1.0 The use of Enteral Nutrition vs. Parenteral Nutrition January 31st 2009

Recommendation:
Based on one level 1 and 12 level 2 studies, when considering nutrition support for critically ill patients, we strongly recommend the use of Enteral Nutrition over Parenteral Nutrition.

Discussion: The committee noted the homogenous results related to the effect of parenteral nutrition on infectious complications across several studies that when aggregated, resulted in a large effect size with narrow confidence intervals. Safety, cost and feasibility considerations favoured the use of EN over PN. The committee noted the results of the subgroup analysis of the studies in which the PN group received more calories and had higher blood sugars than the EN group. The increase in mortality or infections could not be attributed to a higher calorie intake or hyperglycemia. The committee also noted the paucity of data relating to malnourished, gastrointestinal compromised patients.

Values	Definition	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
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	3
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	3
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal inconsistencies=2, very consistent=3)	3
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	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	3
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3
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

1.0 Enteral Nutrition vs. Parenteral Nutrition January 31st 2009

Question: Does enteral nutrition compared to parenteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 12 level 2 studies and one level 1 study (Woodcock et al) that were reviewed and meta-analyzed. In the Woodcock study, data from ICU patients only were abstracted and there were 11/38 patients that crossed over between EN and PN group after randomization. The data on mortality and infectious complications from the Moore 1989 study was included in the Moore 1992 meta-analysis whereas data on calorie intake, blood sugars and non septic complications were not and hence appear in the tables for the Moore 1989 study. Apriori, we considered that the harmful effect of PN may be associated with relative overfeeding and hyperglycemia. Accordingly, we conducted a subgroup analysis to determine the effect of excess calories (PN compared to EN) and higher glucose levels (across groups).

Mortality: 12 studies reported on mortality and when these were aggregated, there was no difference in mortality between the groups receiving EN or PN (RR 1.08, 95 % confidence interval 0.70, 1.65, p = 0.7) (See page 1-8). When the trials in which the PN group were fed more calories than the EN group were aggregated, there was no effect seen (RR 1.58, 95% CI 0.75, 3.35, p = 0.2). Similarly, when the trials in which the PN and EN groups were fed isocalorically were aggregated, there was no effect seen (RR 1.08, 95% CI 0.56, 2.06, p = 0.8) (page 1-10). There was not statistical difference across these subgroups (p=0.34). Similarly, subgroup analysis comparing studies in which the PN group had higher blood sugars than the EN group to studies in which there was no difference in blood sugars showed that increased mortality in the PN groups could not be explained by hyperglycemia.

Infections: When the 7 studies which reported infectious complications were statistically aggregated, the meta-analysis showed that EN, compared to PN, was associated with a *significant* reduction in the incidence of infectious complications (RR 0.64, 95 % confidence interval 0.47, 0.87 p =0.004) (see page 1-9). Subgroup analysis showed that the increase in infections could not be attributed to higher calories or hyperglycemia.

LOS, Ventilator days: Data not aggregated statistically due to insufficient data. There was no difference found in LOS (Rapp, Adams, Kudsk, Moore 1992) or ventilator days (Rapp, Adams Kudsk, Kalfarentzos) between the groups receiving EN or PN.

Other complications: Of the 11 studies that reported on nutritional intake, 5 found that PN was associated with a higher calorie intake (Rapp, Young, Moore, Kudsk, Woodcock {Blood sugar values in the Woodcock pertain to the entire group, not the ICU population}), the remaining 6 reported no significant difference in intakes between the groups (Adams, Hadley, Cerra, Dunham, Borzotta, Kalfarantzos).

5 studies reported on hyperglycemia and in 3 of these, EN was associated with a lower incidences of hyperglycemia compared to PN (Adams p< 0.001), (Borzotta p < 0.05, Kalfarentzos). Two studies showed no difference in blood sugars between the groups receiving EN and PN (Moore 1989, Rapp). Three studies showed that EN was associated with an increase in diarrhea (Cerra p < 0.05, Young, Kudsk p < 0.01)) while one showed an association with EN and a reduction in diarrhea (Borzotta p < 0.05) and one study showed no difference (Adam). EN was also associated with an increase in vomiting (Cerra p < 0.05) and a less favourable neurological outcome at 3 months (p =0.05) in brain injured patients (Young p =0.05, this significance disappeared after 6months and 1 year. More overall nutrition related complications were noted in EN vs PN (Dunham).

