1.0 The Use of Enteral Nutrition vs. Parenteral Nutrition March 2013

2013 Recommendation: *Based on one level 1 and 13 level 2 studies, when considering nutrition support for critically ill patients, we strongly recommend the use of enteral nutrition over parenteral nutrition.*

2013 Discussion: The committee noted that with the addition of 2 new RCTs (Casas 2007 and Chen 2011), there were no changes in the treatment effect on mortality or infections. There was no evidence to support the need for changes in the validity of the studies, the homogeneity of the results, the adequacy of the control group, the biological plausibility, generalizability, cost, feasibility and safety of the intervention as evidenced by the new scoring of these values. The committee agreed that the recommendation for the use of enteral vs parenteral nutrition not be changed.

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.*

2009 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.

Semi Quantitative Scoring

Values	Definition	2009 Score	2013 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	0 (mortality) 3 (infection)
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	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	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	3	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	3
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal inconsistencies=2, very consistent=3)	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	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	3
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3	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	2

1.0 Enteral Nutrition vs. Parenteral Nutrition March 2013

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

Summary of evidence: There were thirteen 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. 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.

Mortality: A total of 12 studies reported on mortality and when these were aggregated, there was no difference in mortality between the groups receiving EN or PN (RR 1.09, 95% CI 0.71, 1.67, p = 0.71, heterogeneity I^2=25%; 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 1.40, 95% CI 0.82, 2.38, p = 0.22, heterogeneity I^2=34%; 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 0.72, 95% CI 0.38, 1.34, p=0.30, heterogeneity I^2=2%; figure 1). There was a trend towards a significant difference in these subgroups (p=0.11; 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 0.21, 4.15, p=0.93, heterogeneity I^2=29%; figure 2).

Infections: When the 9 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 0.58, 95% CI 0.41, 0.80, p=0.04, heterogeneity I^2=29%; figure 3). 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 0.49, 95% CI 0.34, 0.71, p=0.0001, heterogeneity I^2=0%; figure 3). When the trials in which the PN and EN groups were fed isocalorically were aggregated, EN compared to PN was associated with a reduction in infectious complications (RR 0.80, 95% CI 0.56, 1.13, p=0.20, heterogeneity I^2=0%; figure 3). There There was a trend towards a significant difference in these subgroups (p=0.06; figure 3). Another subgroup analysis showed that the increase in infections could not be attributed to higher calories or hyperglycemia (RR 0.81, 95% CI 0.56, 1.18, p=0.27, heterogeneity I^2=5%; figure 4).

LOS, Ventilator days: A total of 6 studies reported on hospital length of stay and when the data were aggregated there were no differences between the groups receiving EN or PN (WMD -0.35, 95% CI -1.76, 1.05, p=0.62, heterogeneity I^2=18%; figure 5). Only 3 studies reported on ICU LOS and when the data were aggregated, the use of EN was associated with a significant reduction in ICU LOS (WMD -0.82, 95% CI -1.29, 0.34,

p=0.0007, heterogeneity I^2=0%; figure 6). Data on ventilator days was not aggregated statistically due to insufficient data. When looking at the individual studies,there were no differences found in ventilator days (Rapp, Adams Kudsk, Kalfarentzos) between the groups receiving EN or PN.

Nutritional 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). A total of 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).

Other Complications: 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). Six studies reported on diarrhea.

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 # (%)† EN	Mortality # (%)† PN	Infections # (%)‡ EN	Infections # (%)‡ 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	ICU 7/31 (22)	ICU 8/35 (23)	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)
7. Kudsk 1992	Abdominal trauma N=98	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=37	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	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	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	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)	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	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	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)

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 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	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	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) 2088 2572 p=NS 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% 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	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 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 p=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 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	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) 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	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)
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	
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)

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
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reported data pertaining to ICU patients only
NS = not statistically significant

