9.4a Composition of Parenteral Nutrition: Glutamine Supplementation

There were no new randomized controlled trials since the 2015 update but quality of life (QOL) outcomes have been added to the summary of evidence and a mortality subgroup analysis comparing single vs multi-centre studies.

Question: Compared to standard parenteral nutrition (PN), does glutamine-supplemented PN result in improved clinical outcomes in critically ill patients?

Summary of Evidence: There were 31 studies on IV glutamine supplementation included that were done in ICU patients ranging from pancreatitis, trauma, burns to sepsis. While in majority of the studies the intervention and control groups received parenteral nutrition/amino acids progressing to enteral nutrition, in three studies patients only received enteral nutrition (Palmese 2006, Ozgultekin 2008, and Eroglu 2009). In one study, the dosage of glutamine was questionably lower than the other studies (0.002 gm/kg/day) and hence the data from this study was not included in the meta-analyses (Yang 2007). To elucidate the effects of free glutamine vs. dipeptides and isonitrogenous vs. non isonitrogenous feeding on outcomes, subgroup analyses were done.

Mortality: Of the 29 studies that reported mortality, two were not included in the analysis since one reported data from a sub-group (Goeters 2002), and in one the glutamine dosage administered was questionably low (Yang 2007). When the remaining 27 studies were aggregated, IV glutamine supplementation was associated with a trend towards a reduction in overall mortality (RR 0.87, 95% CI 0.75, 1.01, p =0.07, heterogeneity I^2=0%; figure 1) in patients on EN or PN. The following subgroup analyses were done:

EN vs PN: In the studies in which patients received IV glutamine plus PN, glutamine supplementation was associated with a trend in the reduction in overall mortality (RR 0.86, 95% CI 0.74, 1.01, P=0.07, heterogeneity I^2=0%; figure 1). When the studies in which patients received IV glutamine and enteral nutrition (Palmese 2006, Luo 2008, Ozgultekin 2008, Eroglu 2009) were aggregated, glutamine supplementation had no effect on overall mortality (RR 0.94, 95% CI 0.61, 1.47, p=0.79, heterogeneity I^2=0%; figure 1). The test for subgroup differences was not significant (p=0.71).

Single vs Multi Centre: In the 21 studies that were completed at a single centre, IV glutamine supplementation was associated with a significant reduction in overall mortality (RR 0.75, 95% CI 0.60, 0.93, P=0.009, heterogeneity I^2=0%; figure 2). In the 6 multi-centre studies, IV glutamine supplementation had no effect (RR 1.00, 95% CI 0.81, 1.23, P=0.98, heterogeneity I^2=0%; figure 2). Therefore, the signal towards reduced overall mortality in the glutamine supplemented group is driven by the single centre studies. There was a trend in subgroup differences (p=0.06).

In the 15 studies that reported hospital mortality, a significant reduction in hospital mortality was seen when the data were aggregated (RR 0.70, 95% CI 0.53, 0.92, P = 0.01, heterogeneity I^2=0%; figure 3). There was only 1 study that reported hospital mortality and fed patients enterally (Luo 2008), but there was no mortality observed in that study and, therefore, a subgroup analysis was not completed. The following subgroup analysis was done:

> **Single vs Multi Centre:** In the 12 studies that were completed at a single centre, IV glutamine supplementation was associated with a significant reducation in hospital mortality (RR 0.67, 95% CI 0.49, 0.91, P=0.01, heterogeneity I^2=0%; figure 3). In the 3 multi-centre studies, IV glutamine supplementation had no effect (RR 0.85, 95% CI 0.46, 1.55, P=0.59, heterogeneity I^2=0%; figure 3). Therefore, the signal towards reduced hospital mortality in the glutamine supplemented group is driven by the single centre studies. The test for subgroup differences was not significant (p=0.49).

There was no difference in hospital or overall mortality when the studies that used free glutamine (L-glutamine) were compared to those using dipeptides (L-alanyl-L-glutamine) or when isonitrogenous studies were compared to non-isonitrogenous (figures not shown, see page 18 for breakdown of studies).