Cost: Four studies reported a cost savings with the use of EN vs PN (Adams, Cerra, Borzotta and Kalfarentzos)

Conclusions:

1) The use of EN compared to PN is not associated with a reduction in mortality in critically ill patients.
2) The use of EN compared to PN is associated with a significant reduction in the number of infectious complications in the critically ill.
3) No difference found in ventilator days or LOS between groups receiving EN or PN.
4) Insufficient data to comment on other complications; hyperglycemia or higher calories not found to result in higher mortality of infections.
5) EN is associated with a cost savings when compared to PN.

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 EN vs PN in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				EN	PN	EN	PN
1. Rapp 1983	Head Injured patients n = 38 (<Ideal weight)	C.Random: not sure ITT: no Blinding: no (4)	EN vs PN	9/18 (50)	3/20 (15)	NR	NR
2. Adams 1986	Trauma patients undergoing laporotomy N= 46 36/46 ICU patients	C.Random: not sure ITT: yes Blinding: no (8)	EN vs PN	1/23 (4)	3/23 (13)	15/23 (65)	17/23 (74)
3. Young 1987	Brain injured patients N = 58	C.Random: not sure ITT: no Blinding: no (6)	EN vs PN	10/28 (36)	10/23 (43)	5/28 (18)	4/23 (17)
4. Peterson 1988	Critically ill patients with abdominal trauma N = 59	C.Random: not sure ITT: no Blinding: no (5)	EN vs PN	NR	NR	2/21 (10)	8/25 (32)
5. Cerra 1988	ICU patients post sepsis N = 70 (hypermetabolic patients)	C.Random: not sure ITT: no Blinding: no (2)	EN vs PN	7/31 (22) ICU	8/35 (23) ICU	NR	NR
6. Moore 1989	Abdominal trauma patients N = 75	C.Random: yes ITT: no Blinding: no (10)	EN vs PN	NR	NR	5/29 (17)	11/30 (37)

Table 1. (continued) Randomized studies evaluating EN vs. PN in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
				EN	PN	EN	PN
7. Kudsk 1992	Abdominal trauma N = 98	C.Random: not sure ITT: no Blinding: single (10)	EN vs PN	1/51 ICU	1/45 ICU	9/51 (16)	18/45 (40)
8. Moore 1992	Meta-analysis High risk surgical patients N = 230	C.Random: NR ITT: NR Blinding: NR (NA)	EN vs PN	6/118 (5) ICU 8/118 (7) 30 day	7/112 (6) ICU 11/112 (10) 30 day	19/118 (16)	39/112 (35)
9. Dunham 1994	Blunt trauma N = 37	C.Random: not sure ITT: no Blinding: no (8)	EN vs PN	1/12 (7)	1/15 (8)	NR	NR
10. Borzotta 1994	Closed head injury N = 59	C.Random: not sure ITT: no Blinding: no (6)	EN vs PN	5/28 (18)	1/21 (5)	51/28 per group	39/21 per group
11. Hadfield 1995	ICU patients, mainly cardiac bypass N = 24	C.Random: not sure ITT: no Blinding: no (7)	EN vs PN	2/13 (15) ICU	6/11 (55) ICU	NR	NR
12. Kalfarentzos 1997	Severe acute pancreatitis N = 38	C.Random: not sure ITT: no Blinding: single (9)	EN vs PN	1/18 (6) ICU	2/20 (10) ICU	5/18 (28)	10/20 (50)
13. Woodcock 2001	Patients needing nutrition support N=562 ICU patients N =38 (all degrees of malnutirition)	C.Random: yes ITT: yes Blinding: single (12)	EN vs PN	9/17 (53)	5/21 (24)	6/16 (38)	11/21 (52)

C.Random: concealed randomization
* median/mean values, no standard deviation hence not included in meta-analysis
‡ refers to the # of patients with infections unless specified
** data on ICU patients obtained directly from authors

