

2.0 Early vs. Delayed nutrient intake

June 28th, 2005

Recommendation:

Based on 10 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). 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. 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, Cani P, Ponche F, Bleichner G. 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, Mehninger 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.

Values	definition	Score : 0, +, ++, +++
Effect size	magnitude of the absolute risk reduction attributable to the intervention listed—a higher score indicates a larger effect size	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	2+ (for infections)
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	similar direction of findings among trials—a higher score indicates greater similarity of direction of findings among trials	2+
Safe	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+
Feasible	ease of implementing the intervention listed—a higher score indicates greater ease of implementing the intervention in an average ICU	2+
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+

2.0 Early vs. Delayed nutrient intake

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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 10 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, enteral nutrition was started within 24-48 hours of admission/resuscitation.

Mortality: All 10 studies looked at the effect of early EN on mortality and when these were aggregated, when compared to delayed nutrient intake, early enteral nutrition was associated with a trend towards a reduction in mortality (RR 0.65, 0.41-1.02, $p = 0.06$) (See figure page 2-5).

Infections: 8 studies reported on infections and of these only 6 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 trend towards a reduction in infectious complications (RR = 0.78, 95 % confidence intervals 0.60, 1.01, $p = 0.06$) (see figure page 2-6).

LOS and Ventilator days: 9 studies looked at LOS (7 reported on ICU LOS, 6 reported on hospital LOS). When the results were meta-analyzed, early enteral nutrition had no effect on ICU stay (SMD = 0.07, 95 % confidence intervals -0.25, 0.38, $p = 0.67$) or hospital length of stay (RR = -0.04, 95 % confidence intervals - 0.51, 0.43, $p = 0.86$) (See figures page 2-6 and 2-7). 5 studies reported on ventilator days and all showed no significant differences between the early vs. delayed fed groups (SMD 0.12, 95 % CI -0.19, 0.43, $p=0.45$) (see figure page 2-7).

Other: All 9 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 trend towards a 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

Deleted: Conclusions: ¶
Remove the Taylor study as it does not compare early vs late EN. Chantrasakul study not to be excluded. ¶
1) No difference in mortality, LOS or ventilator days between critically ill patients receiving early vs late enteral nutrition. ¶
2) Insufficient evidence that early enteral nutrition maybe associated with an increase in infections in trauma patients

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

Study	Population	Methods (score)	Intervention Early vs delayed intake	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 = 38	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)	NA	NA
5) Singh 1998	Non traumatic intestinal perforation and peritonitis 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 2004	Multiple trauma patients, ICU N = 52	C.Random: not sure ITT: yes Blinding: no (7)	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)
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 2001	Post laporotomy for severe pancreatitis and peritonitis N = 60	C.Random: not sure ITT: yes Blinding: no (6)	EN post-op < 12 hrs 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)	
9) 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)

10) 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)
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Table 1 (continued). Randomized studies evaluating early EN vs. delayed nutrient intake in critically ill patients

2-3

Study	LOS days		Ventilator days		Cost		Other	
	Early EN	delayed	Early EN	delayed	Early EN	delayed	Early EN	delayed
1) Moore 1986	NA	NA	NA	NA	\$ 16,280 ± 2146	\$ 19,636 ± 3396	14/32 (44) 12/32 (38)	15/31 (48) NA
2) Chiarelli 1990	Hospital 69.2 ± 10.4 (10)	Hospital 89 ± 18.9 (10)	NA	NA	NA	NA	8.8 ± 4.1 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)	NA	NA	30 ± 6 1.3 ± 0.3 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)	NA	NA	1885.2 ± 38.3 1850.3 ± 248.4	633.4 ± 83.7 717.31 ± 142
5) Singh 1998	Hospital 14 ± 6.9 (19)	Hospital 13 ± 7.0 (18)	NA	NA	NA	NA	11/21 (52) 2610 ± 337 5.1 ± 0.7	13/22 (59) 516 ± 156 -10.8 ± 3.1
6) Kompan 2004	ICU 15.9 ± 9.7 (27)	ICU 20.6 ± 18.5 (25)	12.9 ± 8.1 (27)	15.6 ± 16.1 (25)	NA	NA	1175 ± 485	803 ± 545
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)	NA	NA	1509 ± 45 22/12	1174 ± 425 28/15
8) 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)	NA	NA	NA	NA	1295 ± 327	473 ± 156

