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 18 randomized controlled trials (level 2 studies) comparing early enteral nutrition (EN) vs. delayed nutrient intake (i.e., delayed EN, parenteral nutrition [PN] or oral diet). In all the trials except one, EN in the intervention group was started within 24-48 hours of admission/resuscitation. There were 11 studies comparing early vs. delayed EN and 7 studies where early EN was compared to no EN/IV fluids.

Mortality: When the data from the 18 studies that looked at the effect of early EN on mortality were aggregated, when compared to delayed nutrient intake, early EN was associated with a trend towards a reduction in mortality (RR 0.71, 95% CI 0.51, 1.00, p=0.05, 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 0.79, 95% CI 0.51, 1.24, p=0.30, heterogeneity I^2=0%; figure 1). The difference between the two subgroups was not significant (p=0.4; 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 EN 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: Seventeen studies looked at LOS (7 reported on ICU LOS only, 4 reported on hospital LOS only and 6 reported on both ICU and hospital LOS). When the results were meta-analyzed, early EN had no effect on ICU stay (WMD -1.22, 95% CI -3.52, 1.07, p=0.30, heterogeneity I^2=44%; figure 3) or hospital length of stay (WMD -1.34, 95% CI -7.69, 5.02 p = 0.68, heterogeneity I^2=51%; figure 4). A total of 9 studies reported on ventilator days and based on the aggregated data from 8 of these studies was aggregated, there were no significant differences between the early vs. delayed fed groups (WMD -0.75, 95% CI -3.15, 1.65, p =0.54, heterogeneity I^2=47%; figure 5).

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

Conclusions:

1) Early enteral nutrition compared to delayed nutrient intake may be associated with a trend towards a reduction in mortality in critically ill patients.
2) Early enteral nutrition compared to delayed nutrient intake is associated with a significant reduction in infectious complications.
3) Early enteral nutrition compared to delayed nutrient intake has no effect on ICU or hospital length of stay.
4) Early enteral nutrition compared to delayed nutrient intake is associated with improved 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 # (%)† 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) positive blood cultures	7/10 (70) positive 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	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	3/29 (10)	3/30 (10)	14/29 (48)	15/30 (50)

	N=59		kcals/day vs.EN post tracheostomy placement + IV glucose				
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)
17) Ostadrahimi 2016	Burn pts with TBSA 20-90% N=41	C.Random: No ITT: No Blinding: No (6)	Early enteral feeding within the first hour of admission, reaching goal EN by day 3 vs hospital routine diet ad libitum (liquid food for 2 days after injury followed by chow diet)	**2-Day Hospital** 3/21 (14.3%)	**2-Day Hospital** 4/20 (20%)	NR	NR
18) Sun 2019	Septic patients admitted to ICU N=56	C.Random: Yes ITT: No Blinding: No (7)	Early enteral feeding within 24-48 hrs post admission vs. delayed feeding starting 4 days post admission. Both received peptide based then whole protein formula starting at 15-20 ml/hr, increasing by 15-20 ml q 6-8 hrs. Parenteral nutrition was used to supplement enteral nutrition if intake was <60% after day 7	**28 day** 4/26 (15.4%)	**28 day** (6/27 (22.2%)	NR	NR

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

Study	LOS days Early EN	LOS days Delayed	Ventilator days Early EN	Ventilator days Delayed	Other Early EN	Other Delayed
1) Moore 1986	NR	NR	NR	NR	**Complications** 14/32 (44) **Feed Intolerance** 12/32 (38)	**Complications** 15/31 (48) **Feed Intolerance** NR
2) Chiarelli 1990	**Hospital** 69.2 ± 10.4 (10)	**Hospital** 89 ± 18.9 (10)	NR	NR	**Days to positive Nitrogen Balance** 8.8 ± 4.1 p<0.05 **Intestinal Complications** 2/10 (20)	**Days to positive Nitrogen Balance** 24.1 ± 6.9 **Intestinal Complications** 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)	**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)	**Calorie Intake (kcal/kg/day)** 19 ± 5 **Protein Intake (gm/kg/day)** 0.9 ± 0.2 **Organ System Failure** 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)	**Calories Received in Week 1** 1885.2 ± 38.3 **Calories Received in Week 2** 1850.3 ± 248.4	**Calories Received in Week 1** 633.4 ± 83.7 **Calories Received in Week 2** 717.31 ± 142
5) Singh 1998	**Hospital** 14 ± 6.9 (19)	**Hospital** 13 ± 7.0 (18)	NR	NR	**Complications** 11/21 (52) **Calorie Intake by Day 7** 2610 ± 337 **Nitrogen Balance by Day 7** 5.1 ± 0.7	**Complications** 13/22 (59) **Calorie Intake by Day 7** 516 ± 156 **Nitrogen Balance by Day 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)	**EN Received on Day 4 (mls)** 1340 ± 473 p=0.009	**EN Received on Day 4 (mls)** 703 ± 701
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)	**Calorie Intake** 1509 ± 45 p< 0.02 **Feed Infusion Complications** 22/12	**Calorie Intake** 1174 ± 425 **Feed Infusion Complications** 28/15