ITT: intent to treat
NR: not reported
† presumed hospital mortality unless otherwise specified

± ( ) : mean ± Standard deviation (number)
reported data pertaining to ICU patients only
NS = not statistically significant

Table 1. (continued) Randomized studies evaluating EN vs. PN in critically ill patients

Study	LOS days		Ventilator days		Cost		Other	
	EN	PN	EN	PN	EN	PN	EN	PN
1. Rapp 1983	49.4 * Hospital	52.6* Hospital	10.3*	10.4*	NR	NR	Calorie intake (kcals) 685	1750 p = 0.001 Nitrogen intake (gms) 4.0 10.2 p = 0.002 Hyperglycemia no difference between groups
2. Adams 1986	13 ± 11 (19) ICU 30 ± 21 (19) Hospital	10 ± 10 ICU 31 ± 29 (17) Hospital	12 ± 11 (17)	10 ± 10 (13)	$ 1346.00/day	$ 3729.00/day	Calorie intake (kcals) 2088	2572 NS Hyperglycemia (pt. Days) 24/242 (10) 49/220 (22) p < 0.001 Line problems 13/9 9/7 Diarrhea 3.5 days/patient 3.8 days/patient
3. Young 1987	NR	NR	NR	NR	NR	NR	Calories ÷ BEE x 1.75 59 %	76 % p = 0.02 Protein intake (gm/kg/day) 0.91 ± 0.09 1.35 ± 0.12 p = 0.04 Favourable neurological outcome 3 months 17.9 % 43.5 % Diarrhea 23/28 (82) 13/23 (57)
4. Peterson 1988	13. 2 ± 1.6 (21) Hospital 3.7 ± 0.8 (21) ICU	14.6 ± 1.9 (24) Hospital 4.6 ± 1.0 (25) ICU	NR	NR	NR	NR	Day 5 Calorie Intake (kcals) 2204 ± 173	2548 ± 85 Day 5 Nitrogen Intake (gms) 12.6 ± 1.0 14.8 ± 0.6
5. Cerra 1988	NR	NR	NR	NR	$ 228 ± 59 /day	$ 330 ± 61 /day	Calorie intake 1684 ± 573	2000 ± 20 NS MOSF 7/31 (23) 7/35 (20) Diarrhea 25/31 (81) 9/35 (26) Vomiting 10/31 (32) 10/35 (6)
6. Moore 1989	NR	NR	NR	NR	NR	NR	Calorie intake 1847 ± 123	2261 ± 60 p=0.01 Bood sugars No difference between the groups Non septic complications 6/29 (21 7/30 (23)

Table 1. (continued). Randomized studies evaluating EN vs. PN in critically ill patients