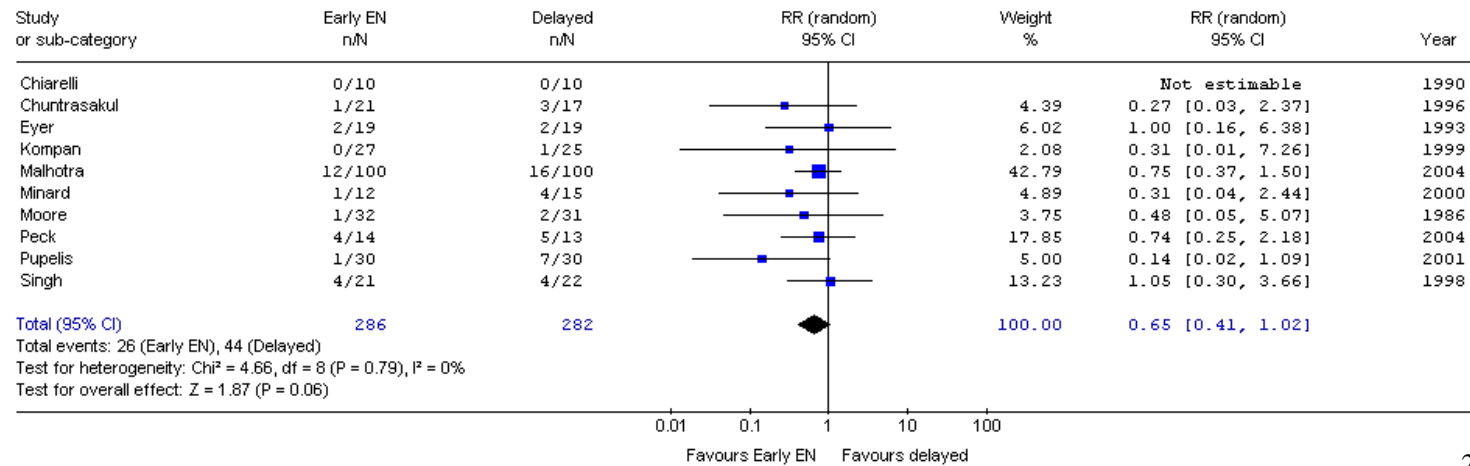
2-4

9) Malhotra 2004	Hospital 10.6 ICU 1.6	Hospital 10.7 ICU 2.10	NA	NA	NA	NA	% 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
10) Peck 2004	Hospital 60 ± 44 (14) ICU 40 ± 32 (14)	Hospital 60 ± 38 (13) ICU 37 ± 33 (13)	32 ± 27 (14)	23 ± 26 (13)	NA	NA	Mean Calorie Intake 2234 2207 Mean calorie intake change per week 156 166

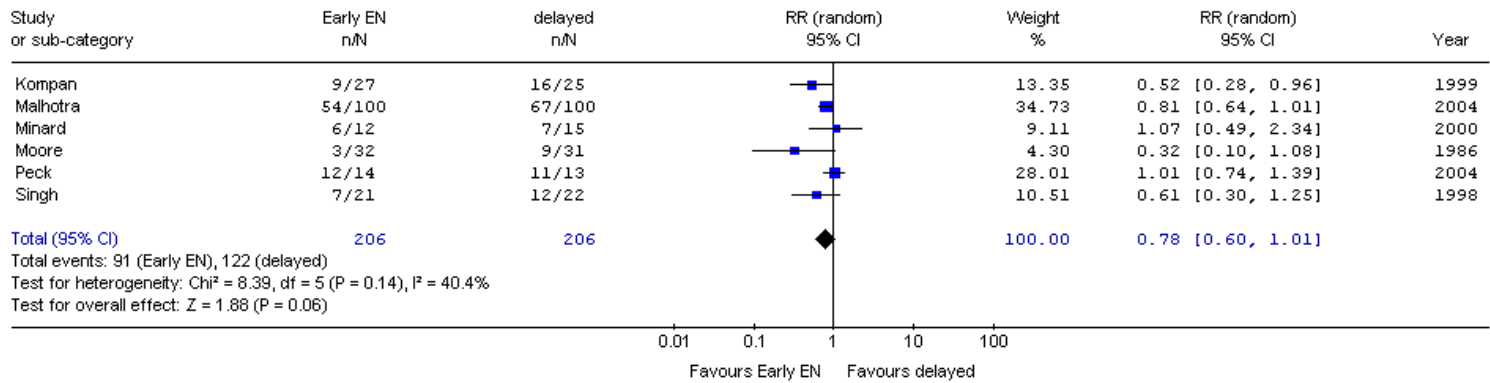
C.Random: concealed randomization
ITT: intent to treat; NA: not available
‡ refers to the # of patients with infections unless specified