8) Pupelis 2000	**ICU** 7 ± 41 (11) **Hospital** 45 ± 96 (11)	**ICU** 6 ± 34 (18) **Hospital** 29 ± 103 (18)	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	**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)	**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	**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)	**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	**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)	**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)	**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	**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
17) Ostadrahimi 2016	**Hospital** 17.64±8.2 (15)	**Hospital** 23.07±11.89 (15)	NR	NR	NR
18) Sun 2019	**ICU** 8.31 ± 4.26 (26)	**ICU** 11.22 ± 5.43 (27)	4.5 ± 2.58 (26)	7.15 ± 3.95 (27)	**Albumin levels on Day 7** 33.51 ± 3.75 31.47 ±3.82 **Number on CRRT** 4/26 (15.4%) 3/27 (11.1%)

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

	Early EN		Delayed/None			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
1.1.1 EN vs IV Fluids/No EN							
Moore 1986	1	32	2	31	2.1%	0.48 [0.05, 5.07]	1986
Chuntrasakul 1996	1	21	3	17	2.5%	0.27 [0.03, 2.37]	1996
Singh 1998	4	21	4	22	7.4%	1.05 [0.30, 3.66]	1998
Pupelis 2000	1	11	5	18	2.9%	0.33 [0.04, 2.45]	2000
Pupelis 2001	1	30	7	30	2.8%	0.14 [0.02, 1.09]	2001
Malhotra 2004	12	100	16	100	24.0%	0.75 [0.37, 1.50]	2004
Subtotal (95% CI)		**215**		**218**	**41.6%**	**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 1990	0	10	0	10		Not estimable	1990
Eyer 1993	2	19	2	19	3.4%	1.00 [0.16, 6.38]	1993
Kompan 1999	0	14	1	14	1.2%	0.33 [0.01, 7.55]	1999
Minard 2000	1	12	4	15	2.7%	0.31 [0.04, 2.44]	2000
Kompan 2004	0	27	1	25	1.2%	0.31 [0.01, 7.26]	2004
Dvorak 2004	0	7	0	10		Not estimable	2004
Peck 2004	4	14	5	13	10.0%	0.74 [0.25, 2.18]	2004
Nguyen 2008	6	14	6	14	15.8%	1.00 [0.43, 2.35]	2008
Moses 2009	3	29	3	30	5.0%	1.03 [0.23, 4.71]	2009
Chourdakis 2012	3	34	2	25	4.0%	1.10 [0.20, 6.12]	2012
Ostradrahimi 2016	3	21	4	20	6.2%	0.71 [0.18, 2.80]	2016
Sun 2019	4	26	6	27	8.8%	0.69 [0.22, 2.18]	2019
Subtotal (95% CI)		**227**		**222**	**58.4%**	**0.79 [0.51, 1.24]**	
Total events	26		34				
Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 9 (P = 0.99); I² = 0%							
Test for overall effect: Z = 1.03 (P = 0.30)							
Total (95% CI)		**442**		**440**	**100.0%**	**0.71 [0.51, 1.00]**	
Total events	46		71				
Heterogeneity: Tau² = 0.00; Chi² = 6.80, df = 15 (P = 0.96); I² = 0%							
Test for overall effect: Z = 1.93 (P = 0.05)							
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.49), I² = 0%							

