1.0 The Use of Enteral Nutrition vs. Parenteral Nutrition

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

Summary of evidence: There were nineteen 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. There have been two more recent, large RCTs, Harvey 2014 and Reignier 2017, which enrolled 2400 and 2410 patients, respectively, across 33 and 44 sites. Other more recent smaller trials included patients fasting for at least 14 days (Xi 2014), patients with moderate traumatic brain injury (Meirelles 2011) and patients with severe acute pancreatitis (Wang 2013, Sun 2013). 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). The Moore 1992 study, which had been included in the 2009 summary, was reviewed again and excluded since it reports results of a meta-analysis and the individual studies have been included. Given concerns about population in the Mereilles 2011 and Wang 2013 studies not being critically ill as no mention of ventilation status and some missing data in the latter study, a sensitivity analysis was also done excluding these two studies.

Mortality: In the two largest studies (Harvey and Reignier), there were no significant differences between the parenteral group and the enteral group in 30 or 28 day mortality (P = 0.57 and 0.33, respectively) or 90 day mortality (P = 0.4 and 0.28, respectively) or hospital mortality (P = 0.44 and 0.25, respectively). However, both studies showed a trend in the reduction in ICU mortality, favoring the PN group (P = 0.13 and 0.17, respectively). When these data were aggregated with the other 16 studies reporting on mortality, there was no difference in overall mortality between the groups receiving EN or PN (RR 1.03, 95% CI 0.93, 1.14, p=0.36, heterogeneity I^2=6%, figure 1). When the trials in which the PN group were fed more calories than the EN group were aggregated, there was no effect seen (RR 1.19, 95% CI 0.86, 1.64, p = 0.30, heterogeneity I^2=31%; figure 1). Similarly, when the trials in which the PN and EN groups were fed isocalorically were aggregated, there was no effect on mortality (RR 1.03, 95% CI 0.93, 1.14, p=0.6, heterogeneity I^2=0%; figure 1). There was no difference in these subgroups (p=0.40; figure 1). In 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 (RR 0.93, 95% CI 0.30, 2.90, p=0.90, heterogeneity I^2=0%; figure 2). In a sensitivity analysis excluding Mereilles 2011, Wang 2013, there was still no difference in mortality between groups (RR 1.05, 95% CI 0.95, 1.15, p=0.32, heterogeneity I^2=7%; figure not shown). When data from the 6 studies reporting on ICU mortality were aggregated, there was no effect seen (RR 1.04, 95% CI 0.97, 1.12, p = 0.28, heterogeneity I^2=0%, figure 3). There was also no effect seen when looking at subgroups where the PN group was fed more than the EN group and where the two groups were fed isocalorically (p = 0.38 and 0.71, respectively, figure 3).

Infections: When the 12 studies which reported on patients with 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 0.74, 95% CI 0.59, 0.91,

p=0.005, heterogeneity I^2=42%; figure 4). When the trials in which the PN group were fed more calories than the EN group were aggregated, EN compared to PN was also associated with a significant reduction in the incidence of infectious complications (RR 0.58, 95% CI 0.39, 0.88, p=0.009, heterogeneity I^2=53%; figure 4). When the trials in which the PN and EN groups were fed isocalorically were aggregated, EN compared to PN had no effect on infectious complications (RR 0.94, 95% CI 0.80, 1,10, p=0.44, heterogeneity I^2=0%; figure 4). There was a significant difference in these subgroups (p=0.03; figure 4). Another subgroup analysis showed that there was a trend between the increase in infections and hyperglycemia (RR 0.79, 95% CI 0.56, 1.11, p=0.17, heterogeneity I^2=0%; figure 5). In a sensitivity analysis excluding Mereilles 2011, EN compared to PN was associated with a significant reduction in infectious complications (RR 0.66, 95% CI 0.50, 0.86, p=0.003, heterogeneity I^2=38%, figure not shown.

LOS, Ventilator days: A total of 9 studies reported on hospital length of stay (in mean and standard deviation) and when the data were aggregated, no effect was seen on hospital LOS (WMD -1.35, 95% CI -3.52, 0.82, p=0.22, heterogeneity I^2=70%; figure 6). Only 6 studies reported on ICU LOS (in mean and standard deviation) and when the data were aggregated, the use of EN was associated with a reduction in ICU LOS (WMD -2.12, 95% CI -4.20, -0.04, p=0.05, heterogeneity I^2=94%; figure 7). A total of 5 studies reported on length of mechanical ventilation (in mean and standard deviation) and when the data were aggregated, there was a trend towards a reduction in ventilator days in the EN fed group (WMD -1.23, 95% CI -2.80, 0.34, p=0.13, heterogeneity I^2=87%, figure 8).

Nutritional complications: Of the 13 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 8 reported no significant difference in intakes between the groups (Adams, Hadley, Cerra, Dunham, Borzotta, Kalfarantzos, Wang, Harvey). A total of 7 studies reported on hyperglycemia and in 4 of these, EN was associated with a lower incidences of hyperglycemia compared to PN (Adams p<0.001), (Borzotta p<0.05, Kalfarentzos) (Mereilles p<0.01). Three studies showed no difference in blood sugars between the groups receiving EN and PN (Moore 1989, Rapp, Harvey). Four studies showed that EN was associated with an increase in diarrhea (Cerra p<0.05, Young, Kudsk p<0.01, Harvey) while one showed an association with EN and a reduction in diarrhea (Borzotta p<0.05) and one study showed no difference (Adam).