± () : mean ± SD =standard deviation (number); (-) : mean (range)
** RR= relative risk, CI= Confidence intervals
† presumed hospital mortality unless otherwise specified

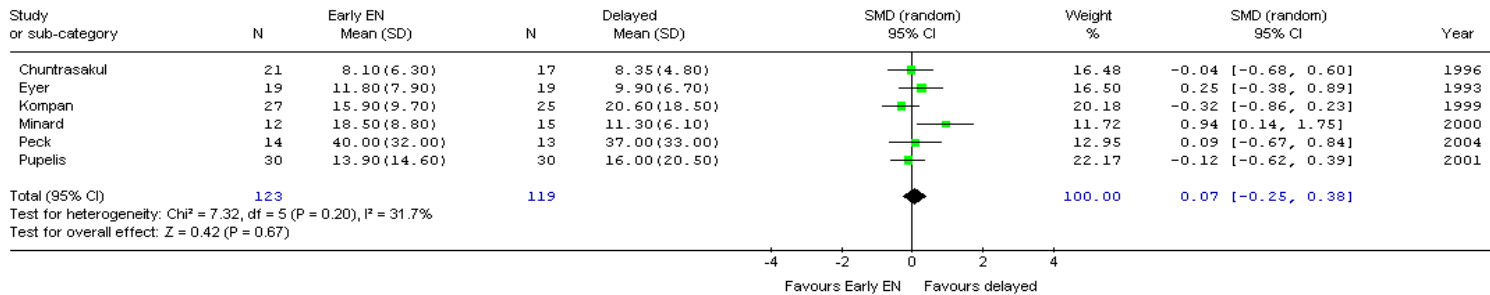
Review: Early Enteral Nutrition vs. delayed nutrient intake
Comparison: 01 Early EN vs. delayed nutrient intake
Outcome: 01 Mortality



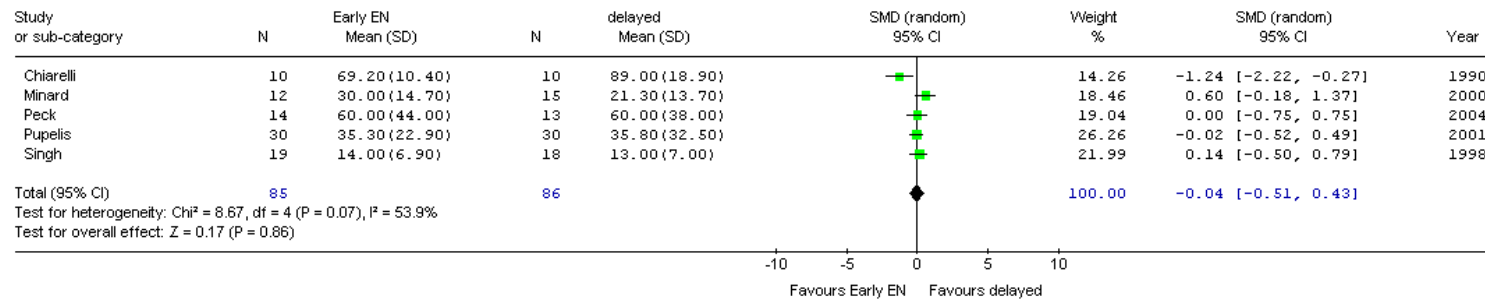
Review: Early Enteral Nutrition vs. delayed nutrient intake
 Comparison: 01 Early EN vs. delayed nutrient intake
 Outcome: 02 Infectious Complications



