7.1 Combination Parenteral Nutrition and Enteral Nutrition

Question: Does the use of parenteral nutrition in combination with enteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: There was one level 1 and nine level 2 studies that were reviewed and meta-analysed.

Mortality: All 10 studies reported on mortality. The meta-analysis shows that there was no effect on mortality with the use of combination EN + PN (RR 1.00, 95% CI 0.70, 1.41, p=0.98, heterogeneity I^2=41%; figure 1). When a sub-group analysis was done comparing the trials where the groups differed in calories received (RR 0.92, 95% CI 0.60, 1.41, p=0.71, heterogeneity I^2=52%; figure 1) to those that were fed isocalorically (RR 1.30, 95% CI 0.74, 2.29, p=0.36, heterogeneity I^2=0%; figure 1), there was no difference in effect. A test for subgroup differences showed no significant differences between these two subgroups (p=0.34).

Infections: When the data from the 5 studies that reported infectious complications were aggregated, the use of combined EN + PN compared to EN had no effect on the overall incidence of infection (RR 1.02, 95% CI 0.89, 1.16, p=0.82, heterogeneity I^2=0%; figure 2).

LOS & ventilator days: When the data from the 6 studies that reported hospital length of stay as a mean ± standard deviation were aggregated, the use of combined EN + PN compared to EN alone was associated with a trend towards a reduction in hospital length of stay (WMD -3.14, 95% CI -6.46, 0.18, p=0.06, heterogeneity I^2=38%; figure 3). When the data from the 5 studies that reported ICU length of stay as a mean ± standard deviation were aggregated, the use of combined EN + PN compared to EN alone had no effect on ICU length of stay (WMD -0.76, 95% CI -2.52, 1.00, p=0.39, heterogeneity I^2=51%; figure 4). When the data from the 4 studies that reported duration of ventilation as a mean ± standard deviation were aggregated, the use of combined EN + PN compared to EN alone had no effect on duration of ventilation (WMD -0.62, 95% CI -1.93, 0.68, p=0.35, heterogeneity I^2=64%; figure 5).

Blood sugars: Blood sugars were significantly higher in the EN + PN group when compared to the EN group but only on day 7 in one study (Bauer et al) ($p<0.05$). Chiarelli et al reported no difference in glycemia between the groups although no numbers were reported. None of the other studies reported on blood sugars.

Physical and Quality of Life Outcomes: Three studies (Chen 2011, Wischmeyer 2017, Ridley 2018) reported on physical outcomes. Within both groups, Chen found a significant improvement in respiratory muscle strength before and after nutrition support. Wischmeyer did not find a difference between groups with respects to handgrip strength at ICU discharge and 6 minute walk test at hospital discharge. However, there was trend towards greater hand grip strength in the EN+PN group vs the EN group at hospital discharge. In comparison, Ridley did not find a difference between groups in hand grip strength at hospital discharge. Ridley also found no difference between groups in the ICU mobility scale at hospital discharge.

Two studies (Wischmeyer 2017, Ridley 2018) reported on quality of life (QOL) outcomes. Wischmeyer looked at the Barthel Index at hospital discharge and the SF-36 at 3 and 6 months. There was a trend towards a greater Barthel Index score in the EN+PN group. For the SF-36 at 3 months, there was no difference in the components with the exception of *general health perceptions*, which showed a trend in improved scores in the EN group vs EN+PN group. At 6 months, there was a trend in improved scores in the *pain index, vitality, social functioning, role emotional, standardized physical component scale and standardized mental component scale*, all favouring the EN+PN group. Ridley did not find a difference between groups in the EQ-5D-3L at hospital discharge or at 90 days.

In summary, there are inconclusive data to make a conclusion on the effects of EN+PN vs EN on quality of life or physical outcomes.