Other Complications: EN was also associated with an increase in vomiting (Cerra p<0.05), Harvey 2014 p <0.001). One study found less favourable neurological outcome at 3 months (p =0.05) in brain injured patients (Young, p=0.05), though this significance disappeared after 6 months and 1 year. More overall nutrition related complications were noted in EN vs PN (Dunham). Seven studies reported on diarrhea. There were significant reductions in the incidence of hypoglycemia (44 patients [3.7%] vs. 74 patients [6.2%]; P = 0.006) in the parenteral group in the largest study (Harvey 2014)

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

Quality of Life (QOL) Outcomes: In a second publication (Harvey 2016), quality of life from the Harvey 2014 study was reported. In the trial, the EuroQol 5-dimension (5-level version) questionnaire (EQ-5D-5L) and a Health Services Questionnaire (to evaluate health and nutrition related

quality of life (QOL)) were completed at 90 days post randomization and 1 year post-randomization with survivors. At 90 days and 1 year post randomization, Harvey et al found that health components from the EQ-5D-5L questionnaire were similar between groups. The results for nutrition related QOL were reported on a scale from 1 (worst possible satisfaction) to 7 (best possible satisfaction). At 90 days post-randomization, there was no difference in the mean response between the PN (mean (SD) of 5.2 (1.6, n=405)) and EN groups (5.1 (1.7, n=378)) (mean difference 0.10, 95% CI, -0.14, 0.33, p=0.43) (data not shown in table). At 1 year, there was also no significant difference (5.3 (1.6) in the PN group (n=338) vs 5.4 (1.6) in the EN group (n=322), mean difference -0.10, 95% CI,-0.35, 0.14, p=0.41) (data not shown in table).

Conclusions:

1) The use of EN compared to PN has no effect on mortality in critically ill patients.
2) The use of EN compared to PN is associated with a reduction in the number of infectious complications in the critically ill in trials where patients in the PN group received more calories than in the EN group.
3) The use of EN compared to PN may be associated with a reduction in ICU LOS and ventilator days, but it has no effecton hospital LOS. Significant heterogeneity limits the inferences from these aggregated analyses.
4) The use of EN compared to PN may not be associated with an improvement in calories due to underfeeding in both groups
5) The use of EN may be associated with increased episodes of vomiting.
6) There is no difference between EN and PN in terms of patient reported outcomes

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 # (%)† EN	Mortality # (%)† PN	Infections # (%)‡ EN	Infections # (%)‡ PN
1. Rapp 1983	Head Injured patients N=38 (<Ideal weight) Single-centre	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 Single-centre	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 (N=51 randomized) Single-centre	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 Single-centre	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) Single-centre	C.Random: not sure ITT: no Blinding: no (2)	EN vs PN	ICU 7/31 (22)	ICU 8/35 (23)	NR	NR
6. Moore 1989	Abdominal trauma patients N=75 Single-centre	C.Random: yes ITT: no Blinding: no (10)	EN vs PN	NR	NR	5/29 (17)	11/30 (37)
7. Kudsk 1992	Abdominal trauma N=98 Single-centre	C.Random: not sure ITT: no Blinding: single (10)	EN vs PN	ICU 1/51 (2)	ICU 1/45 (2)	9/51 (16)	18/45 (40)

8. Dunham 1994	Blunt trauma N=38 Single-centre	C.Random: not sure ITT: no Blinding: no (8)	EN vs PN	1/12 (7)	1/15 (8)	NR	NR
9. Borzotta 1994	Closed head injury N=59 Single-centre	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
10. Hadfield 1995	ICU patients, mainly cardiac bypass N=24 Single-centre	C.Random: not sure ITT: no Blinding: no (7)	EN vs PN	ICU 2/13 (15)	ICU 6/11 (55)	NR	NR
11. Kalfarentzos 1997	Severe acute pancreatitis N=38 Single-centre	C.Random: not sure ITT: no Blinding: single (9)	EN vs PN	ICU 1/18 (6)	ICU 2/20 (10)	5/18 (28)	10/20 (50)
12. Woodcock 2001	Patients needing nutrition support N=562 ICU patients N=38 (all degrees of malnutirition) Single-centre	C.Random: yes ITT: yes Blinding: single (12)	EN vs PN	9/17 (53)	5/21 (24)	6/16 (38)	11/21 (52)
13. Casas 2007	Severe acute pancreatitis; ICU≥72 hrs N=22 Single-centre	C.Random: no/unsure ITT: Yes Blinding: No (8)	EN vs PN	Hospital 0/11 (0)	Hospital 2/11 (18)	1/11 (9)	3/11 (27)
14. Chen 2011	Elderly Patients in respiratory intensive care unit N=147 Single-centre	C.Random: Yes ITT: Yes Blinding: No (7)	EN vs PN	20-day 11/49 (22)	20-day 10/49 (20)	5/49 (10)	18/49 (37)

