1.0 The Use of Enteral Nutrition vs. Parenteral Nutrition May 2015

2015 Recommendation: ***Based on 16 level 2 and 1 level 1 study, when considering nutrition support for critically ill patients, we recommend the use of enteral nutrition over parenteral nutrition in patients with an intact gastrointestinal tract.***

2015 Discussion: The committee noted the inclusion of 4 new trials (Meirelles 2001, Wang 2013, Sun 2013, Harvey 2014), including one that compared early EN to early PN (Sun 2013) and the largest multicentre pragmatic study that showed there was no harm associated with giving PN (Harvey 2014). Despite the multicentre and large sample size of the Harvey study, concerns were raised about the low number of patients that remained on PN after the first 5 days. It was questioned whether the pragmatic approach of providing PN for 5 days in patients with an intact GI tracts in heterogenous patients that were well nourished was the best design to address the question of enteral vs parenteral nutrition. The committee noted that underfeeding occurred in both groups and this also weakens the inference from the results of this study. Despite this, when the data from all trials were aggregated, enteral nutrition was still associated with a significant reduction in infections, a trend towards reduced hospital stay and a significant reduction in ICU length of stay (although few studies contributed to these latter endpoints). The committee concluded that the significant positive effect on infections had to be considered notwithstanding the results of the Harvey study showing no benefit of EN over PN. Nevertheless, given the results of the Harvey study and the potential complications of EN such as vomiting and aspiration, the committee decided to downgrade the recommendation from a “strongly recommend” to “recommend” for the use of EN over PN in patients with an intact GI tract.

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.

Semi Quantitative Scoring

Values	Definition	2013 Score (0,1,2,3)	2015 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	**0 (mortality) 3 (infection)**	**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**	**3**
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

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

Summary of evidence: There were seventeen 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. In the recent pragmatic, randomized trial (Harvey et al NEJM 2014) in 33 ICUs, 2388 patients with unplanned admissions were randomized to be fed through either the parenteral or the enteral within 36 hours after admission and continued for up to 5 days. Other more recent smaller trials included 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 largest study (Harvey et al), there were no significant differences between the parenteral group and the enteral group in 30 days mortality (relative risk in parenteral group, 0.97; 95% confidence interval,0.86 to 1.08; P = 0.57) or 90 day mortality (442 of 1184 patients [37.3%] vs. 464 of 1188 patients [39.1%], P = 0.40)), . When this data was aggregated with the other 15 studies reported on mortality and, there was no difference in mortality between the groups receiving EN or PN (RR 1.04, 95% CI 0.82, 1.33, p=0.75, heterogeneity I^2=11%, 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 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=0.27; 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 1.08, 95% CI 0.83, 1.39, p=0.57, heterogeneity I^2=14%).

Infections: When the 11 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 0.64, 95% CI 0.48, 0.87, p=0.004, heterogeneity I^2=47%; 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 had no effect on infectious complications (RR 0.94, 95% CI 0.80, 1,10, p=0.44, heterogeneity I^2=0%; figure 3). There was a significant difference in these subgroups (p=0.001; figure 3). 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 4). In a sensitivity analysis excluding Mereilles 2011 and Wang 2013, EN compared to PN was associated with a significant reduction in infectious complications (RR 0.58, 95% CI 0.41, 0.8, p=0.001, heterogeneity I^2=29%, figure not shown).

LOS, Ventilator days: A total of 7 studies reported on hospital length of stay (in mean and standard deviation) and when the data were aggregated, EN was associated with a trend towards a reduction in hospital LOS (WMD -0.67, 95% CI -1.57, 0.24, p=0.15, heterogeneity I^2=2%; figure 5). Only 4 studies reported on ICU LOS (in mean and standard deviation) and when the data were aggregated, the use of EN was associated with a significant reduction in ICU LOS (WMD -0.80, 95% CI -1.23, -0.37, p=0.0003, heterogeneity I^2=0%; figure 6). A total of 4 studies reported on length of mechanical ventilation (in mean and standard deviation) and when the data were aggregated, no effect was seen (WMD -0.38, 95% CI -0.98, 0.21, p=0.21, heterogeneity I^2=0%, figure 7).

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).

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) The use of EN compared to PN was associated with a significant reduction in ICU LOS and a trend towards a reduction in hospital LOS, but no difference found in ventilator days.
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.