Conclusions: When compared to EN alone,

1) PN in combination with EN has no effect on mortality in critically ill patients
2) PN in combination with EN has no effect on infectious complications in critically ill patients
3) PN in combination with EN may be associated with a reduction in hospital length of stay but has no effect on ICU LOS in critically ill patients.
4) PN in combination with EN has no effect on duration of ventilation in critically ill patients.
5) PN in combination with EN may be associated with some improvements in long-term physical function of surviving critically ill patients.
6) PN in combination with EN is associated with a higher cost compared to EN alone.

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 combined EN + PN in critically ill patients

Study	Population	Methods (score)	Intervention (both interventions started at same time)	Mortality # (%)†		Infections # (%)‡	
				EN + PN	EN	EN + PN	EN
1) Herndon 1987	Burns > 50 % TBSA N = 28	C.Random: not sure ITT: yes Blinding: no (6)	EN + PN vs EN EN + PN group received significantly more calories than EN group	8/13 (62)	8/15 (53)	NR	NR
2) Herndon 1989	Burn patients N = 39	C.Randomization: not sure ITT: yes Blinding: no (7)	EN+ PN vs EN EN + PN group received significantly more calories than EN group	> Day 14 10/16 (63)	> Day 14 6/23 (26)	NR	NR
3) Dunham 1994*	Blunt trauma N = 37	C.Random: not sure ITT: no Blinding: no (8)	EN+ PN vs EN EN + PN group given same calories as EN	3/10 (30)	1/12 (8.3)	NR	NR
4) Chiarelli 1996	ICU patients medical and surgical N = 24	C.Random: not sure ITT: yes Blinding: no (8)	EN+ PN vs EN EN + PN were given 33 kcal/kg/day, EN were given 31 kcals/kg/day	3/12 (25)	4/12 (33)	6/12 (50)	3/12 (25)
5) Bauer 2000	Patients from 2 ICUs N =120 (all degrees of malnutrition)	C.Random: not sure ITT: yes Blinding: double (12)	EN+ PN vs EN + placebo. EN + PN received 24.6 ± 4.9 kcal/kg/day vs. EN group 14.2 ± 6.5 kcal/kg/day (p< 0.0001)	< Day 4 3/60 (5) 90-day 17/60 (28)	< Day 4 4/60 (6.7) 90-day 18/60 (30)	39/60 (65)	39/60 (65)
6) Abrishami 2010	SIRS patients with APACHE II > 10 N=20	C.Random: not sure ITT: yes Blinding: no (7)	EN vs.EN + PN Metoclopramide if GRV >300mL Non isocaloric/isonitrogenous	2/10 (20)	1/10 (10)	NR	NR

7) Chen 2011*	Elderly Patients in respiratory intensive care unit N=147	C.Random: yes ITT: yes Blinding: no (7)	EN + PN: EN as above + PN to make up kcal and nitrogen deficit vs EN: 100ml/hr=goal rate; metoclopramide if GRV >200mL, NJ if not tolerating NG Non-isocaloric/isonitrogenous	20-day 3/49 (6)	20-day 11/49 (22)	6/49 (12)	5/49 (10)
8) Heidegger 2012	ICU patients requiring at least 5 days of treatment with no contraindication to EN, not achieving 60% of energy target (equation based) by end of D3 N=305	C.Random yes ITT: yes Blinding: single (13)	EN vs EN+PN to make up energy target verified by indirect calorimetry in 65% of patients. EN progression encouraged in both groups. Non-isocaloric/isonitrogenous	ICU 8/153 (5) 28-day 20/153 (13)	ICU 11/152 (7) 28-day 28/152 (18)	Day 4 to 28** 77/153 (50)	Day 4 to 28** 85/152 (56)
9) Wischmeyer 2017	Adult (≥18 years) mixed ICU patients with BMI <25 or >35. Multi-centre. N=125	C.Random: yes ITT: yes Blinding: no (9)	sPN adjusted daily to reach 100% of goal calories in combination with EN vs standard EN. Non-isonitrogenous, non-isocaloric.	ICU 7/52 (13.5) Hospital 8/52 (15.4)	ICU 13/73 (17.8) Hospital 17/73 (23.3)	Newly acquired 38/52	Newly acquired 46/73
10) Ridley 2018	Adult (≥16 years), mixed ICU patients. Multi-centre N=99	C.Random: yes ITT: yes Blinding: no (9)	sPN to provide 0, 40 or 80% of goal energy based on amount of EN received vs En as per usual care. Both groups dosed at 25 kcal/kg/d, or if on RRT or ECMO 30 kcal/kg/d. Isocaloric, non-isonitrogenous.	ICU 15/51 Hospital 16/51 90-day 19/51 180-day 19/51	ICU 11/48 Hospital 11/48 90-day 13/48 180-day 13/48	NR	NR