15. Meirelles 2011	Adult patients with moderate traumatic brain injury N=22 Single-centre	C.Random: No ITT: No Blinding: No (5)	EN vs PN	Unspecified 1/12 (8.3)	Unspecified 1/10 (10)	Total infectious complications 2/12 (16.7) Pneumonia (cases) 2/12 (16.7) Sepsis (cases) 0	Total infectious complications 4/10 (40) Pneumonia (cases) 2/10 (20) Sepsis (cases) 2/10 (20)
16. Wang 2013	Patients 18-45 years with severe acute pancreatitis N=183 Single-centre	C.Random: No ITT: No Blinding: Double (7)	EN vs PN	Hospital 3/61 (5)	Hospital 7/60 (12)	Pancreatic sepsis 13/61 (21) MODS 15/61 (24.6)	Pancreatic sepsis 24/60 (40) MODS 22/60 (36.7)
17. Sun 2013	Severe acute pancreatitis admitted to surgical ICU N=60 Single-centre	C.Random: No ITT: No Blinding: No (6)	EN vs PN	Hospital 2/30 (7)	Hospital 1/30 (3)	Pancreatic 3/30 (10) MODS 5/30 (17) SIRS 12/30 (40)	Pancreatic 10/30 (33) MODS 13/30 (43) SIRS 22/30 (73)
18. Harvey 2014	Adult patients admitted to a general ICU N=2400 Multi-centre	C.Random: Yes ITT: Yes Blinding: No (8)	EN vs PN	ICU 352/1197 (29.4) Hospital 450/1186 (37.9) 30-day 409/1195 (34.2) 90-day 464/1188 (39.1)	ICU 317/1190 (26.6) Hospital 431/1185 (36.4) 30-day 393/1188 (33.1) 90-day 442/1184 (37.3)	Total infectious complications 194/1197 (16.2)** Infectious complications per pt 0.21 +/- 0.5 Pneumonia 143/1197 (11.9) Bloodstream inf 21/1197 (1.8) Surgical inf 12/1197 (1.0)	Total infectious complications 194/1191 (16.3)** Infectious complications per pt 0.22 +/- 0.6 Pneumonia 135/1191 (11.3) Bloodstream inf 27/1191 (2.9) Surgical inf 10/1191 (0.8)
19. Xi 2014	ICU pts fasting at least 14 days, eligible for EN. Single Centre. N=45	C.Random: No ITT: Yes Blinding: No (7)	EN vs PN	28-day 0/22	28-day 0/23	Positive blood cultures 4/22 Sepsis 4/22 (17)	Positive blood cultures 0/23 Sepsis 5/23 (23)

20. Reignier 2017	Mechanically ventilated ICU pts receiving vasopressor support for shock. Multi-centre. N=2410	C.Random: Yes ITT: Yes Blinding: No (11)	EN vs PN	ICU 429/1202 (33) Hospital 498/1202 (36) 28-day 443/1202 (37) 90-day 530/1185 (45)	ICU 405/1208 (31) Hospital 479/1208 (34) 28-day 422/1208 (35) 90-day 507/1192 (43)	ICU acquired 173/1202 (14)	ICU acquired 194/1208 (16)

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/infections obtained directly from author

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

Study	LOS days		Ventilator days		Cost		Other	
	EN	PN	EN	PN	EN	PN	EN	PN
1. Rapp 1983	Hospital 49.4*	Hospital 52.6*	10.3*	10.4*	NR	NR	Mean Calorie Intake (kcals) in study 685 1750 p=0.001 Nitrogen Intake (gms) 4.0 10.2 p=0.002 N balance/24hrs, p=0.002 -17.6 -10.9 Hyperglycemia no difference between groups	
2. Adams 1986	ICU 13 ± 11 (19) Hospital 30 ± 21 (19)	ICU 10 ± 10 (17) Hospital 31 ± 29 (17)	12 ± 11 (17)	10 ± 10 (13)	$1346/day	$3729/day	Calorie Intake (kcals) in study 2088 2572 p=NS Caloric adequacy 73% 89% N balance/24 hrs -8.7±6.8 -4.1±4.6 Hyperglycemia (pt days) 24/242 (10) 49/220 (22) p<0.001 Line Problems 13/9 9/7 Diarrhea (days/pt) 3.5 3.8	
3. Young 1987	NR	NR	NR	NR	NR	NR	Calories ÷ BEE x 1.75 59% ± 5.13% 75.6% ± 4.26% p=0.02 Protein Intake (gm/kg/day) 0.91 ± 0.09 1.35 ± 0.12 p=0.004 Favourable Neurological Outcome (3 months) 17.9 % 43.5 % Diarrhea 23/28 (82) 13/23 (57)	

4. Peterson 1988	ICU 3.7 ± 0.8 (21) Hospital 13. 2 ± 1.6 (21)	ICU 4.6 ± 1.0 (25) Hospital 14.6 ± 1.9 (24)	NR	NR	NR	NR	Day 5 Calorie Intake (kcals) 2204 ± 173 2548 ± 85 P=0.04 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	NON PROTEIN Calorie Intake 1684 ± 573 2000 ± 20 p=NS Protein g/d 80±26 88±20 N-balance/d -3.4±10 0.4±3.8 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	Non-protein Calorie Intake, day 5 1847 ± 123 2261 ± 60 p=0.01 Nitrogen intake, day 5, p=0.01 12.4±0.8 15.4±0.4 N balance, day 5, p=NS -0.3±0.1 0.1±0.8 Blood Sugars no difference between the groups Non-septic Complications 6/29 (21) 7/30 (23)
7. Kudsk 1992	Hospital 20.5 ± 19.9 (51)	Hospital 19.6 ± 18.8 (45)	2.8 ± 4.9 (51)	3.2 ± 6.7 (45)	NR	NR	NON PROTEIN Calorie Intake (kcal/kg/day) 15.7 ± 4.2 19.1 ± 3.3 p<0.05 Diarrhea 11/51 (22) 7/45 (16)