Figure 1. Studies comparing EN vs PN: Mortality

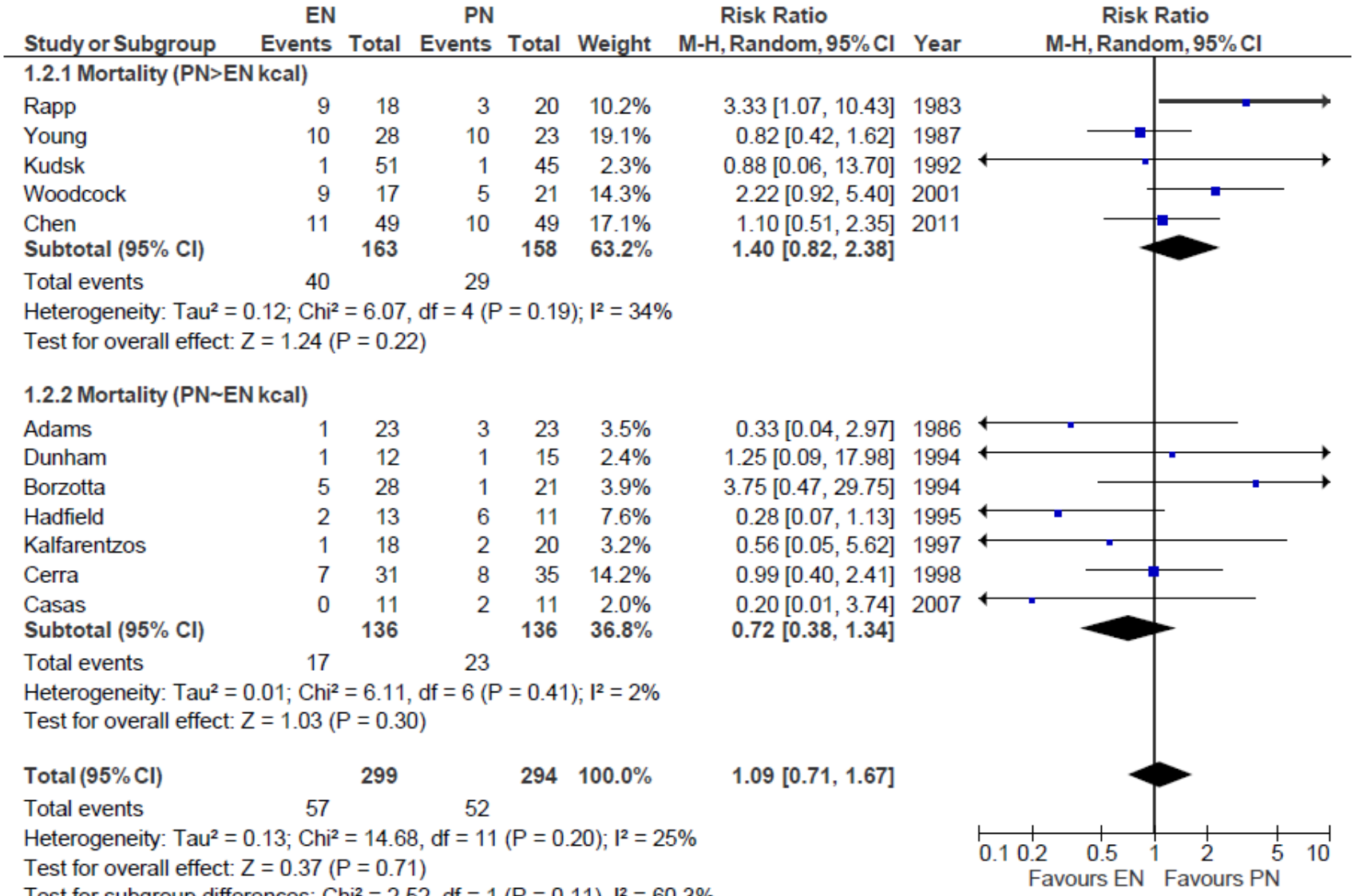

Figure 2. Mortality in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

	EN		PN			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**	**M-H, Random, 95% CI**
Adams	1	23	3	23	33.3%	0.33 [0.04, 2.97]	1986	
Borzotta	5	28	1	21	36.0%	3.75 [0.47, 29.75]	1994	
Kalfarentzos	1	18	2	20	30.7%	0.56 [0.05, 5.62]	1997	
Total (95% CI)		**69**		**64**	**100.0%**	**0.93 [0.21, 4.15]**		
Total events	7		6					