*Pertains to EN+PN vs EN comparison; for the Chen EN+PN vs PN comparison see section 1.0
**Date obtained from authors

Table 1. Randomized studies evaluating combination parenteral nutrition and enteral nutrition in critically ill patients (continued)

Study	LOS days		Ventilator days		Other	
	EN + PN	EN	EN + PN	EN	EN + PN	EN
1) Herndon 1987	NR	NR	NR	NR	NR	
2) Herndon 1989	NR	NR	NR	NR	NR	
3) Dunham 1994*	NR	NR	NR	NR	Nutrition related complications 5/10 (50)	3/12 (25)
4) Chiarelli 1996	Hospital 37± 13 (12)	Hospital 41 ± 23 (12)	19 ± 6 (12)	19 ± 2 (12)	NR	
5) Bauer 2000	ICU 16.9 ± 11.8 (60) Hospital 31.2 ± 18.5 (60)	ICU 17.3 ± 12.8 (60) Hospital 33.7 ± 27.7 (60)	11 ± 9 (60)	10 ± 8 (60)	Glycemia on day 7 (g/L) 1.16 ± 0.36	1.31 ± 0.49
6) Abrishami 2010	ICU 25.7 Hospital 37.4	ICU 27.7 Hospital 36.5	NR	NR	NR	
7) Chen 2011	ICU 6.75 ± 1.75 (49) Hospital 17.3 ± 2.47 (49)	ICU 9.09 ± 2.75 (49) Hospital 23.32 ± 5.6 (49)	5.76 ± 1.56 (49)	7.95 ± 2.11 (49)	"Other complications" 8/49 (16)	10/49 (20)
8) Heidegger 2012	ICU 13 ± 10 (153) Hospital 31 ± 23 (153)	ICU 13 ± 11 (152) Hospital 32 ± 23 (152)	60 ± 111 hrs (153) 2.5 ± 4.625 (153)	66 ± 101 hrs (152) 2.75 ± 4.21 days (152)	Similar glucose control in the EN+PN and EN groups Target < 8 mmol/l	

9) Wischmeyer 2017	ICU** 16.7 ± 13.5 (52) Hospital** 39.9 ± 61.9 (52)	ICU** 14.2 ± 9.2 (73) Hospital** 29.6 ± 22.6 (73)	11.1 ± 11.3 (52)**	10.4 ± 8.7 (73)**	NR
10) Ridley 2018	ICU** 13 ± 10 (51) Hospital 22 ± 21 (51)	ICU** 13.9 ± 11.7 (48) Hospital 23 ± 17 (48)	12.2 ± 8.31 (51)**	12.8 ± 10.1 (48)**	Vomiting 13/51 8/48

C.Random: concealed randomization
ICU: intensive care unit
* Dunham: only looked at data pertaining to EN+PN vs EN (not EN +PN vs PN)
± ( ) : mean ± Standard deviation (number)
**data obtained from author in mean and SD
ITT: intent to treat; NA: not available
LOS: length of stay
† presumed hospital mortality unless otherwise specified
‡ refers to the # of patients with infections unless specified