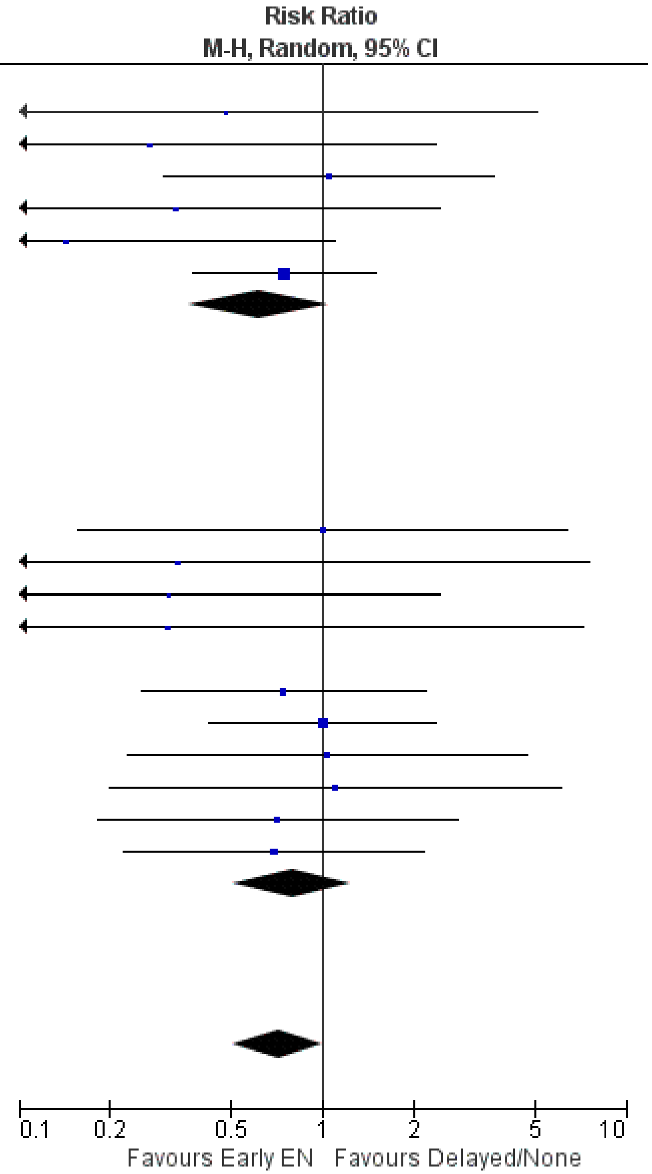


Figure 2. Studies comparing early EN vs delayed nutrient intake: Infectious complications

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%							

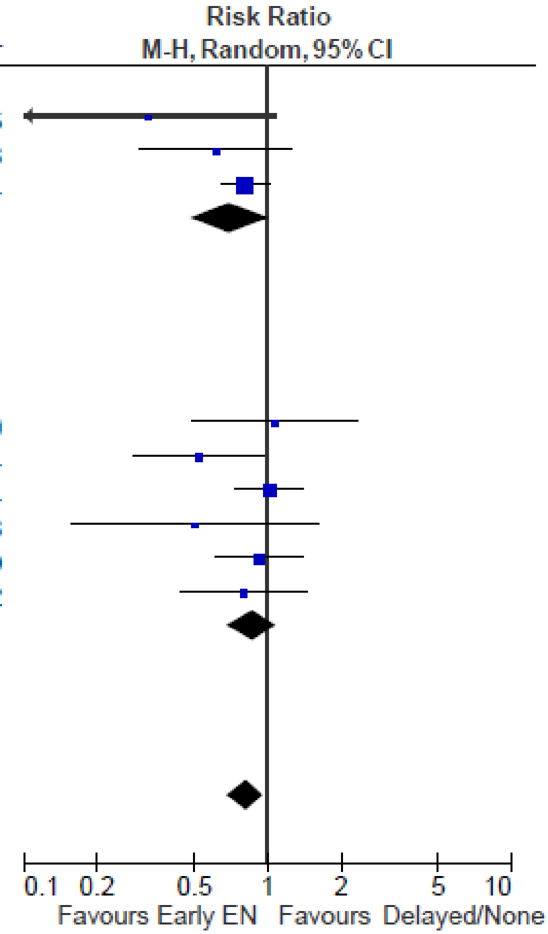


Figure 3. Studies comparing early EN vs delayed nutrient intake: ICU LOS

	Early EN			Delayed/None				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Eyer 1993	11.8	7.9	19	9.9	6.7	19	12.7%	1.90 [-2.76, 6.56]	1993
Chuntrasakul 1996	8.1	6.3	21	8.35	4.8	17	16.4%	-0.25 [-3.78, 3.28]	1996
Minard 2000	18.5	8.8	12	11.3	6.1	15	9.8%	7.20 [1.34, 13.06]	2000
Pupelis 2000	7	41	11	6	34	18	0.6%	1.00 [-27.87, 29.87]	2000
Pupelis 2001	13.9	14.6	30	16	20.5	30	5.2%	-2.10 [-11.11, 6.91]	2001
Peck 2004	40	32	14	37	33	13	0.8%	3.00 [-21.55, 27.55]	2004
Kompan 2004	15.9	9.7	27	20.6	18.5	25	6.2%	-4.70 [-12.82, 3.42]	2004
Nguyen 2008	11.3	3	14	15.9	7.1	14	14.7%	-4.60 [-8.64, -0.56]	2008
Chourdakis 2012	24.8	7.6	34	28.5	8.9	25	13.7%	-3.70 [-8.02, 0.62]	2012
Sun 2019	8.31	4.26	26	11.22	5.43	27	19.9%	-2.91 [-5.53, -0.29]	2019
Total (95% CI)			**208**			**203**	**100.0%**	**-1.22 [-3.52, 1.07]**	