Heterogeneity: Tau² = 0.50; Chi² = 2.80, df = 2 (P = 0.25); I² = 29%
Test for overall effect: Z = 0.09 (P = 0.93)

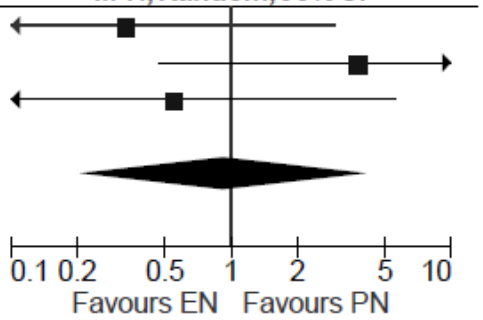

Figure 3. Studies comparing EN vs PN: Infectious complications

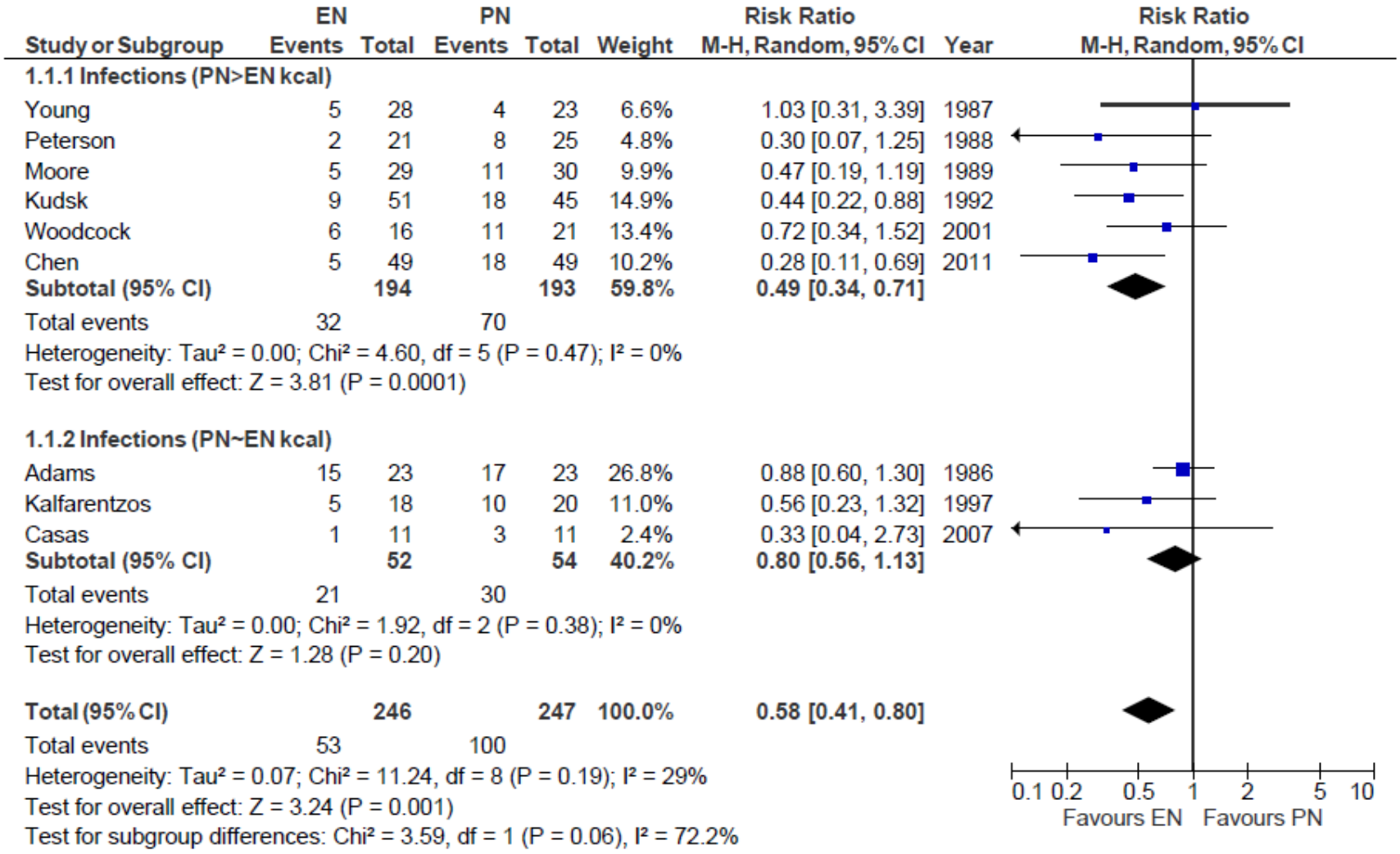

Figure 4. Infections in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

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	81.8%	0.88 [0.60, 1.30]	1986
Kalfarentzos	5	18	10	20	18.2%	0.56 [0.23, 1.32]	1997
Total (95% CI)		**41**		**43**	**100.0%**	**0.81 [0.56, 1.18]**	
Total events	20		27				

Heterogeneity: Tau² = 0.01; Chi² = 1.05, df = 1 (P = 0.30); I² = 5%
Test for overall effect: Z = 1.10 (P = 0.27)

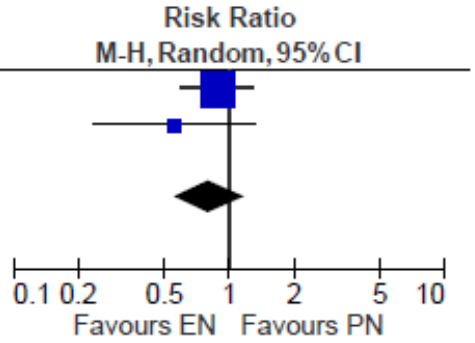