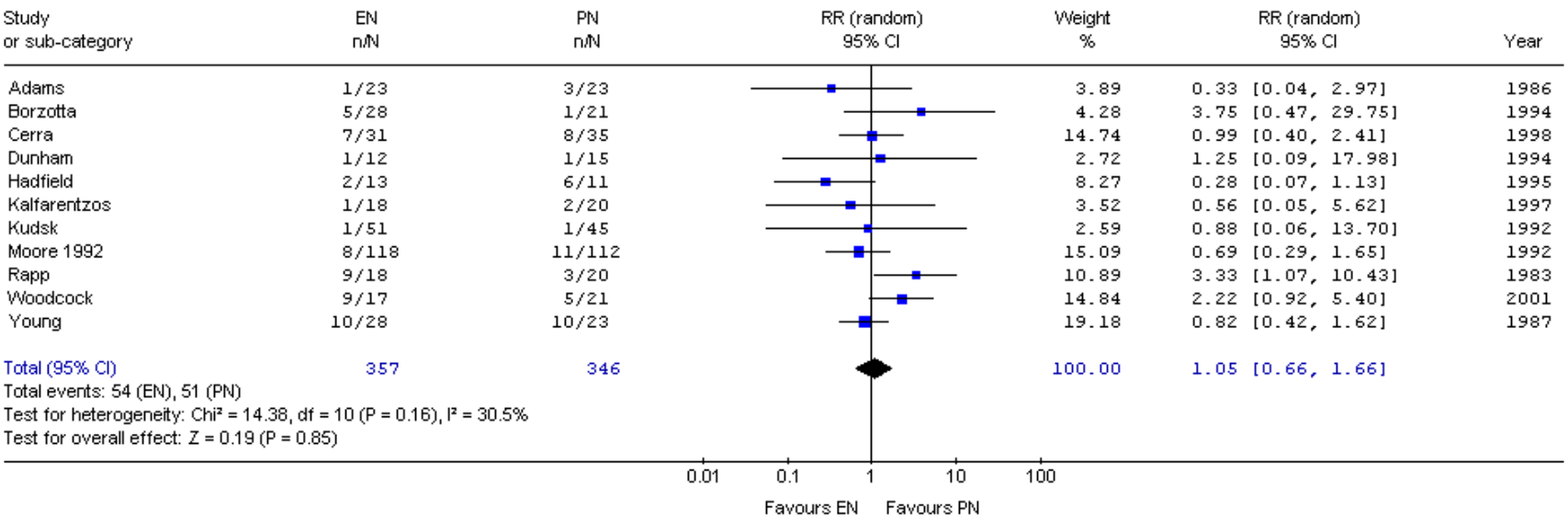
Study	LOS days		Ventilator days		Cost		Other	
	EN	PN	EN	PN	EN	PN	EN	PN
7. Kudsk 1992	20.5 ± 19.9 (51) Hospital	19.6 ± 18.8 (45) Hospital	2.8 ± 4.9 (51)	3.2 ± 6.7 (45)	NR	NR	Calorie intake (Kcal/kg/day) 15.7 ± 4.2	19.1 ± 3.3 p < 0.05 Diarrhea 11/51 7/45
8. Moore 1992	17.0* Hospital 4.4* ICU	22* Hospital 7.3* ICU	NR	NR	NR	NR	NR	NR
9. Dunham 1994	NR	NR	NR	NR	NR	NR	Calorie intake No difference between the groups Protein intake No difference between the groups Nutrition related complications 3/12 (25)	2/15 (13)
10. Borzotta 1994	39 ± 23.1 Hospital assumed	36.9 ± 14 Hospital assumed	NR	NR	$ 121,941.00	$ 112,450.00	Calorie intake No difference between the groups Placement complications 3/28 Aspiration 3/28 Hyperglycemia 12/28 (44) Diarrhea 30 %	0/21 0/21 16/21 (76) 62 %
11. Hadfield 1995	NR	NR	NR	NR	NR	NR	NR	NR
12. Kalfarentzos 1997	11 (5-21) * ICU 40 (25-83) * Hospital	12 (5-24)* ICU 39 (22-73) * Hospital	15 (6-16) *	11 (7-31)*	Savings of 70 pounds/day	NR	Calorie intake (kcal/kg/day) 24.1 Protein intake (gm/kg/day) 1.43 Hyperglycemia 4/18 (22)	24.5 NS 1.45 NS 9/20 (45)
13. Woodcock 2001	33.2 ± 43 (16)	27.3 ± 18.7 (18)	NR	NR	NR	NR	% Target intake achieved 54.1 % < 80% target intake 62.5 %	96.7 % p< 0.001 6.3 % p < 0.001