8. 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)
9. Borzotta 1994	Hospital (assumed) 39 ± 23.1	Hospital (assumed) 36.9 ± 14	NR	NR	$121,941	$112,450	Calorie Intake no difference between the groups Placement Complications 3/28 (11) 0/21 (0) Aspiration 3/28 (11) 0/21 (0) Hyperglycemia 12/28 (44) 16/21 (76) P=<0.05 Diarrhea 30% 62%
10. Hadfield 1995	NR	NR	NR	NR	NR	NR	
11. Kalfarentzos 1997	ICU 11 (5-21)* Hospital 40 (25-83)*	ICU 12 (5-24)* Hospital 39 (22-73)*	15 (6-16)*	11 (7-31)*	£70/day savings	NR	Non-protein Calorie Intake (kcal/kg/day) 24.1 24.5 p=NS Protein Intake (gm/kg/day) 1.43 1.45 p=NS Hyperglycemia 4/18 (22) 9/20 (45) P=NR
12. Woodcock 2001	33.2 ± 43 (16)	27.3 ± 18.7 (18)	NR	NR	NR	NR	% Target Intake Achieved 54.1% 96.7% p<0.001 < 80% Target Intake 62.5% 6.3% p<0.001

13. Casas 2007	Hospital 30.2 (average)	Hospital 30.7 (average)	NR	NR	NR	NR	Kcal/kg/d, p=ns, n=11 in both groups 20.09±1.83 20.8±1.68 P=NS Nitrogen g/kg/d, p<0.005 0.148±0.016 0.186±0.009
14. Chen 2011	ICU 9.09 ± 2.75 Hospital 23.32 ± 5.6	ICU 9.60 ± 3.06 Hospital 22.24 ± 3.27	7.95 ± 2.11	8.23 ± 2.42	NR	NR	Non-infectious Complications 10/49 (20) 21/49 (43) Gastric Residuals 6/49 (12) 0/49 (0) Diarrhea 6/49 (12) 8/49 (16)
15. Meirelles 2011	ICU 14 (5-26)	ICU 14 (6-24)	NR	NR	NR	NR	Kcal over 5 days 5958 +/- 3619 6586 +/- 1052 P=0.34 Mean daily N-balance, p=0.34 -4.6g/day -5.9g/day Blood Glucose (mg/dl) 102.4 (91.6 – 113.2) 134.4 (122.6-146.2) p < 0.0111
16. Wang 2013	NR	NR	NR	NR	NR	NR	NR
17. Sun 2013	ICU 9 (5-14)	ICU 12 (8-21)	*NR*	NR	NR	NR	NR
18. Harvey 2014	ICU 11.3 ± 12,5 (1197) Hospital 26.8 ± 33.2 (1186)	ICU 12 ± 13.5 (1190) Hospital 27.5 ± 33.9 (1185)	8.2 ± 9.3 (1197)	8.7 ± 11,5 (1189)	NR	NR	Vomiting 1/1197 (0.1) 1/1197 (0.1) Aspiration/Regurgitation 4/1197 (0.3) 2/1191 (0.2) Diarrhea 250/1197 (21) 192/1191 (16.2) Total kcal received during intervention period (kcal/kg) 74 ± 44 89 ± 44 P=NR Total protein received during intervention period (g/kg) 3 ± 2 3 ± 2
19. Xi 2014	ICU 8.52 ± 3.6 (22) Hospital 20.43 ± 10.49 (22)	ICU 20.33 ± 4.47 (23) Hospital 38.76 ± 15.04 (23)	2.96 ± 1.74 (22)	8.62 ± 3.6 (23)	Hospital cost x 10^4 1.45 ±0.25	Hospital cost x 10^4 3.47 ± 0.69	NR

20. Reignier 2017	ICU 9.0 (5.0-16.0) 13.7±16.1** N=1201 Hospital 17.0 (8.0-32.0) 25.1±28.4** N=1202	ICU 10.0 (5.0-17.0) 13.7±13.9** N=1207 Hospital 18.0 (9.0-33.0) 25.9±27.0** N=1208	10.7±14.4** N=1201	10.9±12.6** N=1207	NR	NR	Diarrhea 432/1202 (36) 393/1208 (33) Kcal/kg/d 17.8 ± 5.5 19.6 ± 5.3 P<0.0001 Protein g/kg/d 0.7 ± 0.2 0.8 ± 0.2 P<0.0001

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 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 2. Quality of Life (QOL) Outcomes

Study	QOL outcomes			
	EN	PN	EN	PN
	N=544	N=558	N=473	N=467
18. Harvey 2014	EQ-5D-5L components at 90 days post-randomization		EQ-5D-5L components at 1 year post-randomization	
	Mobility: No problems		Mobility: No problems	
	168	170	172	166
	Mobility: Slight problems		Mobility: Slight problems	
	108	118	90	93
	Mobility: Moderate problems		Mobility: Moderate problems	
	142	135	99	114
	Mobility: Severe problems		Mobility: Severe problems	
	76	75	80	65
	Mobility: Extreme problems		Mobility: Extreme problems	
	50	60	32	29
	Self-care: No problems		Self-care: No problems	
	293	299	287	280
	Self-care: slight problems		Self-care: slight problems	
	113	106	71	87
	Self-care: Moderate problems		Self-care: Moderate problems	
	72	85	71	60
	Self-care: Severe problems		Self-care: Severe problems	
	29	31	24	20
	Self-care: Extreme problems		Self-care: Extreme problems	
	37	37	20	20
	Usual Activities: No problems		Usual Activities: No problems	