Table 2. Physical and Quality of Life (QOL) Outcomes

Study	Physical Outcomes EN+PN	 EN	QOL outcomes EN+PN	 EN
7) Chen 2011	Changes in respiratory muscle strength before and after nutrition support (cmH_2O) Before On day 7 28.34 ± 9.49 34.32 ± 15.43 P=0.025	 Before On day 7 26.75 ± 11.6 32.3 ± 10.03 P=0.011	NR	
9) Wischmeyer 2017	Handgrip at ICU discharge 9 (43) [unable-25]	 unable (62) [unable-18] P=0.21 Handgrip at hospital discharge 12 (36) [unable-33] unable (56) [unable-20] P=0.14 6 minute walk test at hospital discharge Unable (40) [unable-0] unable (60) [unable-unable] P=0.2	Barthel Index at hospital discharge 61.1 ± 32.4 (28)	 46.5 ± 32.1 (41) P=0.08 SF-36 3 Months: Physical Functioning 34.8 ± 31.5 (24, 63%) 39.4 ±34.3 (30, 55%) P=0.76 SF-36 3 Months: Role-physical 32.8 ± 32.6 (25, 66%) 30.2 ±31.8 (30, 55%) P=0.59 SF-36 3 Months: Pain Index 66.4 ± 27.3 (24, 63%) 59.1 ± 28.8 (28, 52%) P=0.44 SF-36 3 Months: General health perceptions

		49.5 ± 24.3 (24, 63%) 61.2 ± 18.3 (27, 50%) P=0.14 SF-36 3 Months: Vitality 51.0 ± 21.7 (24, 63%) 52.8 ± 21.4 (28, 52%) P=0.72 SF-36 3 Months: Social Functioning 56.5 ± 28.2 (25, 66%) 60.4 ± 31.8 (30, 55%) P=0.56 SF-36 3 Months: Role emotional 65.3 ± 34.4 (25, 63%) 63.2 ± 34.6 (29, 54%) P=0.88 SF-36 3 Months: Mental health index 76.1 ± 18.5 (23, 61%) 72.9 ± 18.7 (28, 52%) P=0.39 SF-36 3 Months: Standardized physical component scale 33.3 ± 10.1 (22, 58%) 35.3 ± 10.8 (27, 50%) P=0.38 SF-36 3 Months: Standardized mental component scale 51.5 ± 10.0 (22, 58%) 50.0 ± 10.5 (27, 50%) P=0.38 SF-36 6 Months: Physical Functioning 50.8 ± 36.5 (20, 53%) 39.3 ±34.0 (31, 57%) P=0.21 SF-36 6 Months: Role-physical 47.5 ± 33.4 (20, 53%) 40.2 ± 33.1 (32, 59%) P=0.43 SF-36 6 Months: Pain Index 68.6 ± 28.2 (20, 53%) 52.5 ± 31.0 (31, 57%) P=0.08 SF-36 6 Months: General health perceptions 56.8 ± 26.2 (20, 53%) 50.9 ± 20.6 (31, 57%) P=0.46 SF-36 6 Months: Vitality 59.1 ± 21.7 (20, 53%) 47.8 ± 21.2 (31, 57%) P=0.06 SF-36 6 Months: Social Functioning 68.8 ± 32.6 (20, 53%) 50.4 ± 32.2 (31, 57%) P=0.06 SF-36 6 Months: Role emotional

		72.13 ± 30.3 (20, 53%) 52.2 ± 41.0 (32, 59%) P=0.10 SF-36 6 Months: Mental health index 70.5 ± 24.9 (20, 53%) 66.1 ± 22.5 (31, 57%) P=0.36 SF-36 6 Months: Standardized physical component scale 39.3 ± 10.2 (20, 53%) 35.8 ± 11.2 (30, 55%) P=0.17 SF-36 6 Months: Standardized mental component scale 49.0 ± 13.5 (20, 53%) 43.2 ± 14.8 (30, 55%) P=0.11
10) Ridley 2018	Hand grip at hospital d/c, kg, mean (SD) 19 (13.5), n=19 20 (8), n=24 P=0.71 ICU mobility scale at hospital d/c, median (IQR) 9 [5-10], n=25 8 [4-10], n=33 P=0.58	EQ-5D-3L hospital d/c mean (SD) 0.25 (0.34), n=27 0.32 (0.36), n=17 P=0.54 90 days median (IQR) 0.69 (0.24), n=35 0.76 (0.23), n=29 P=0.29 180 days, mean (SD) 0.75 (0.26), n=35 0.77 (0.24), n=29 P=0.76

Note: Only studies reporting on these outcomes are shown in this table.