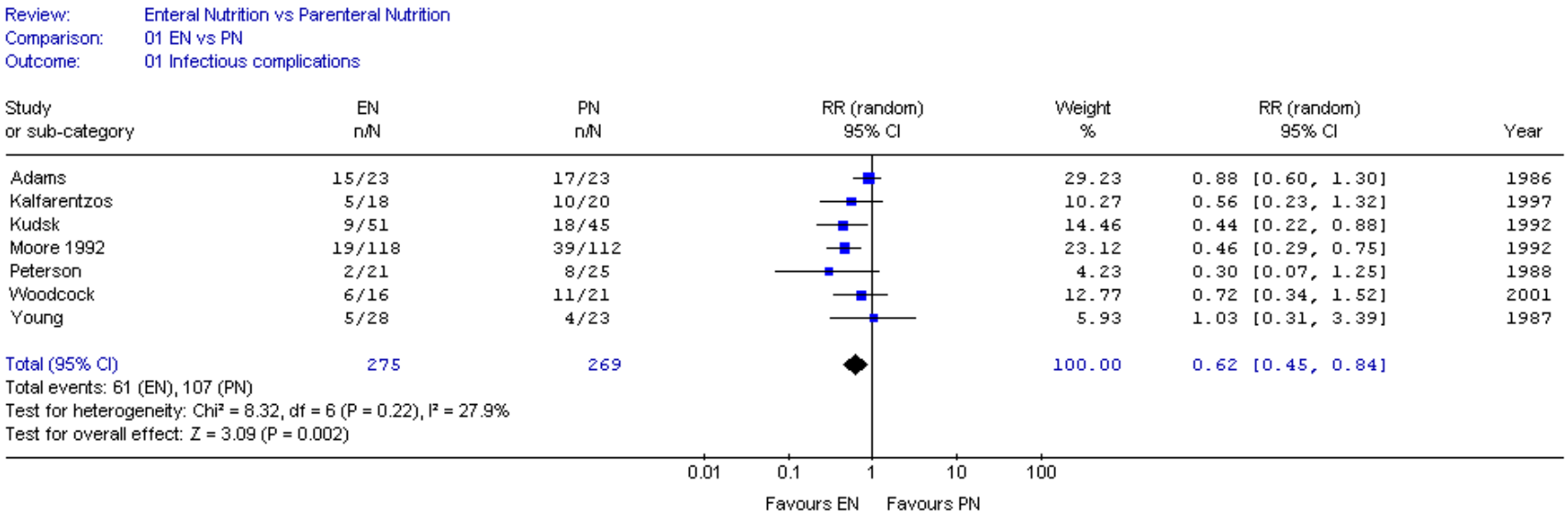
C.Random: concealed randomization
* median/mean values, no standard deviation hence not included in meta-analysis
‡ refers to the # of patients with infections unless specified
** data on ICU patients obtained directly from authors

ITT: intent to treat
NR: not reported
† presumed hospital mortality unless otherwise specified

± ( ) : mean ± Standard deviation (number)
reported data pertaining to ICU patients only
NS = not statistically significant

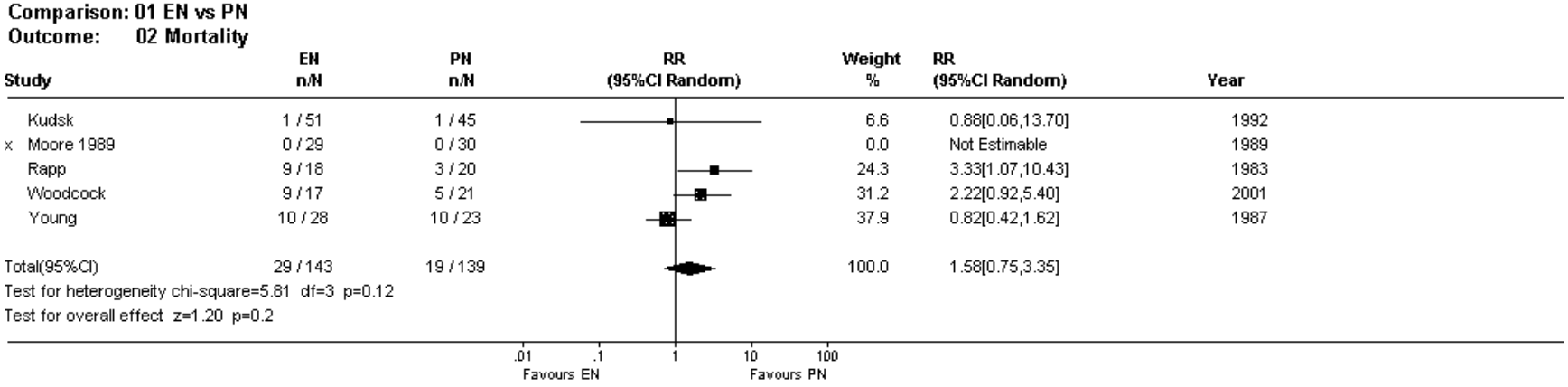
Review: Enteral Nutrition vs Parenteral Nutrition
Comparison: 01 EN vs PN
Outcome: 02 Mortality