	119	Usual Activities: Slight problems	131	163	Usual Activities: Slight problems	151
	131	Usual Activities: Moderate problems	123	104	Usual Activities: Moderate problems	110
	130	Usual Activities: Severe problems	140	99	Usual Activities: Severe problems	103
	67	Usual Activities: Extreme problems	74	62	Usual Activities: Extreme problems	65
	97	Pain/discomfort: No problems	90	45	Pain/discomfort: No problems	38
	178	Pain/discomfort: Slight problems	173	159	Pain/discomfort: Slight problems	145
	163	Pain/discomfort: Moderate problems	150	136	Pain/discomfort: Moderate problems	139
	133	Pain/discomfort: Severe problems	162	125	Pain/discomfort: Severe problems	111
	54	Pain/discomfort: Extreme problems	56	54	Pain/discomfort: Extreme problems	42
	16	Anxiety/depression: No problems	17	11	Anxiety/depression: No problems	18
	239	Anxiety/depression: Slight problems	242	235	Anxiety/depression: Slight problems	218
	142	Anxiety/depression: Moderate problems	158	91	Anxiety/depression: Moderate problems	109
	114	Anxiety/depression: Severe problems	111	95	Anxiety/depression: Severe problems	95
	35	Anxiety/depression: Extreme problems	28	41	Anxiety/depression: Extreme problems	30
	14		19	11		15
	N=1197		N=1191	N=1197		N=1191
	EQ-5D-5L Utility Score (survivors), mean (SD)			EQ-5D-5L Utility Score (survivors), mean (SD)		
	0.654 (0.283)		0.655 (0.282)	0.683 (0.292)		0.684 (0.285)
	QALYs			QALYs		
	0.050 (0.049)		0.051 (0.048)	0.335 (0.332)		0.348 (0.333)
	P=0.46			P=0.35		