Figure 1. Overall Mortality

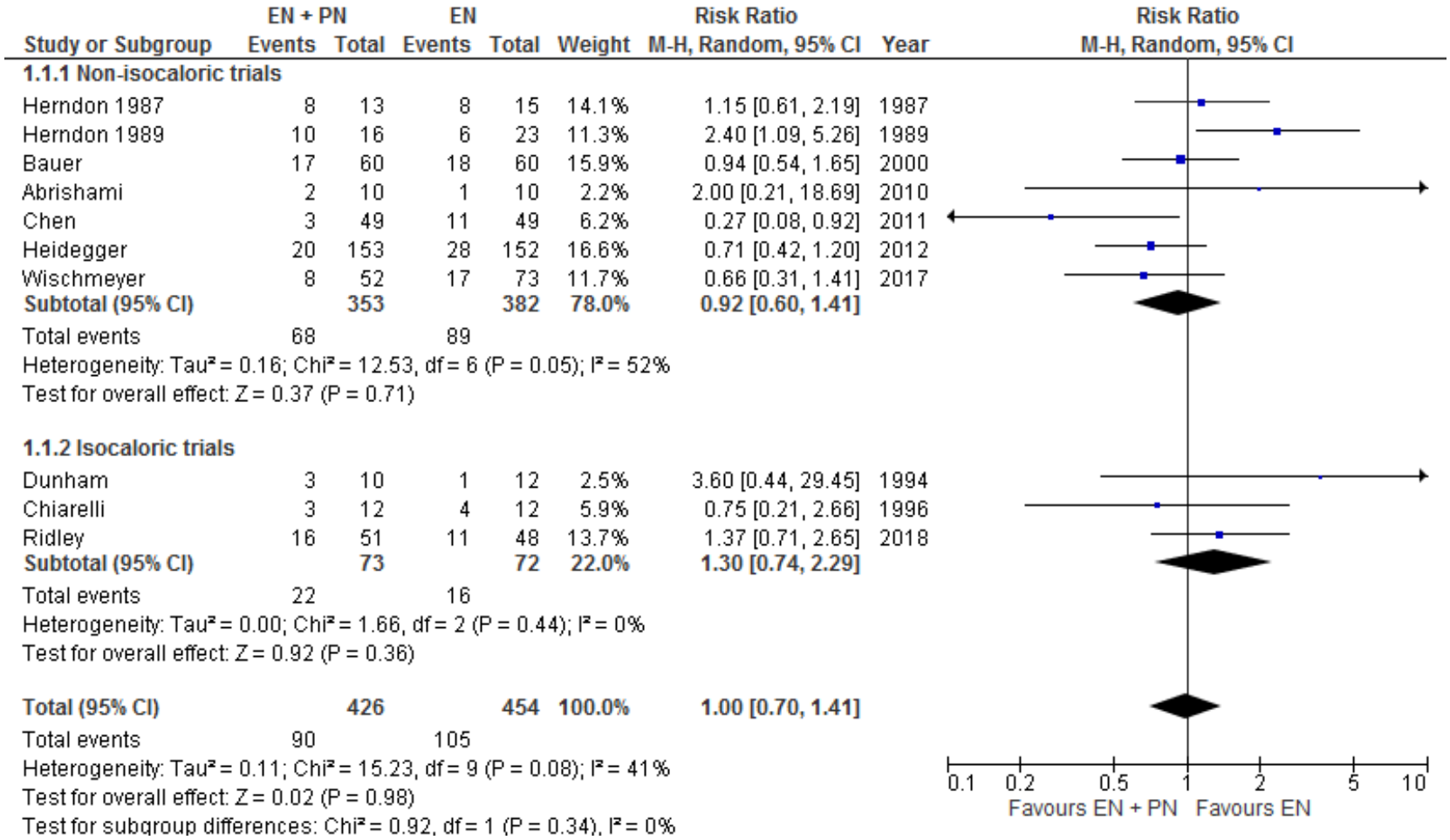

Figure 2. Infectious complications

Study or Subgroup	EN +PN Events	EN +PN Total	EN Events	EN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Chiarelli	6	12	3	12	1.4%	2.00 [0.65, 6.20]	1996
Bauer	39	60	39	60	26.1%	1.00 [0.77, 1.30]	2000
Chen	6	49	5	49	1.4%	1.20 [0.39, 3.67]	2011
Heidegger	77	153	85	152	40.2%	0.90 [0.73, 1.11]	2012
Wischmeyer	38	52	46	73	30.9%	1.16 [0.91, 1.48]	2017
Total (95% CI)		**326**		**346**	**100.0%**	**1.02 [0.89, 1.16]**	
Total events	166		178				

Heterogeneity: Tau² = 0.00; Chi² = 3.91, df = 4 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

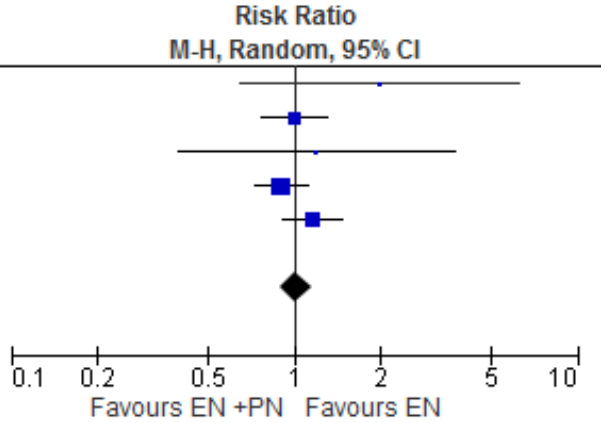

Figure 3. Hospital LOS

Study or Subgroup	EN + PN Mean	EN + PN SD	EN + PN Total	EN Mean	EN SD	EN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Chiarelli	37	13	12	41	23	12	4.5%	-4.00 [-18.95, 10.95]	1996
Bauer	31.2	18.5	60	33.7	27.7	60	11.8%	-2.50 [-10.93, 5.93]	2000
Chen	17.3	2.47	49	23.32	5.6	49	43.8%	-6.02 [-7.73, -4.31]	2011
Heidegger	31	23	153	32	23	152	22.5%	-1.00 [-6.16, 4.16]	2012
Wischmeyer	39.9	61.9	52	29.6	22.6	73	3.3%	10.30 [-7.30, 27.90]	2017
Ridley	22	21	51	23	17	48	14.0%	-1.00 [-8.51, 6.51]	2018
Total (95% CI)			**377**			**394**	**100.0%**	**-3.14 [-6.46, 0.18]**	

Heterogeneity: Tau² = 5.78; Chi² = 8.00, df = 5 (P = 0.16); I² = 38%
Test for overall effect: Z = 1.85 (P = 0.06)