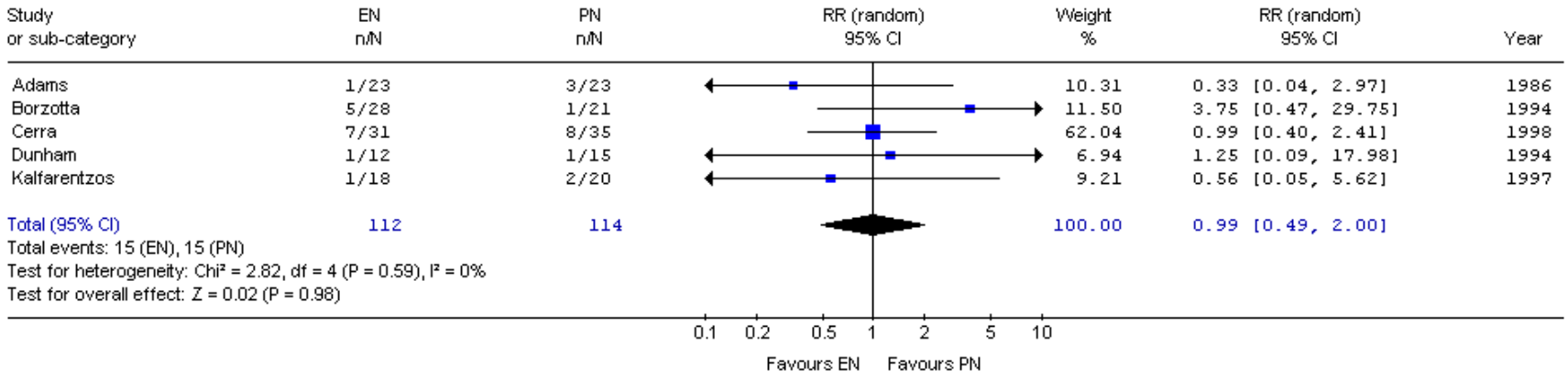
Subgroup analysis EN vs PN

Mortality in studies where the PN group received more calories than the EN group



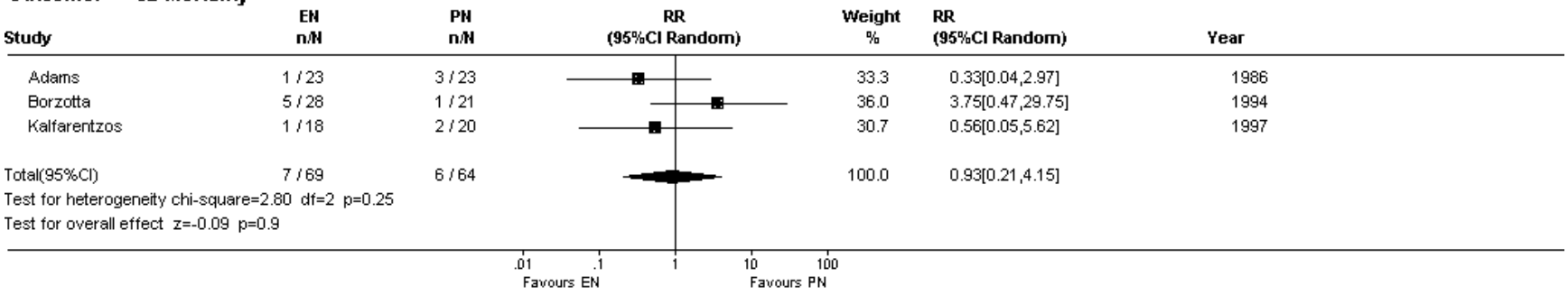
Mortality in studies where the PN group received similar calories to the EN group

Review: Enteral Nutrition vs Parenteral Nutrition
Comparison: 01 EN vs PN
Outcome: 02 Mortality