Heterogeneity: Tau² = 5.12; Chi² = 16.12, df = 9 (P = 0.06); I² = 44%
Test for overall effect: Z = 1.04 (P = 0.30)

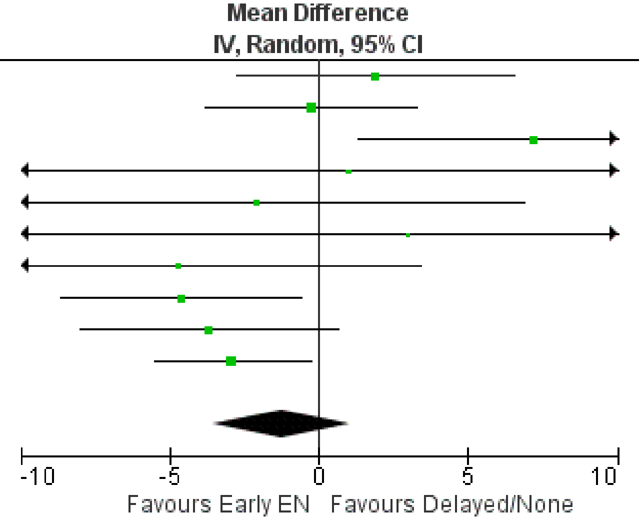


Figure 4. Studies comparing early EN vs delayed nutrient intake: Hospital LOS

	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	13.1%	-19.80 [-33.17, -6.43]	1990
Singh	14	6.9	19	13	7	18	27.1%	1.00 [-3.48, 5.48]	1998
Minard	30	14.7	12	21.3	13.7	15	16.4%	8.70 [-2.13, 19.53]	2000
Pupelis 2000	45	96	11	29	103	18	0.7%	16.00 [-58.04, 90.04]	2000
Pupelis 2001	35.3	22.9	30	35.8	32.5	30	12.2%	-0.50 [-14.73, 13.73]	2001
Peck	60	44	14	60	38	13	3.7%	0.00 [-30.95, 30.95]	2004
Dvorak	53	34.4	7	37.9	14.6	10	4.7%	15.10 [-11.94, 42.14]	2004
Ostradrahimi	17.64	8.2	15	23.07	11.89	15	22.1%	-5.43 [-12.74, 1.88]	2016
Total (95% CI)			**118**			**129**	**100.0%**	**-1.34 [-7.69, 5.02]**	

Heterogeneity: Tau² = 33.62; Chi² = 14.40, df = 7 (P = 0.04); I² = 51%
Test for overall effect: Z = 0.41 (P = 0.68)

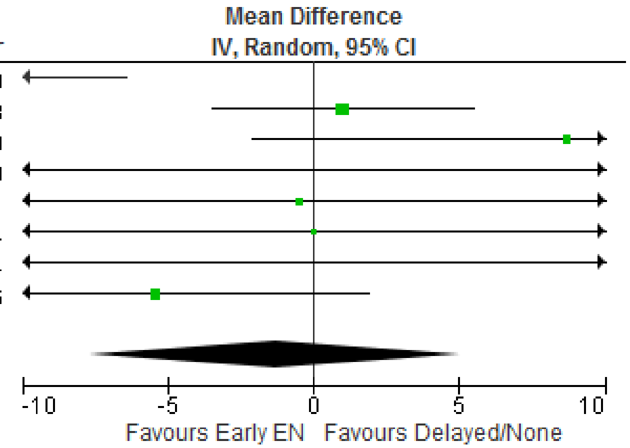
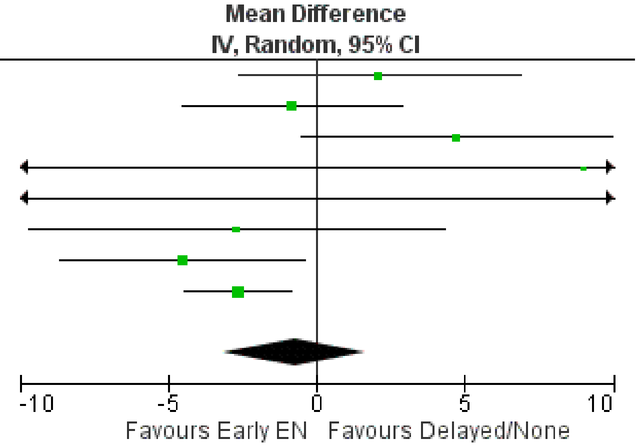