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

Figure 1. Studies comparing EN vs PN: Overall Mortality

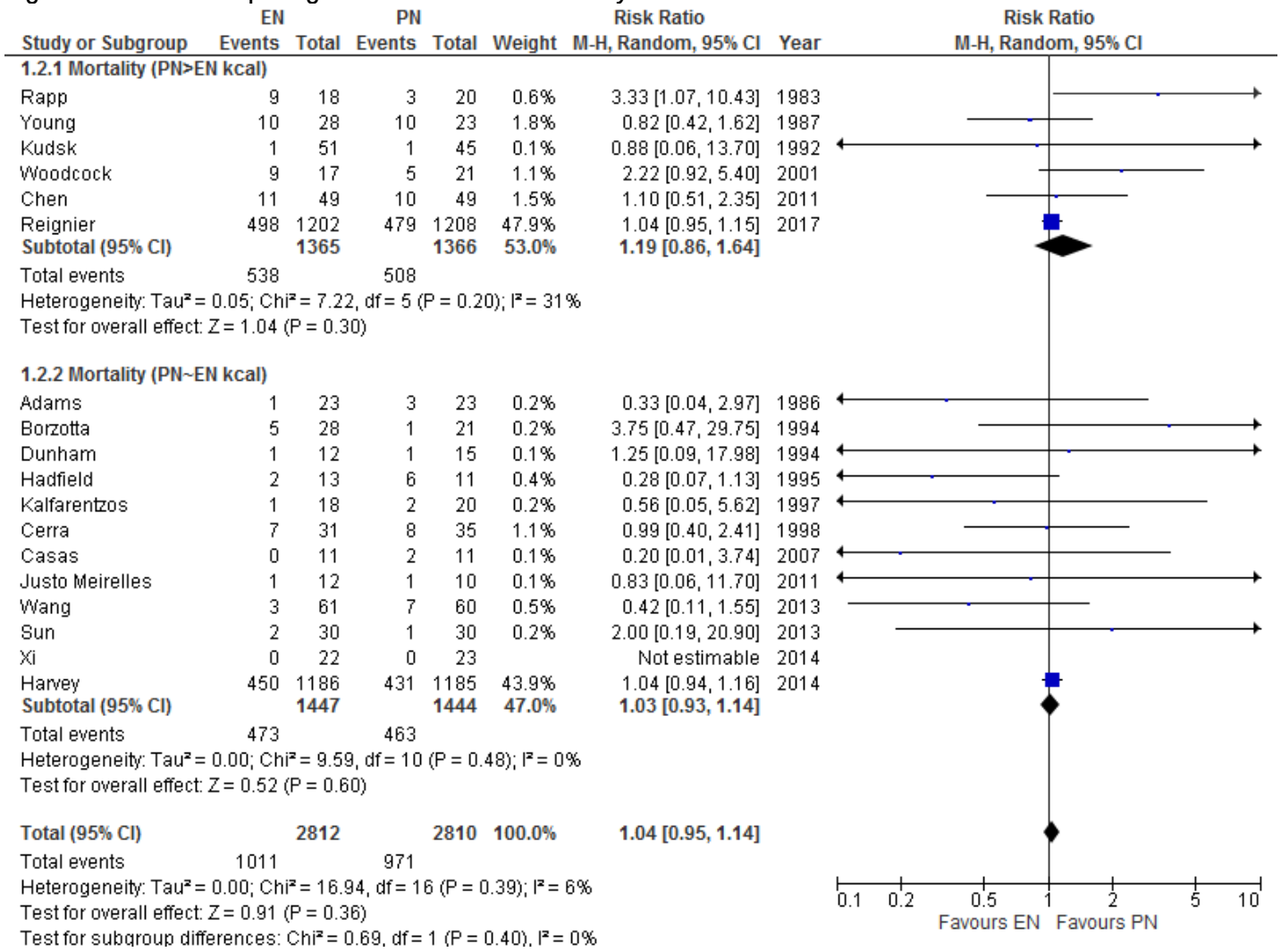

Figure 2. Overall mortality in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Adams	1	23	3	23	27.1%	0.33 [0.04, 2.97]	1986
Borzotta	5	28	1	21	30.2%	3.75 [0.47, 29.75]	1994
Kalfarentzos	1	18	2	20	24.2%	0.56 [0.05, 5.62]	1997
Meirelles	1	12	1	10	18.6%	0.83 [0.06, 11.70]	2011
Total (95% CI)		**81**		**74**	**100.0%**	**0.93 [0.30, 2.90]**	
Total events	8		7				

Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

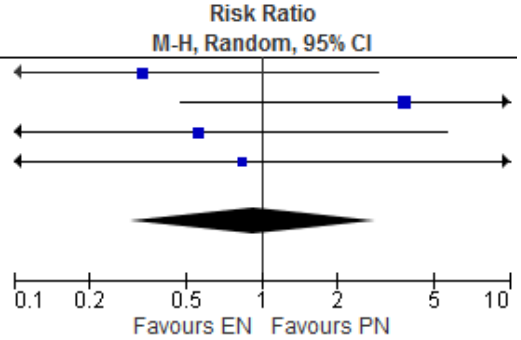

Figure 3. ICU Mortality

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.19.1 Mortality (PN>EN kcal)							
Kudsk	1	51	1	45	0.1%	0.88 [0.06, 13.70]	1992
Reignier	498	1202	479	1208	53.4%	1.04 [0.95, 1.15]	2017
Subtotal (95% CI)		**1253**		**1253**	**53.5%**	**1.04 [0.95, 1.15]**	
Total events	499		480				

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.38)

1.19.2 Mortality (PN~EN kcal)							
Hadfield	2	13	6	11	0.3%	0.28 [0.07, 1.13]	1995
Kalfarentzos	1	18	2	20	0.1%	0.56 [0.05, 5.62]	1997
Cerra	7	31	8	35	0.6%	0.99 [0.40, 2.41]	1998
Harvey	450	1186	431	1185	45.6%	1.04 [0.94, 1.16]	2014
Subtotal (95% CI)		**1248**		**1251**	**46.5%**	**0.93 [0.63, 1.36]**	
Total events	460		447				

Heterogeneity: Tau² = 0.05; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.38 (P = 0.71)

Total (95% CI)		**2501**		**2504**	**100.0%**	**1.04 [0.97, 1.12]**	
Total events	959		927				

Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 5 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%