Mortality in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

Comparison: 01 EN vs PN
Outcome: 02 Mortality

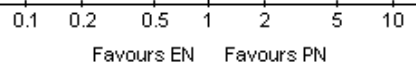


Infections in studies where the PN group received more calories than the EN group

Review: Enteral Nutrition vs Parenteral Nutrition
Comparison: 01 EN vs PN
Outcome: 01 Infectious complications

Study or sub-category	EN n/N	PN n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Kudsk	9/51	18/45		24.21	0.44 [0.22, 0.88]	1992
Moore 1992	19/118	39/112		49.66	0.46 [0.29, 0.75]	1992
Peterson	2/21	8/25		5.63	0.30 [0.07, 1.25]	1988
Woodcock	6/16	11/21		20.50	0.72 [0.34, 1.52]	2001
Total (95% CI)	206	203		100.00	0.49 [0.35, 0.69]	

Total events: 36 (EN), 76 (PN)
Test for heterogeneity: Chi² = 1.61, df = 3 (P = 0.66), I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)

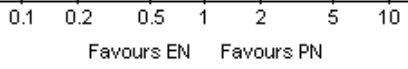


Infections in studies where the PN group received similar calories to the EN group

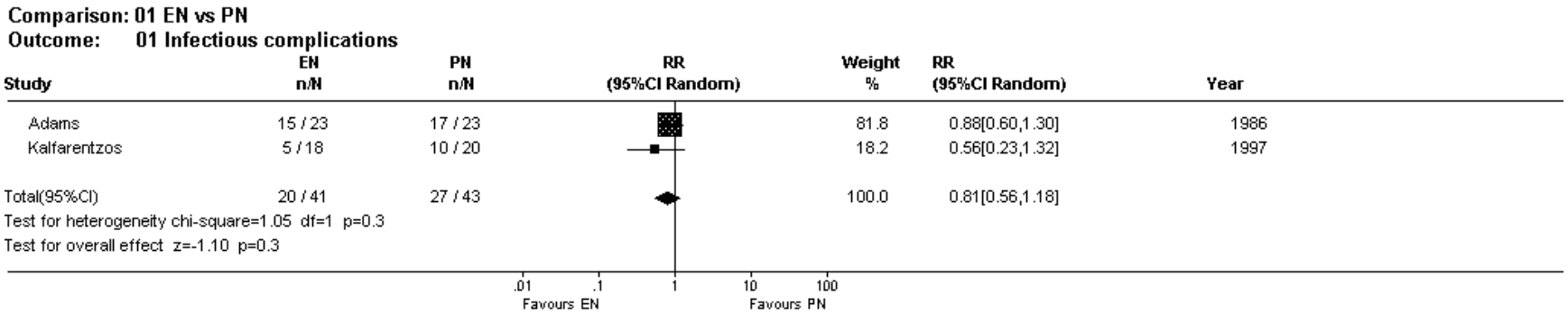
Review: Enteral Nutrition vs Parenteral Nutrition
Comparison: 01 EN vs PN
Outcome: 01 Infectious complications

Study or sub-category	EN n/N	PN n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Adams	15/23	17/23		81.78	0.88 [0.60, 1.30]	1986
Kalfarentzos	5/18	10/20		18.22	0.56 [0.23, 1.32]	1997
Total (95% CI)	41	43		100.00	0.81 [0.56, 1.18]	

Total events: 20 (EN), 27 (PN)
Test for heterogeneity: Chi² = 1.05, df = 1 (P = 0.30), I² = 5.0%
Test for overall effect: Z = 1.10 (P = 0.27)



Infections in studies with hyperglycemia where the PN group had higher blood sugars than the EN group



TOPIC: Enteral Nutrition vs. Parenteral Nutrition (EN vs. PN)