Figure 5. Studies comparing early EN vs delayed nutrient intake: Ventilator days

	Early EN			Delayed/None				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Eyer 1993	10.2	8.1	19	8.1	6.8	19	14.3%	2.10 [-2.66, 6.86]	1993
Chuntrasakul 1996	5.29	6.3	21	6.12	5.3	17	18.3%	-0.83 [-4.52, 2.86]	1996
Minard 2000	15.1	7.5	12	10.4	6.1	15	12.7%	4.70 [-0.55, 9.95]	2000
Peck 2004	32	27	14	23	26	13	1.4%	9.00 [-10.99, 28.99]	2004
Dvorak 2004	31.8	35	7	20.9	14.4	10	0.7%	10.90 [-16.52, 38.32]	2004
Kompan 2004	12.9	8.1	27	15.6	16.1	25	8.6%	-2.70 [-9.71, 4.31]	2004
Nguyen 2008	9.2	3.4	14	13.7	7.1	14	16.6%	-4.50 [-8.62, -0.38]	2008
Sun 2019	4.5	2.58	26	7.15	3.95	27	27.4%	-2.65 [-4.44, -0.86]	2019
Total (95% CI)			**140**			**140**	**100.0%**	**-0.75 [-3.15, 1.65]**	

Heterogeneity: $Tau^2 = 4.64$; $Chi^2 = 13.22$, df = 7 (P = 0.07); $I^2 = 47\%$
Test for overall effect: Z = 0.61 (P = 0.54)



References

Included Studies

1. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma—a prospective, randomized study. J Trauma. 1986 Oct;26(10):874-81.
2. Chiarelli A, Enzi G, Casadei A, Baggio B, Valerio A, Mazzoleni F. Very early nutrition supplementation in burned patients. Am J Clin Nutr. 1990 Jun;51(6):1035-9.
3. Eyer SD, Micon LT, Konstantinides FN, Edlund DA, Rooney KA, Luxenberg MG,Cerra FB. Early enteral feeding does not attenuate metabolic response after blunt trauma. J Trauma. 1993 May;34(5):639-43.
4. Chuntrasakul C, Siltharm S, Chinswangwatanakul V, Pongprasobchai T, Chockvivatanavanit S, Bunnak A. Early nutritional support in severe traumatic patients. J Med Assoc Thai 1996 Jan; 79(1):21-6.
5. Singh G, Ram RP, Khanna SK. Early post-operative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. J Am Coll Surg. 1998 Aug;187(2):142-6.
6. Kompan L, Kremzar B, Gadzijev E, Prosek M. Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury.Intensive Care Med. 1999 Feb;25(2):157-61.
7. Minard G, Kudsk KA, Melton S, Patton JH, Tolley EA. Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries.JPEN J Parenter Enteral Nutr. 2000 May-Jun;24(3):145-9.
8. Pupelis G, Austrums E, Jansone A, Sprucs R, Wehbi H. Randomised trial of safety and efficacy of postoperative enteral feeding in patients with severe pancreatitis: preliminary report. Eur J Surg 2000;166(5):383-7.
9. Pupelis G, Selga G, Austrums E, Kaminski A. Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. Nutrition. 2001 Feb;17(2):91-4.
10. Dvorak MF, Noonan VK, Belanger L, Bruun B, Wing PC, Boyd MC, Fisher C. Early versus late enteral feeding in patients with acute cervical spinal cord injury: a pilot study. Spine. 2004 May 1;29(9):E175-80.
11. Kompan L, Vidmar G, Spindler-Vesel A, Pecar J. Is early enteral nutrition a risk factor for gastric intolerance and pneumonia? Clin Nutr. 2004 Aug;23(4):527-32.
12. Malhotra A, Mathur AK, Gupta S. Early enteral nutrition after surgical treatment of gut perforations: a prospective randomised study. J Postgrad Med. 2004 Apr-Jun;50(2):102-6.
13. Peck MD, Kessler M, Cairns BA, Chang YH, Ivanova A, Schooler W. Early enteral nutrition does not decrease hypermetabolism associated with burn injury. J Trauma. 2004 Dec;57(6):1143-9.
14. Nguyen NQ, Fraser RJ, Bryant LK, Burgstad C, Chapman MJ, Bellon M, Wishart J, Holloway RH, Horowitz M. The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critcally ill patients. Crit Care Med 2008;36(5):1655-6.
15. Moses V, Mahendri NV, John G, Peter JV, Ganesh A. Early hypocaloric enteral nutritional supplementation in acute organophosphate poisoning--a prospective randomized trial. Clin Toxicol (Phila). 2009 May;47(5):419-24.
16. Chourdakis M, Kraus MM, Tzellos T, Sardeli C, Peftoulidou M, Vassilakos D, et al. Effect of early compared with delayed enteral nutrition on endocrine function in patients with traumatic brain injury: an open-labeled randomized trial. JPEN Journal of parenteral and enteral nutrition. 2012;36(1):108-16.
17. Ostadrahimi A, Nagili B, Asghari-Jafarabadi M, Beigzali S, Zalouli H, Lak S. A proper enteral nutrition support improves sequential organ failure score and decreases length of stay in hospital in burned patients. Iranian Red Crescent Medical Journal. 2016 Feb;18(2)
18. Sun JK, Zhang WH, Chen WX, Wang X, Mu XW. Effects of early enteral nutrition on Th17/Treg cells and IL-23/IL-17 in septic patients. World J Gastroenterol. 2019 Jun 14;25(22):2799-2808. doi: 10.3748/wjg.v25.i22.2799. PMID: 31236002; PMCID: PMC6580355.