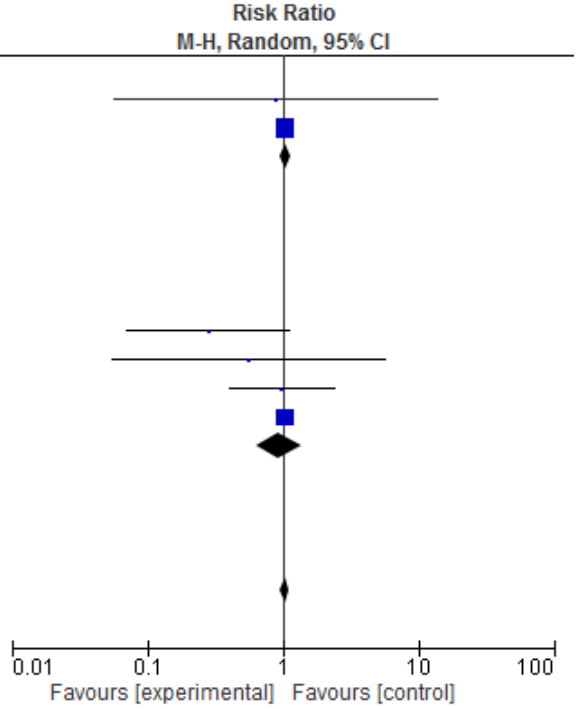

Figure 4. Studies comparing EN vs PN: Infectious complications

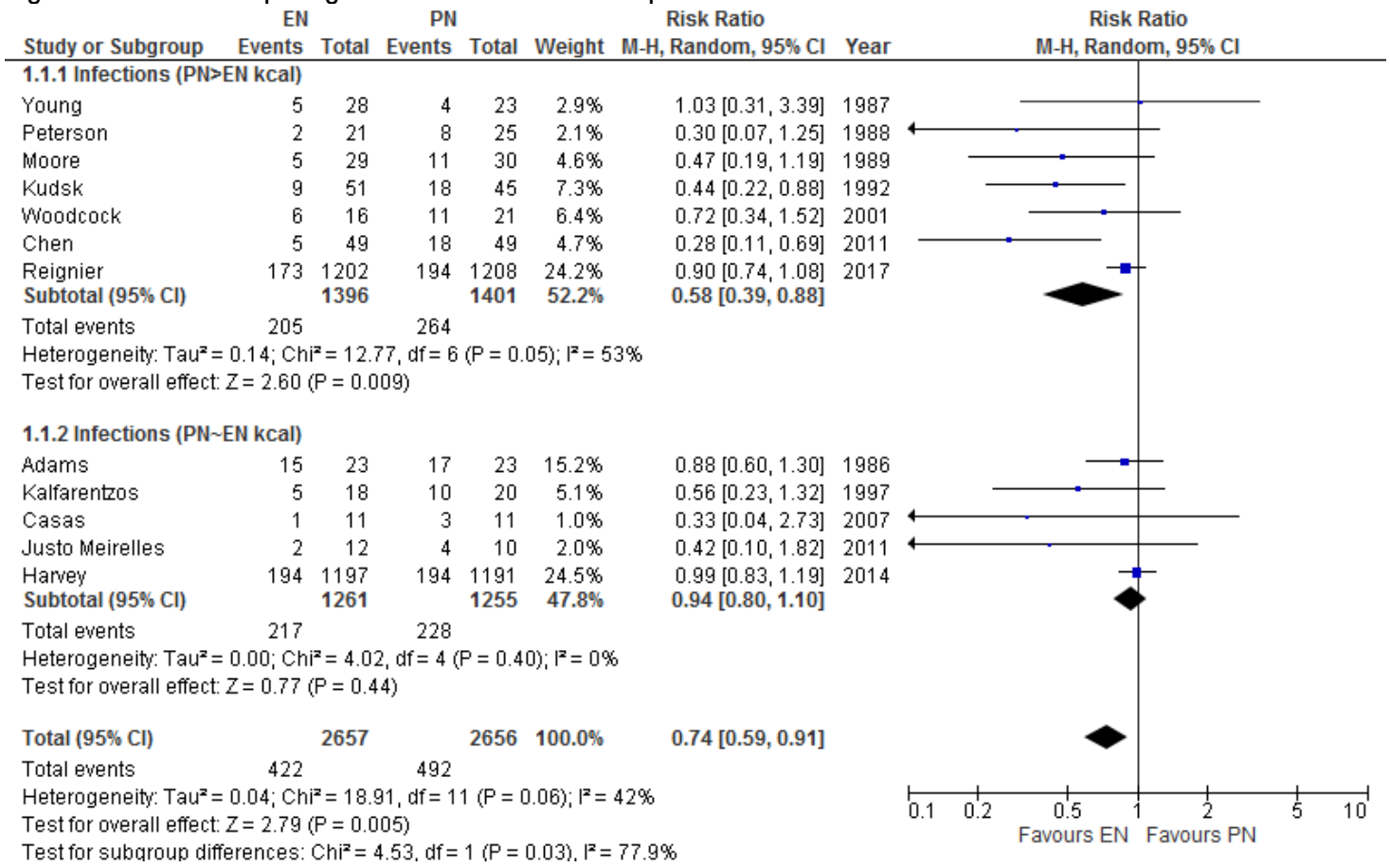

Figure 5. Infections in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Adams	15	23	17	23	79.0%	0.88 [0.60, 1.30]	1986
Kalfarentzos	5	18	10	20	15.7%	0.56 [0.23, 1.32]	1997
Meirelles	2	12	4	10	5.4%	0.42 [0.10, 1.82]	2011
Total (95% CI)		**53**		**53**	**100.0%**	**0.79 [0.56, 1.11]**	
Total events	22		31				

Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)

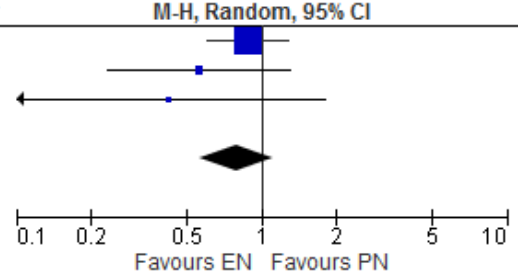

Figure 6. Hospital LOS

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.3.1 Hospital LOS (PN>EN kcal)									
Peterson	13.2	1.6	21	14.6	1.9	21	23.3%	-1.40 [-2.46, -0.34]	1988
Kudsk	20.5	19.9	51	19.6	18.8	45	5.9%	0.90 [-6.85, 8.65]	1992
Woodcock	33.2	43	16	27.3	18.7	18	0.9%	5.90 [-16.87, 28.67]	2001
Chen	23.32	5.6	49	22.24	3.27	49	21.0%	1.08 [-0.74, 2.90]	2011
Reignier	25.1	28.4	1202	25.9	27	1208	19.6%	-0.80 [-3.01, 1.41]	2017
Subtotal (95% CI)			**1339**			**1341**	**70.7%**	**-0.47 [-1.75, 0.81]**	

Heterogeneity: Tau² = 0.63; Chi² = 5.84, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 0.72 (P = 0.47)