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)

15. Meirelles 2011	Adult patients with moderate traumatic brain injury N=22	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	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	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=2388	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)

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	**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)
15. Meirelles 2011	**ICU** 14 (5-26)	**ICU** 14 (6-24)	NR	NR	NR	NR	**Kcal over 5 days** 5958 +/- 3619 6586 +/- 1052 **Mean daily N-balance** -4.6g/day -5.9g/day **Blood Glucose (mg/dl)** 102.4 (91.6 – 113.2) 134.4 (122.6-146.2) $p < 0.01$
16. Wang 2013	NR	NR	NR	NR	NR	NR	

17. Sun 2013	**ICU** 9 (5-14)	**ICU** 12 (8-21)	***NR***	NR	NR	NR	**NR**
17. 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 **Total protein received during intervention period (g/kg)** 3 + 2 3 + 2

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

Figure 1. Studies comparing EN vs PN: Mortality

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Mortality (PN>EN kcal)							
Rapp	9	18	3	20	4.2%	3.33 [1.07, 10.43]	1983
Young	10	28	10	23	10.3%	0.82 [0.42, 1.62]	1987
Kudsk	1	51	1	45	0.8%	0.88 [0.06, 13.70]	1992
Woodcock	9	17	5	21	6.6%	2.22 [0.92, 5.40]	2001
Chen	11	49	10	49	8.6%	1.10 [0.51, 2.35]	2011
Subtotal (95% CI)		**163**		**158**	**30.4%**	**1.40 [0.82, 2.38]**	
Total events	40		29				
Heterogeneity: Tau² = 0.12; Chi² = 6.07, df = 4 (P = 0.19); I² = 34%							
Test for overall effect: Z = 1.24 (P = 0.22)							
1.2.2 Mortality (PN~EN kcal)							
Adams	1	23	3	23	1.2%	0.33 [0.04, 2.97]	1986
Dunham	1	12	1	15	0.8%	1.25 [0.09, 17.98]	1994
Borzotta	5	28	1	21	1.3%	3.75 [0.47, 29.75]	1994
Hadfield	2	13	6	11	2.9%	0.28 [0.07, 1.13]	1995
Kalfarentzos	1	18	2	20	1.1%	0.56 [0.05, 5.62]	1997
Cerra	7	31	8	35	6.5%	0.99 [0.40, 2.41]	1998
Casas	0	11	2	11	0.7%	0.20 [0.01, 3.74]	2007
Meirelles	1	12	1	10	0.8%	0.83 [0.06, 11.70]	2011
Sun	2	30	1	30	1.0%	2.00 [0.19, 20.90]	2013
Wang	3	61	7	60	3.2%	0.42 [0.11, 1.55]	2013
Harvey	450	1186	431	1185	50.0%	1.04 [0.94, 1.16]	2014
Subtotal (95% CI)		**1425**		**1421**	**69.6%**	**1.03 [0.93, 1.14]**	
Total events	473		463				
Heterogeneity: Tau² = 0.00; Chi² = 9.59, df = 10 (P = 0.48); I² = 0%							
Test for overall effect: Z = 0.52 (P = 0.60)							
Total (95% CI)		**1588**		**1579**	**100.0%**	**1.04 [0.82, 1.33]**	
Total events	513		492				
Heterogeneity: Tau² = 0.03; Chi² = 16.94, df = 15 (P = 0.32); I² = 11%							
Test for overall effect: Z = 0.32 (P = 0.75)							
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.5%							

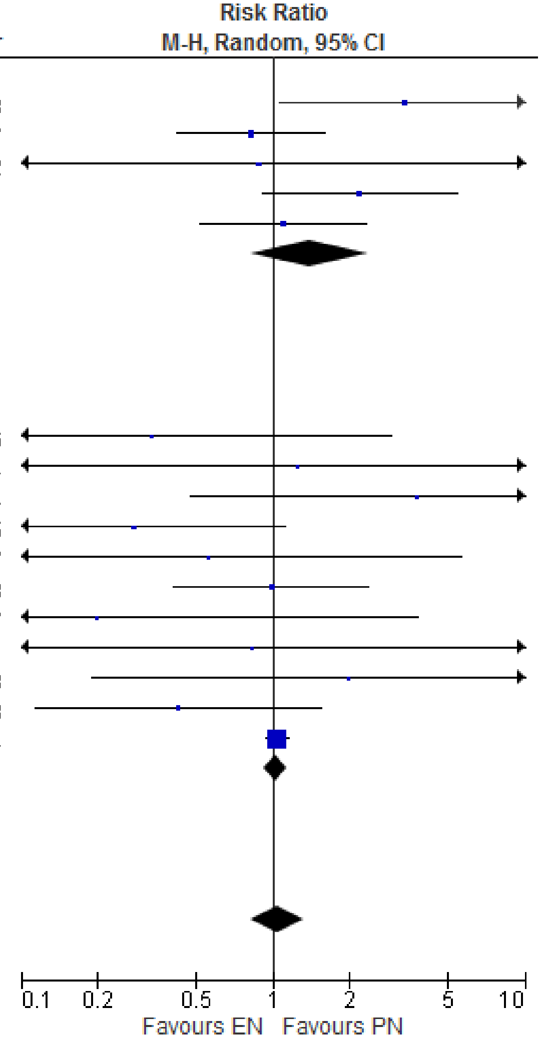

Figure 2. Mortality in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

	EN		PN			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	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)