Excluded Studies	Reasons
Ryan JA Jr, Page CP, Babcock L. Early postoperative jejunal feeding of elemental diet in gastrointestinal surgery. Am Surg. 1981 Sep;47(9):393-403.	Elective surgery patients
Seri S, Aquilio E. Effects of early nutritional support in patients with abdominal trauma. Ital J Surg Sci. 1984;14(3):223-7.	Not ICU patients
Grahm TW, Zadrozny DB, Harrington T. The benefits of early jejunal hyperalimentation in the head-injured patient. Neurosurgery 1989 Nov;25(5):729-35.	Pseudo-randomized
Jones TN, Moore FA, Moore EE, McCroskey BL. Gastrointestinal symptoms attributed to jejunostomy feeding after major abdominal trauma – a critical analysis. Crit Care Med 1989 Nov;17(11):1146-50.	No clinical outcomes
Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma--reduced septic morbidity. J Trauma. 1989 Jul;29(7):916-22; discussion 922-3.	Surgery patients
Schroeder D, Gillanders L, Mahr K, Hill GL. Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. JPEN J Parenter Enteral Nutr. 1991 Jul-Aug;15(4):376-83.	Elective surgery patients
The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med. 1991 Aug 22;325(8):525-32.	Elective surgery patients
Binderow SR, Cohen SM, Wexner SD, Nogueras JJ. Must early postoperative oral intake be limited to laparoscopy? Dis Colon Rectum. 1994 Jun;37(6):584-9.	Elective surgery patients
Jenkins ME, Gottschlich MM, Warden GD. Enteral feeding during operative procedures in thermal injuries. J Burn Care Rehabil 1994 Mar-Apr;15(2):199-205.	Pediatric population
Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Di Carlo V. Benefits of early postoperative enteral feeding in cancer patients. Infusionsther Transfusionsmed 1995 Oct;22(5):280-4.	Elective surgery patients
Brown DN, Miedema BW, King PD, Marshall JB. Safety of early feeding after percutaneous endoscopic gastrostomy. J Clin Gastroenterol. 1995 Dec;21(4):330-1.	Elective surgery patients
Hasse JM, Blue LS, Liepa GU, Goldstein RM, Jennings LW, Mor E, Husberg BS, Levy MF, Gonwa TA, Klintmalm GB. Early enteral nutrition support in patients undergoing liver transplantation. JPEN J Parenter Enteral Nutr. 1995 Nov-Dec;19(6):437-43.	Elective surgery patients
Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. Ann Surg. 1995 Jul;222(1):73-7.	Elective surgery patients
Seenu V, Goel AK. Early oral feeding after elective colorectal surgery: is it safe. Trop Gastroenterol. 1995 Oct-Dec;16(4):72-3.	Elective surgery patients
Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut 1996;39(6):833-5.	Surgery patients
Carr CS, Ling KD, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. BMJ. 1996 Apr 6;312(7035):869-71.	Elective surgery patients
Choudhry U, Barde CJ, Markert R, Gopalswamy N. Percutaneous endoscopicgastrostomy: a randomized prospective comparison of early and delayed feeding. Gastrointest Endosc. 1996 Aug;44(2):164-7. PubMed PMID: 8858322.	Elective surgery patients
Ortiz H, Armendariz P, Yarnoz C. Is early postoperative feeding feasible in elective colon and rectal surgery? Int J Colorectal Dis. 1996;11(3):119-21.	Elective surgery patients
Hartsell PA, Frazee RC, Harrison JB, Smith RW. Early postoperative feeding after elective colorectal surgery. Arch Surg. 1997 May;132(5):518-20; discussion 520-1.	Elective surgery patients
Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, Shike M, Brennan MF. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg. 1997 Oct;226(4):567-77.	Not ICU patients
Schilder JM, Hurteau JA, Look KY, Moore DH, Raff G, Stehman FB, Sutton GP. A prospective controlled trial of early postoperative oral intake following major abdominal gynecologic surgery. Gynecol Oncol. 1997 Dec;67(3):235-40.	Elective surgery patients
Wang S, Wang S, Li A. [A clinical study of early enteral feeding to protect the gut function in burned patients] [Article in Chinese]. Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi. 1997 Jul;13(4):267-71.	Unclear if ICU patients; No clinical outcomes
Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respiratory mechanics and	Elective surgery patients