1.3.2 Hospital LOS (PN~EN kcal)									
Adams	30	21	19	31	29	17	1.6%	-1.00 [-17.71, 15.71]	1986
Borzotta	39	23.1	28	36.9	14	21	3.7%	2.10 [-8.34, 12.54]	1994
Harvey	26.8	33.2	1186	27.5	33.9	1185	17.8%	-0.70 [-3.40, 2.00]	2014
Xi	20.43	10.49	22	38.76	15.04	23	6.2%	-18.33 [-25.88, -10.78]	2014
Subtotal (95% CI)			**1255**			**1246**	**29.3%**	**-4.90 [-14.93, 5.12]**	

Heterogeneity: Tau² = 80.86; Chi² = 19.37, df = 3 (P = 0.0002); I² = 85%
Test for overall effect: Z = 0.96 (P = 0.34)

Total (95% CI)			**2594**			**2587**	**100.0%**	**-1.35 [-3.52, 0.82]**	

Heterogeneity: Tau² = 4.96; Chi² = 26.79, df = 8 (P = 0.0008); I² = 70%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0%

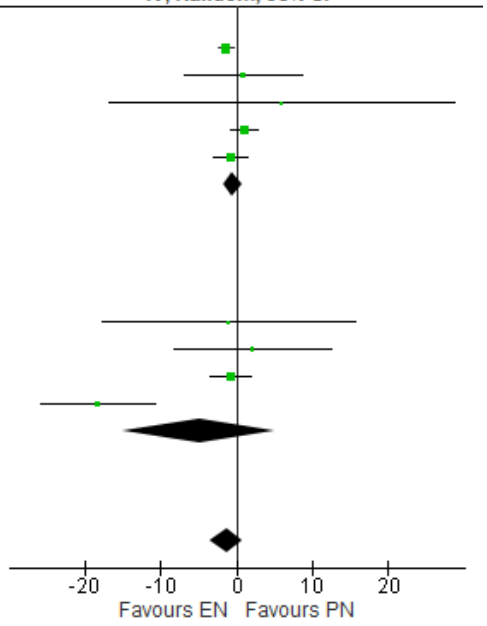

Figure 7. ICU LOS

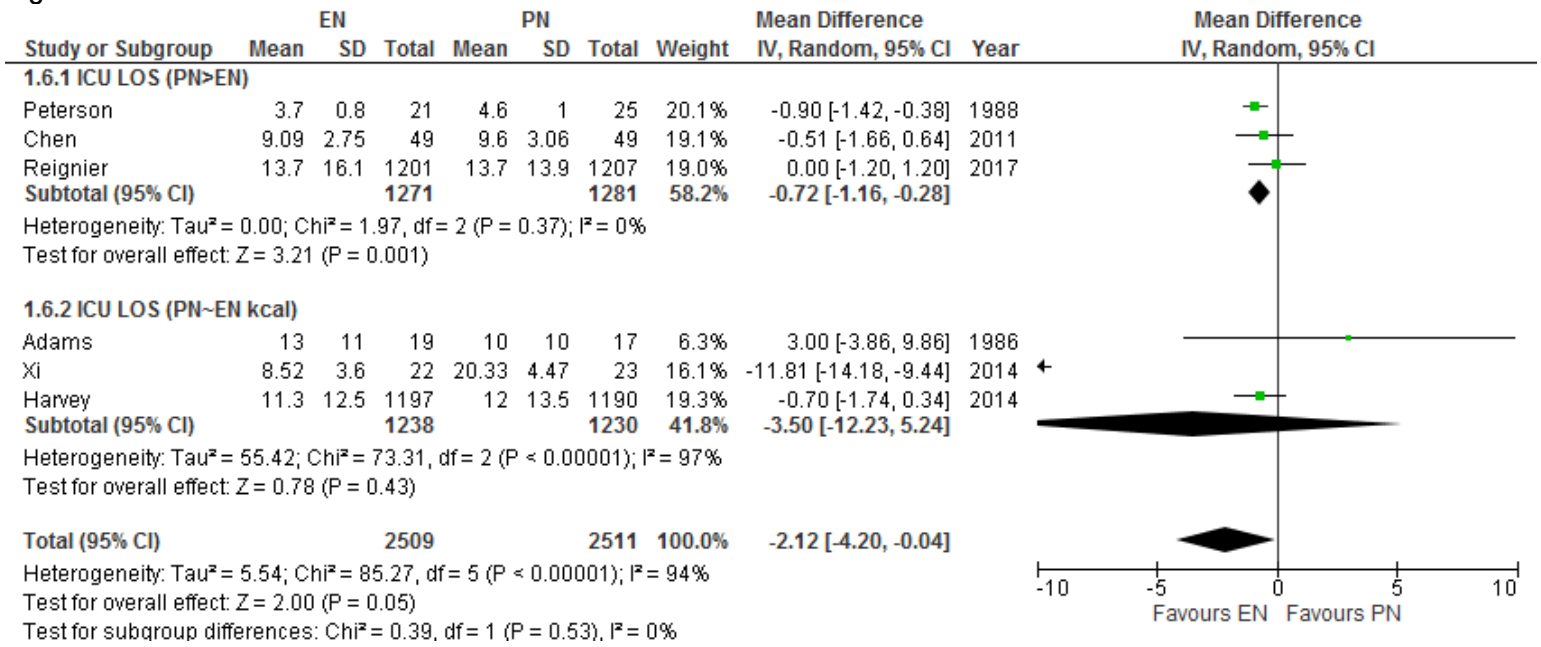

Figure 8. Mechanical Ventilation