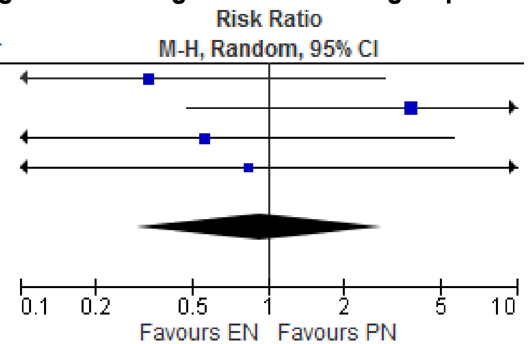

Figure 3. Studies comparing EN vs PN: Infectious complications

Study or Subgroup	EN Events	EN Total	PN Events	PN Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Infections (PN>EN kcal)							
Young	5	28	4	23	5.0%	1.03 [0.31, 3.39]	1987
Peterson	2	21	8	25	3.7%	0.30 [0.07, 1.25]	1988
Moore	5	29	11	30	7.4%	0.47 [0.19, 1.19]	1989
Kudsk	9	51	18	45	10.8%	0.44 [0.22, 0.88]	1992
Woodcock	6	16	11	21	9.8%	0.72 [0.34, 1.52]	2001
Chen	5	49	18	49	7.6%	0.28 [0.11, 0.69]	2011
Subtotal (95% CI)		**194**		**193**	**44.5%**	**0.49 [0.34, 0.71]**	
Total events	32		70				
Heterogeneity: Tau² = 0.00; Chi² = 4.60, df = 5 (P = 0.47); I² = 0%							
Test for overall effect: Z = 3.81 (P = 0.0001)							
1.1.2 Infections (PN~EN kcal)							
Adams	15	23	17	23	18.2%	0.88 [0.60, 1.30]	1986
Kalfarentzos	5	18	10	20	8.2%	0.56 [0.23, 1.32]	1997
Casas	1	11	3	11	1.9%	0.33 [0.04, 2.73]	2007
Meirelles	2	12	4	10	3.5%	0.42 [0.10, 1.82]	2011
Harvey	194	1197	194	1191	23.8%	0.99 [0.83, 1.19]	2014
Subtotal (95% CI)		**1261**		**1255**	**55.5%**	**0.94 [0.80, 1.10]**	
Total events	217		228				
Heterogeneity: Tau² = 0.00; Chi² = 4.02, df = 4 (P = 0.40); I² = 0%							
Test for overall effect: Z = 0.77 (P = 0.44)							
Total (95% CI)		**1455**		**1448**	**100.0%**	**0.64 [0.48, 0.87]**	
Total events	249		298				
Heterogeneity: Tau² = 0.09; Chi² = 18.71, df = 10 (P = 0.04); I² = 47%							
Test for overall effect: Z = 2.91 (P = 0.004)							
Test for subgroup differences: Chi² = 10.08, df = 1 (P = 0.001), I² = 90.1%							

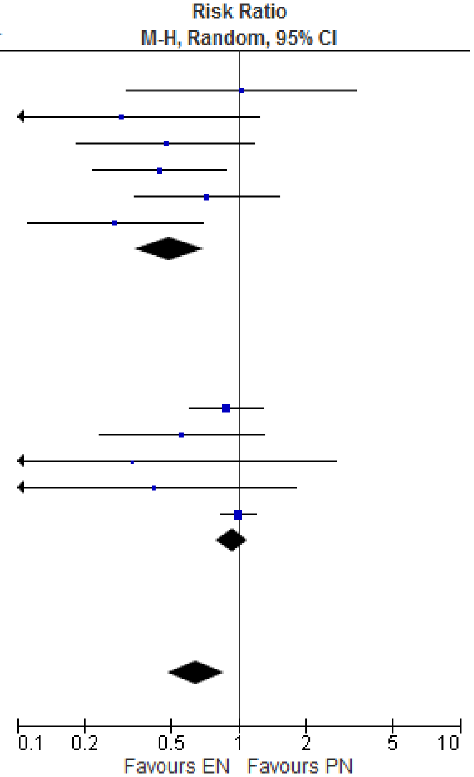

Figure 4. Infections in studies with hyperglycemia where the PN group had higher blood sugars than the EN group