decreased mobility. Ann Surg. 1997 Sep;226(3):369-77	
McCarter TL, Condon SC, Aguilar RC, Gibson DJ, Chen YK. Randomized prospective trial of early versus delayed feeding after percutaneous endoscopic gastrostomy placement. Am J Gastroenterol. 1998 Mar;93(3):419-21.	Not ICU patients
Stein J, Schulte-Bockholt A, Sabin M, Keymling M. A randomized prospective trial of immediate vs. next-day feeding after percutaneous endoscopic gastrostomy in intensive care patients. Intensive Care Med. 2002;28(11):1656-1660. doi:10.1007/s00134-002-1473-5	Not ICU patients
Schwenk W, Böhm B, Haase O, Junghans T, Müller JM. Langenbecks. Laparoscopic versus conventional colorectal resection: a prospective randomised study of postoperative ileus and early postoperative feeding. Arch Surg. 1998 Mar;383(1):49-55.	Elective surgery patients
Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomized trial. Aust N Z J Surg. 1998 Feb;68(2):125-8.	Elective surgery patients
Beier-Holgersen R, Brandstrup B. Influence of early postoperative enteral nutrition versus placebo on cell-mediated immunity, as measured with the Multitest CMI. Scand J Gastroenterol. 1999 Jan;34(1):98-102. PubMed PMID: 10048740.	Elective surgery patients
Zaloga GP. Early enteral nutritional support improves outcome: hypothesis or fact? Crit Care Med 1999 Feb;27(2):259-61.	Review paper
Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut. 2000 Jun;46(6):813-8.	Elective surgery patients
Powell JJ, Murchison JT, Fearon KC, Ross JA, Siriwardena AK. Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. Br J Surg. 2000 Oct;87(10):1375-81. PubMed PMID: 11044164.	EN vs no nutrition
Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ. 2001 Oct 6;323(7316):773-6.	Meta-analysis
Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med 2001 Dec;29(12):2264-70.	Meta-analysis
Peng YZ, Yuan ZQ, Xiao GX.Burns. Effects of early enteral feeding on the prevention of enterogenic infection in severely burned patients. 2001 Mar;27(2):145-9.	No clinical outcomes
Soliani P, Dell'Abate P, Del Rio P, Arcuri MF, Salsi P, Cortellini P, Sianesi M. [Early enteral nutrition in patients treated with major surgery of the abdomen and the pelvis] [Article in Italian] Chir Ital. 2001 Sep-Oct;53(5):619-32.	Elective surgery patients
de Aguilar-Nascimento JE, Göelzer J. [Early feeding after intestinal anastomoses: risks or benefits?] [Article in Portuguese] Rev Assoc Med Bras. 2002 Oct-Dec;48(4):348-52.	Elective surgery patients
Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V, Kollef MH. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. JPEN J Parenter Enteral Nutr. 2002 May-Jun;26(3):174-81.	Pseudo-randomized
Page RD, Oo AY, Russell GN, Pennefather SH. Intravenous hydration versus naso-jejunal enteral feeding after esophagectomy: a randomised study. Eur J Cardiothorac Surg. 2002 Nov;22(5):666-72. PubMed PMID: 12414028.	Not ICU patients
Zhao G, Wang CY, Wang F, Xiong JX. Clinical study on nutrition support in patients with severe acute pancreatitis. World J Gastroenterol. 2003 Sep;9(9):2105-8.	Not early vs delayed EN
Feo CV, Romanini B, Sortini D, Ragazzi R, Zamboni P, Pansini GC, Liboni A. Early oral feeding after colorectal resection: a randomized controlled study. ANZ J Surg. 2004 May;74(5):298-301.	Elective surgery patients
Kaur N, Gupta MK, Minocha VR. Early enteral feeding by nasoenteric tubes in patients with perforation peritonitis. World J Surg 2005 Aug;29(8):1023-7.	Not ventilated patients as confirmed by authors
Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004080.	Systematic review
Chen G, Han C. Economic evaluation of early enteral nutrition in severely burned patients. Chinese Journal of Clinical Nutrition. 2006;1:003.	No clinical outcomes
Dong GH, Cai JF, Hao J, Zhong QG, Li YJ. [Effect of early enteral nutrition onimmune function of the patients after operation for severe abdominal trauma]. Zhonghua Wei Chang Wai Ke Za Zhi. 2006 Mar;9(2):145-7. Chinese.	Elective surgery patients
Wasiak J, Cleland H, Jeffery R. Early versus delayed enteral nutrition support for burn injuries. Cochrane Database Syst Rev. 2006 Jul	Systematic review