Article inclusion log
Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill, ventilated patients (no elective surgical patients)
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	Lim	Br J Surg 1981		√	Cancer pts, not ICU pts
2	Sako	J Surg Oncol 1981		√	Cancer pts, not ICU pts
3	Rapp	J Neurosurg 1983	√		
4	Seri	It J Surg Sci 1984		√	Excluded April 2002 as not likely ICU patients
5	Wiedeck	Anaesthesist 1984		√	Elective surgery patients
6	Quayle	Clin Nutr 1984		√	Patients not critically ill
7	Bauer	Infusionstherapie 1984		√	Unclear if ICU patients
8	Costalat	Chirugie 1985		√	Elective surgery patients
9	Adams	J Trauma 1986	√		
10	Bower	Arch Surg 1986		√	Elective surgery pts
11	Fletcher	Surgery 1986		√	Surgery patients
12	Hadley	Neurosurgery 1986	√		
13	Young	J Neurosurg 1987	√		
14	Young	J Neurosurg 1987		√	No significant outcomes
15	Peterson	Surgery 1988	√		
16	Cerra	Surgery 1988	√		
17	Greenberg	Gut 1988		√	Not ICU pts
18	Moore	J Trauma 1989	√		
19	Hamaoui	JPEN J Parenter Enteral Nutr 1990		√	Elective surgery pts.
20	Kudsk	Ann Surg 1992	√		
21	Moore	Ann Surg 1992		√	Meta-analysis, excluded based on methodology
22	Von Meyenfeldt	Clin Nutr 1992		√	Elective surgery pts
23	Gonzalez-Huix	Am J Gastroenterol 1993		√	Cancer pts, not ICU pts
24	Iovinelli	JPEN J Parenter Enteral Nutr. 1993		√	Elective surgery pts
25	Dunham	Trauma 1994	√		
26	Kudsk	Gut 1994		√	Duplicate study of '92
27	Wicks	Lancet 1994		√	Elective surgery pts
28	Borzotta	J Trauma 1994	√		
29	Hadfield	Am J Resp Crit Care Med 1995	√		
30	Hernandez-Aranda	Nutr Hosp 1996		√	Not RCT, not ICU patients
31	Suchner	Nutrition 1996		√	No significant outcomes
32	Baigrie	Aust N Z J Surg. 1996		√	Elective surgery
33	Kalfrantzos	Brit Journal Surg 1997	√		
34	Georgiannos	Int Surg 1997		√	Not ICU patients
35	Reynolds	JPEN J Parenter Enteral Nutr 1997		√	Cancer pts, not ICU pts
36	Gioanotti	Arch Surg 1997		√	Cancer pts, not ICU pts

37	Sand	Eur J Surg 1997		√	Cancer pts, not ICU pts
38	Shirabe	Hepatogastroenterology 1997		√	Cancer pts, not ICU pts
39	McClave	JPEN J Parenter Enteral Nutr 1997		√	Not ICU pts
40	Windsor	Gut 1998		√	Not ICU pts.
41	Braga	Crit Care Med 1998		√	Elective surgery patients
42	Woodcock	Nutrition 2001	√		
43	Braunschweig	Am J Clin Nutr 2001		√	Meta-analysis, individual studies used
44	Pacelli	Arch Surg 2001		√	Elective surgery pts.
45	Braga	Crit Care Med 2001		√	Elective surgery patients
46	Bozetti	Lancet 2001		√	Elective surgery patients
47	Heyland	Can J Surg 2001		√	Meta-analysis but excluded because population is surgical pts
48	Braunschweig	Am J Clin Nutr. 2001		√	Meta-analysis, individual studies used
49	Huang	Clin Nutr 2002		√	Not Randomized
50	Abou-Assi	Am J Gastroenterology 2002		√	Not ICU pts
51	Rayes	Nutrition 2002		√	Elective surgery pts
52	Louie	Can J Surg 2005		√	Not ICU pts
53	Peter	Crit Care Med. 2005		√	Meta-analysis, but individual studies used
54	Simpson	Intensive Care Med 2005		√	Meta-analysis, but individual studies used
55	Eckerwall	Ann Surg 2006		√	Not ICU pts
56	Petrov	Dig Surg 2006			Unable to confirm if pts were in ICU. Contacted authors but did not get needed details
57	Chen	Burns 2007		√	No clinical outcomes
58	Petrov	Clinical Nutrition 2007		√	Systematic review, Individual studies looked at
59	Lam	Burns 2008		√	Pseudo-randomized
60	Petrov	Aliment Pharmacol Ther		√	Systematic review, Individual studies looked at

I = included, E = excluded

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