99] 2004
Nguyen 14 9.20(3.40) 14 13.70(7.10) 22.33 -4.50 [-8.62, -0.38] 2008
Total (95% CI) 114 113 100.00 0.03 [-3.01, 3.06]
Test for heterogeneity: Chi² = 10.45, df = 6 (P = 0.11), I² = 42.6%
Test for overall effect: Z = 0.02 (P = 0.99)
-10
-5
0
5
10
Favours treatment
Favours control

TOPIC: 2.0 Early Vs Delayed Nutrient Intake

Article inclusion log
Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill human patients (no elective surgery.)
Intervention: EN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

	Author	Journal	I	E	Why Rejected
1	Ryan	Am Surg 1981		√	Elective surgery pts
2	Seri	Ital J Surg Sci 1984		√	Not ICU pts
3	Moore	J Trauma 1986	√		
4	Grahm	Neurosurgery 1989		√	Pseudorandomized
5	Jones	Crit Care Med 1989		√	No clinical outcomes
6	Moore	J Trauma 1989		√	Surgery pts
7	Chiarelli	Am J Clin Nutr 1990	√		
8	Schroeder	JPEN 1991		√	Elective surgery pts
9	The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group	N Engl J Med 1991		√	Elective surgery pts
10	Eyer	J Trauma 1993	√		
11	Binderow	Dis Colon Rectum		√	Elective surgery pts
12	Jenkins	J Burn Care Rehab 1994		√	Paediatric population
13	Braga	Infusionther Tran 1995		√	Elective surgery pts
14	Hasse	JPEN 1995		√	Elective surgery pts
15	Seenu	Trop Gastroenterol 1995		√	Elective surgery pts
16	Reissman	Annals of Surgery 1995		√	Elective surgery pts
17	Beier-Holgersen R	Gut 1996		√	Not ICU patients
18	Carr	BMJ 1996		√	Elective surgery pts
19	Chuntrasakul	J Med Assoc Thai 1996	√		
20	Ortiz	Int J Colorectal Dis 1996		√	Elective surgery pts
21	Hartsell	Arch Surg 1997		√	Elective surgery pts
22	Heslin	Annals of Surgery 1997		√	Cancer pts
23	Schilder	Gynecol Oncol 1997		√	Elective surgery pts
24	Watters	Annals of Surgery 1997		√	Elective surgery pts
25	Wang	Zhonghua Zheng Xing Shao Syhang Wai Ke Za Zhi		√	Unclear if ICU pts, No clinical outcomes
26	McCarter	Am J Gast 1998		√	Not ICU pts
27	Schwenk	Langenbecks Arch Surg 1998		√	Elective surgery
28	Singh	J Am Coll Surg 1998	√		
29	Stewart	Aus NZ J Surg 1998		√	Elective surgery pts
30	Zaloga	Crit Care Med 1999		√	Not RCT, review
31	Taylor	Crit Care Med 1999	√		
32	Kompan	Intensive Care Med 1999	√		

33	Beattie	Gut 2000		√	Elective surgery pts
34	Minard	JPEN J Parenter Enteral Nutr 2000	√		
35	Pupelis	Eur J Surg 2000	√		
36	Lewis	BMJ 2001		√	Systematic review, ICU studies included
37	Marik	Crit Care Med 2001		√	Meta-analysis, ICU studies included
38	Peng	Burns 2001		√	No clinical outcomes
39	Pupelis	Nutrition 2001	√		
40	Soliani	Chir Ital 2001		√	Elective surgery/cancer pts
41	de Aguilar-Nascimento	Rev Assoc Med Bras 2002		√	Elective surgery
42	Ibrahim	JPEN 2002		√	Pseudorandomized
43	Dvorak	Spine 2004	√		
44	Feo	ANZ J Surg 2004		√	Elective surgery pts
45	Kompan	Clin Nutr 2004	√		
46	Malhotra	J Postgrad Med 2004	√		
47	Peck	J Trauma 2004	√		
48	Kaur	World J Surg 2005		√	Not ventilated patients as confirmed by authors
49	Andersen	The Cochrane Collaboration 2006		√	Systematic review, Individual studies looked at
50	Wasiak	The Cochrane Collaboration 2006		√	Systematic review, Individual studies looked at
51	Wasiak	J Hum Nutr Diet 2007		√	Systematic review, Individual studies looked at
52	Nguyen	Crit Care Med 2008	√		

I = included, E = excluded

References

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