19;3:CD005489.	
Wasiak J, Cleland H, Jeffery R. Early versus late enteral nutritional support in adults with burn injury: a systematic review. J Hum Nutr Diet. 2007 Apr;20(2):75-83.	Systematic review
Bechtold ML, Matteson ML, Choudhary A, Puli SR, Jiang PP, Roy PK. Early versus delayed feeding after placement of a percutaneous endoscopic gastrostomy: a meta-analysis. Am J Gastroenterol. 2008 Nov;103(11):2919-24.	Meta-analysis
Petrov MS, Pylypchuk RD, Emelyanov NV. Systematic review: nutritional support in acute pancreatitis. Aliment Pharmacol Ther. 2008 Sep 15;28(6):704-12. Review. PubMed PMID: 19145726.	Meta-analysis
Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med. 2009 Dec;35(12):2018-27. Epub 2009 Sep 24. PubMed PMID: 19777207.	Meta-analysis
Lidder PG, Lewis S, Duxbury M, Thomas S. Systematic review of postdischarge oral nutritional supplementation in patients undergoing GI surgery. Nutr Clin Pract. 2009 Jun-Jul;24(3):388-94. Review.	Meta-analysis
Minig L, Biffi R, Zanagnolo V, Attanasio A, Beltrami C, Bocciolone L, Botteri E, Colombo N, Iodice S, Landoni F, Peiretti M, Roviglione G, Maggioni A. Reduction of postoperative complication rate with the use of early oral feeding in gynecologic oncologic patients undergoing a major surgery: a randomized controlled trial. Ann Surg Oncol. 2009 Nov;16(11):3101-10.	Meta-analysis
Minig L, Biffi R, Zanagnolo V, Attanasio A, Beltrami C, Bocciolone L, Botteri E, Colombo N, Iodice S, Landoni F, Peiretti M, Roviglione G, Maggioni A. Early oral versus "traditional" postoperative feeding in gynecologic oncology patients undergoing intestinal resection: a randomized controlled trial. Ann Surg Oncol. 2009 Jun;16(6):1660-8.	Elective surgery patients
Bakker OJ, van Santvoort HC, van Brunschot S, Ahmed Ali U, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Brink MA, Dejong CH, van Geenen EJ, van Goor H, Heisterkamp J, Houdijk AP, Jansen JM, Karsten TM, Manusama ER, Nieuwenhuijs VB, van Ramshorst B, Schaapherder AF, van der Schelling GP, Spanier MB, Tan A, Vecht J, Weusten BL, Witteman BJ, Akkermans LM, Gooszen HG; Dutch Pancreatitis Study Group. Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial. Trials. 2011 Mar 10;12:73.	Study protocol
Barlow R, Price P, Reid TD, Hunt S, Clark GW, Havard TJ, Puntis MC, Lewis WG. Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. Clin Nutr. 2011 Oct;30(5):560-6. Epub 2011 May 20. PubMed PMID: 21601319.	Elective surgery patients
Nguyen NQ, Besanko LK, Burgstad C, Bellon M, Holloway RH, Chapman M, Horowitz M, Fraser RJ. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. Crit Care Med. 2012 Jan;40(1):50-4.	Same data as reported by Nguyen 2008
Kesey J, Dissanaike S. A protocol of early aggressive acceleration of tube feeding increases ileus without perceptible benefit in severely burned patients. J Burn Care Res. 2013 Sep-Oct;34(5):515-20.	Not RCT
Wang X, Dong Y, Han X, Qi X-Q, Huang C-G, Hou L. (2013) Nutritional Support for Patients Sustaining Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prospective Studies. PLoS ONE. 8(3): e58838.	Meta-analysis
Bakiner O, Bozkirli E, Giray S, Arlier Z, Kozanoglu I, Sezgin N, Sariturk C, Ertorer E. Impact of early versus late enteral nutrition on cell mediated immunity and its relationship with glucagon like peptide-1 in intensive care unit patients: a prospective study. Crit Care. 2013 Jun 20;17(3):R123.	Not critically ill
Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, BoermeesterMA, Dejong CH, van Goor H, Bosscha K, Ahmed Ali U, et al.; Dutch Pancreatitis Study Group. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med 2014;371:1983–1993.	Not critically ill
Li CH, Chen DP, Yang J. Enteral Nutritional Support in Patients with Head Injuries After Craniocerebral Surgery. Turk Neurosurg. 2015;25(6):873-6.	No clinical outcomes
Stimac D, Poropat G, Hauser G, Licul V, Franjic N, Valkovic Zujic P, Milic S. Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: A randomized clinical trial. Pancreatology. 2016 Jul-Aug;16(4):523-8.	Not critically ill