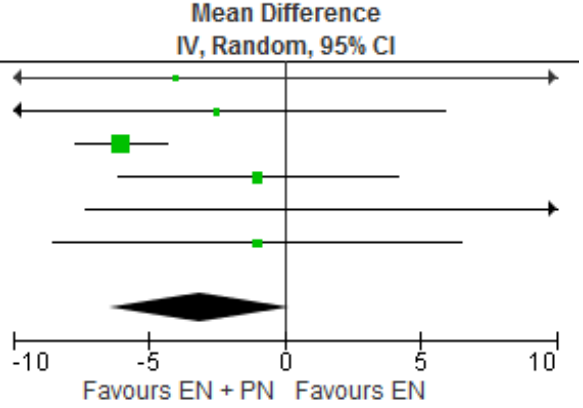

Figure 4. ICU LOS

Study or Subgroup	EN + PN Mean	SD	Total	EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Bauer	16.9	11.8	60	17.3	12.8	60	11.7%	-0.40 [-4.81, 4.01]	2000
Chen	6.75	1.75	49	9.09	2.75	49	39.2%	-2.34 [-3.25, -1.43]	2011
Heidegger	13	10	153	13	11	152	24.5%	0.00 [-2.36, 2.36]	2012
Wischmeyer	16.7	13.5	52	14.2	9.2	73	12.4%	2.50 [-1.73, 6.73]	2017
Ridley	13	10	51	13.9	11.7	48	12.1%	-0.90 [-5.20, 3.40]	2018
Total (95% CI)			**365**			**382**	**100.0%**	**-0.76 [-2.52, 1.00]**	

Heterogeneity: Tau² = 1.84; Chi² = 8.10, df = 4 (P = 0.09); I² = 51%
Test for overall effect: Z = 0.85 (P = 0.39)

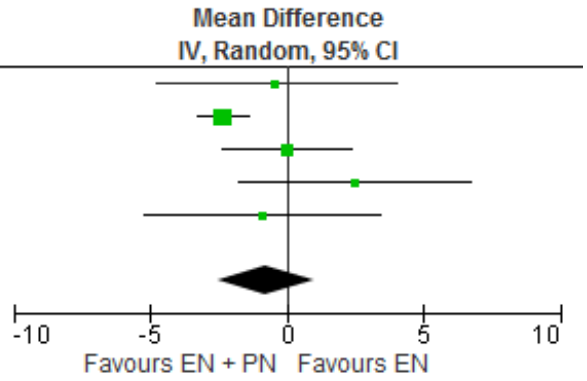

Figure 5. Ventilator days

Study or Subgroup	EN + PN Mean	SD	Total	EN Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Chiarelli	19	6	12	19	2	12	9.6%	0.00 [-3.58, 3.58]	1996
Bauer	11	9	60	10	8	60	12.0%	1.00 [-2.05, 4.05]	2000
Chen	5.76	1.56	49	7.95	2.11	49	31.1%	-2.19 [-2.92, -1.46]	2011
Heidegger	2.5	4.625	153	2.75	4.21	152	28.7%	-0.25 [-1.24, 0.74]	2012
Wischmeyer	11.1	11.3	52	10.4	8.7	73	9.3%	0.70 [-2.96, 4.36]	2017
Ridley	12.2	8.31	51	12.8	10.1	48	9.3%	-0.60 [-4.26, 3.06]	2018
Total (95% CI)			**377**			**394**	**100.0%**	**-0.62 [-1.93, 0.68]**	

Heterogeneity: Tau² = 1.29; Chi² = 13.92, df = 5 (P = 0.02); I² = 64%
Test for overall effect: Z = 0.94 (P = 0.35)