	EN		PN			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**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)

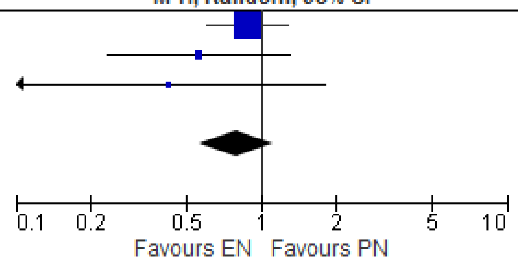

Figure 5. Hospital LOS

	EN			PN				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Adams	30	21	19	31	29	17	0.3%	-1.00 [-17.71, 15.71]	1986
Peterson	13.2	1.6	21	14.6	1.9	21	62.8%	-1.40 [-2.46, -0.34]	1988
Kudsk	20.5	19.9	51	19.6	18.8	45	1.4%	0.90 [-6.85, 8.65]	1992
Borzotta	39	23.1	28	36.9	14	21	0.8%	2.10 [-8.34, 12.54]	1994
Woodcock	33.2	43	16	27.3	18.7	18	0.2%	5.90 [-16.87, 28.67]	2001
Chen	23.32	5.6	49	22.24	3.27	49	23.6%	1.08 [-0.74, 2.90]	2011
Harvey	26.8	33.2	1186	27.5	33.9	1185	11.0%	-0.70 [-3.40, 2.00]	2014
Total (95% CI)			**1370**			**1356**	**100.0%**	**-0.67 [-1.57, 0.24]**	

Heterogeneity: Tau² = 0.05; Chi² = 6.12, df = 6 (P = 0.41); I² = 2%
Test for overall effect: Z = 1.44 (P = 0.15)

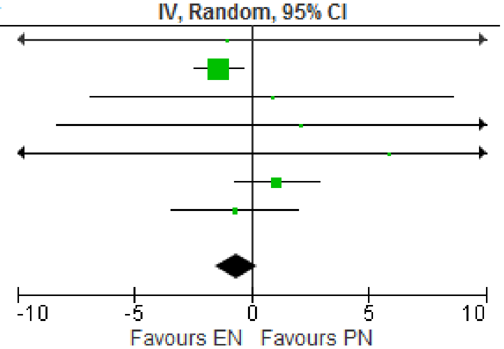

Figure 6. ICU LOS

	EN			PN				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Adams	13	11	19	10	10	17	0.4%	3.00 [-3.86, 9.86]	1986
Peterson	3.7	0.8	21	4.6	1	25	68.6%	-0.90 [-1.42, -0.38]	1988
Chen	9.09	2.75	49	9.6	3.06	49	14.0%	-0.51 [-1.66, 0.64]	2011
Harvey	11.3	12.5	1197	12	13.5	1190	17.0%	-0.70 [-1.74, 0.34]	2014
Total (95% CI)			**1286**			**1281**	**100.0%**	**-0.80 [-1.23, -0.37]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 3.62 (P = 0.0003)

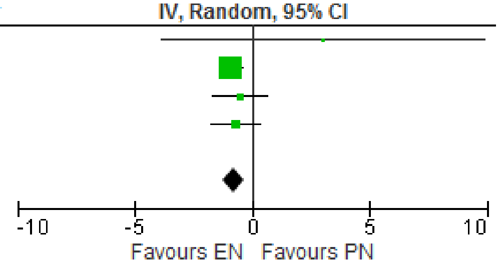

Figure 7. Mechanical Ventilation

	EN			PN				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Adams	12	11	17	10	10	13	0.6%	2.00 [-5.54, 9.54]	1986
Kudsk	2.8	4.9	51	3.2	6.7	45	6.2%	-0.40 [-2.77, 1.97]	1992
Chen	7.95	2.11	49	8.23	2.42	49	43.4%	-0.28 [-1.18, 0.62]	2011
Harvey	8.2	9.3	1197	8.7	11.5	1189	49.8%	-0.50 [-1.34, 0.34]	2014
Total (95% CI)			**1314**			**1296**	**100.0%**	**-0.38 [-0.98, 0.21]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 3 (P = 0.92); I² = 0%

Test for overall effect: Z = 1.27 (P = 0.21)