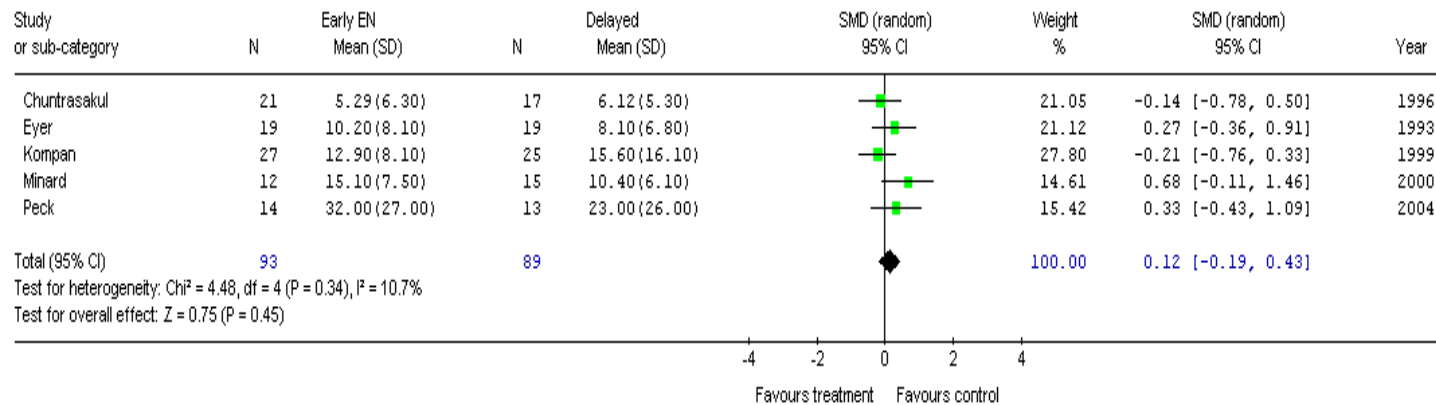
Review: Early Enteral Nutrition vs. delayed nutrient intake
 Comparison: 01 Early EN vs. delayed nutrient intake
 Outcome: 03 ICU LOS



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



Review: Early Enteral Nutrition vs. delayed nutrient intake
 Comparison: 01 Early EN vs. delayed nutrient intake
 Outcome: 05 Ventilator Days



TOPIC: 2.0 Early Vs Delayed Nutrient Intake

(reviewers: Dominique Michaud, Shannon MacKenzie, John Drover and Guiseppe Pagliarello)

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill human patients (no elective sx.)
Intervention: TPN and /or 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.	Eyer	J Trauma 1993	√		
3.	Chiarelli	Am J Clin Nutr 1990	√		
4.	Kompan	Clin Nutr 2004	√		
5.	Taylor	CCMedicine 1999	√		
6.	Minard	JPEN 2000	√		
7.	Chuntrasakul	J Med Assoc Thai 1996	√		
8.	Pupelis	Eur J Surg 2000	√		
9.	Pupelis	Nutrition 2001	√		
10.	Singh	J Am Coll Surg 1998	√		
11.	Moore	J Trauma 1986	√		
12.	Moore	J Trauma 1986		√	Delayed group got TPN
13.	Bier Hogersen	Gut 1996		√	Surgery patients
14.	McCarter	Am J Gast 1998		√	Not ICU patients
15.	Zaloga	CCMedicine 1999		√	Not RCT, review
16.	Grahm	Neurosurgery 1989		√	Not RCT (pseudorandomized)
17.	McDonald	Ann Surgery 1991		√	Not RCT

18.	Peng	Burns 2001		√	No significant outcomes
19.	D'Amelio	Am Surgeon 1994		√	Not RCT
20.	Braga	Infusionther Tran '95		√	Elective surgery patients
21.	Marik	CCMedicine 2001		√	Not all ICU patients, ICU studies included
22.	Ibrahim	JPEN 2002		√	Not RCT, psuedorandomized
23.	Tahtau	Int Med Journal 2000		√	Not RCT
24.	Jenkins	J Burn Care Rehab 1994		√	Not adults
25.	Jones	Crit Care Med 1989		√	No significant outcomes
26.	Austrums	Nutrition 2003		√	Not RCT
27.	Malhotra 2004	J Postgrad Med 2004	√		
28.	Peck 2004	J Trauma 2004	√		

I = included, E = excluded

References

1. 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.
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. Kompan L, Kremzar B, Gadzijevec 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med*. 2001 Oct;29(10):1955-61.
9. 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.
10. 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.
11. 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.
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.