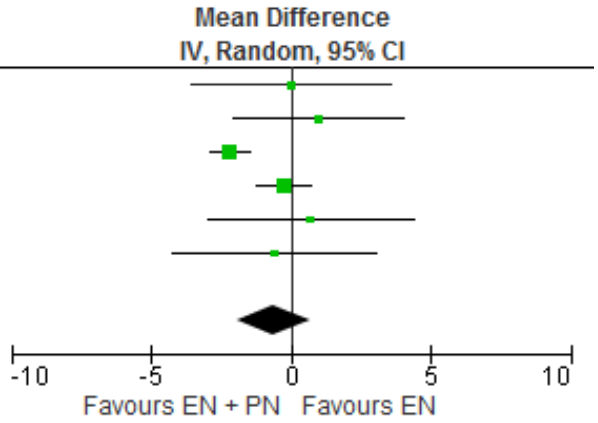

Table 2. Excluded Articles

#	Reason excluded	Citation
1	Excluded as compares EN+PN to PN, not to EN	Hausmann D, Mosebach KO, Caspari R, Rommelsheim K (1985) Combined enteral-parenteral nutrition versus total parenteral nutrition in brain-injured patients. A comparative study. Intensive Care Med 11:80-84
2	Systematic review	Dhaliwal R, Jurewitsch B, Harrietha D, Heyland DK. Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. Intensive Care Med. 2004 Aug;30(8):1666-71. Epub 2004 Jun 8.
3	compares albumin and EN+PN to PN, not EN	Sun B, Gao Y, Xu J, Zhou XL, Zhou ZQ, Liu C, Jiang HC. Role of individually staged nutritional support in the management of severe acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2004 Aug;3(3):458-63.
4	Not ICU patients	Thomas DR, Zdrodowski CD, Wilson MM, Conright KC, Diebold M, Morley JE. A prospective, randomized clinical study of adjunctive peripheral parenteral nutrition in adult subacute care patients. J Nutr Health Aging. 2005 Sep-Oct;9(5):321-5.
5	Elective surgery patients	Nagata S, Fukuzawa K, Iwashita Y, Kabashima A, Kinoshita T, Wakasugi K, Maehara Y. Comparison of enteral nutrition with combined enteral and parenteral nutrition in post-pancreaticoduodenectomy patients: a pilot study. Nutr J. 2009 Jun 11;8:24.
6	Not ICU pts and compares EN+PN to PN	Chen Y, Yang Q, Zhao W, Zhou Z. (2010). safety of application of enteral nutrition in non-blood circulation disorders of elderly patients with intestinal obstruction. Chinese J of Clin Nutr. 18(3); 162-166
7	Elective surgery patients	Cui HY, Zhu MZ, Wei JM, Hua B, Xu JY, Men JF. Comparison of the benefits of combined nutrition support with enteral nutrition and parenteral nutrition versus sole parenteral nutrition support for elderly patients after pancreaticoduodenectomy. Chinese Journal of Clinical Nutrition. 2010; 18(3):153-7
8	Elective cancer surgery patients	Lidder P, Flanagan D, Fleming S, Russell M, Morgan N, Wheatley T, Rahamin J, Shaw S, Lewis S. Combining enteral with parenteral nutrition to improve postoperative glucose control. Br J Nutr. 2010 Jun;103(11):1635-41. Epub 2010 Mar 9.
9	Systematic review, Individual studies included	Al Samaraee A, McCallum IJ, Coyne PE, Seymour K. Nutritional strategies in severe acute pancreatitis: a systematic review of the evidence. Surgeon. 2010 Apr;8(2):105-10. Epub 2010 Feb 16. Review.
10	Elective surgery patients	Kang W, Yu J, Ma Z, Wang J, Ge J, Li Z. Comparison of clinical efficacy between standard sequential early enteral nutrition plus parenteral nutrition and parenteral nutrition support in patients undergoing gastrointestinal surgery: A clinical randomized controlled trial. Chinese Journal of Clinical Nutrition. 2011 Jun;19(3):148-53
11	Unknown if all patients received PN: PN given only when required	Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, Grozovski E, Theilla M, Frishman S, Madar Z. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med. 2011 Apr;37(4):601-9. Epub 2011 Feb 22.
12	pseudo randomized	Fan MC, Wang QL, Fang W, Jiang Y, Li L, Sun P, et al. Early enteral combined with parenteral nutrition treatment for severe traumatic brain injury: effects on immune function, nutritional status and outcomes. Chinese Medical Science Journal 2016;31(4):213–20.
13	meta analyses	Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a combination of enteral and parenteral nutrition for adults in the intensive care unit. Cochrane Database Syst Rev. 2018 Jun 8;6:CD012276.
14	meta analyses	Shi J, Wei L, Huang R, Liao L. Effect of combined parenteral and enteral nutrition versus enteral nutrition alone for critically ill patients: A systematic review and meta-analysis. Medicine (Baltimore). 2018 Oct;97(41):e11874.