Figure 5. Hospital LOS

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
Adams	30	21	19	31	29	17	0.7%	-1.00 [-17.71, 15.71]	1986
Peterson	13.2	1.6	21	14.6	1.9	21	58.4%	-1.40 [-2.46, -0.34]	1988
Kudsk	20.5	19.9	51	19.6	18.8	45	3.2%	0.90 [-6.85, 8.65]	1992
Borzotta	39	23.1	28	36.9	14	21	1.8%	2.10 [-8.34, 12.54]	1994
Woodcock	33.2	43	16	27.3	18.7	18	0.4%	5.90 [-16.87, 28.67]	2001
Chen	23.32	5.6	49	22.24	3.27	49	35.5%	1.08 [-0.74, 2.90]	2011
Total (95% CI)			**184**			**171**	**100.0%**	**-0.35 [-1.76, 1.05]**	

Heterogeneity: Tau² = 0.58; Chi² = 6.12, df = 5 (P = 0.29); I² = 18%
Test for overall effect: Z = 0.49 (P = 0.62)

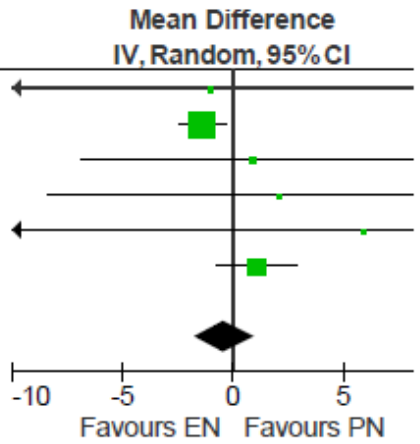

Figure 6. ICU LOS