Infections: When the 13 studies which reported infectious complications were aggregated, glutamine supplementation was associated with a trend towards a reduction in infectious complications (RR 0.89, 95% CI 0.77, 1.03, p = 0.12, heterogeneity I^2 = 39%; figure 4). For the subgroup of studies in which patients received IV glutamine plus PN, glutamine supplementation had no effect on infectious complications (RR 0.91, 95% CI 0.78, 1.07, p = 0.26, heterogeneity I^2 = 41%; figure 4). However, for the subgroup of studies in which patients received IV glutamine and were on enteral nutrition (Palmese 2006, Eroglu 2009), glutamine supplementation was associated with a trend towards a reduction in infectious complications (RR 0.68, 95% CI 0.45, 1.05, p=0.08, heterogeneity I^2=0%; figure 4). The test for subgroup differences was not significant (p=0.21). When the 7 studies which reported pneumonia were aggregated, glutamine supplementation showed no effect (RR 0.85, 95% CI 0.65, 1.10, p = 0.22, heterogeneity I^2=0%; figure 5). Glutamine supplementation had no effect on pneumonia in PN fed patients (RR 0.87, 95% CI 0.66, 1.15, p=0.32, heterogeneity I^2=7%; figure 5) or EN fed patients (RR 0.44, 95% CI 0.11, 1.67, p=0.23, heterogeneity I^2=0%; figure 5). The test for subgroup differences was not significant (p=0.33). There was no difference in infections of pneumonia when the studies that used free glutamine (L-glutamine) were compared to those using dipeptides (L-alanyl-L-glutamine) or when isonitrogenous studies were compared to non-isonitrogenous (figures not shown).

ICU LOS: Fourteen studies reported ICU length of stay as a mean ± standard deviation. Two of these studies were excluded from the analysis: one because it reported data from a subgroup of its study population (Goeters 2002) and another because its low dose of glutamine (0.002 gm/kg/day) could not be confirmed from the authors (Yang 2007). When the remaining 12 studies were aggregated, glutamine supplementation was associated with a trend in reduction in ICU LOS (WMD WMD -1.91, 95% CI -4.10, 0.28, p = 0.09, heterogeneity I^2=90%; figure 6). Glutamine supplementation had no effect on ICU LOS for the subgroup of studies in which patients received IV glutamine plus PN (WMD -2.30, 95% CI -6.50, 1.90, p = 0.28, heterogeneity I^2=89%; figure 6) or EN (WMD -0.47, 95% CI -1.84, 0.90, p = 0.50, heterogeneity I^2= 68%; figure 6). The test for subgroup differences

was not significant (p=0.42). There was no difference in ICU LOS when the studies that used free glutamine (L-glutamine) were compared to those using dipeptides (L-alanyl-L-glutamine) or when isonitrogenous studies were compared to non-isonitrogenous (figures not shown).

Hospital LOS: Twelve studies reported hospital length of stay as a mean ± standard deviation. One of these studies was excluded from the analysis because it reported data from a subgroup of its study population (Goeters 2002). When the remaining 11 studies were aggregated, glutamine supplementation was associated with a significant reduction in hospital LOS (WMD -2.56, 95% CI -4.71, -0.42, p = 0.02, heterogeneity I^2 = 63%; figure 7). None of the 3 studies in which patients only received enteral nutrition reported on hospital LOS and therefore no subgroup analyses were done. There was no difference in hospital LOS when the studies that used free glutamine (L-glutamine) were compared to those using dipeptides (L-alanyl-L-glutamine) or when isonitrogenous studies were compared to non-isonitrogenous (figures not shown).

Mechanical Ventilation: When the data from the 11 studies that reported on mechanical ventilation were aggregated, glutamine supplementation was associated with a significant reduction in the duration (WMD -2.46, 95% CI -3.89, -0.43, p = 0.01, test for heterogeneity 1^2 = 88%; figure 8)

Quality of Life: Powell Tuck et al asked patients about their perceived morbidity and quality of life at entry in the trial and when PN stopped. Though all modalities improved within each group (p<0.0001), there was no statistical difference between groups. Andrews et al completed the SF-12 physical and mental composite scale score and the EQ-5D instrument at 3 and 6 months with survivors and found no significant different between scores.

Conclusions:
1) IV glutamine supplementation may be associated with a reduction in overall mortality and is associated with a significant reduction in hospital mortality but the observed treatment effect is observed exclusively in small, single center studies.
2) IV glutamine supplementation may be associated with a reduction in infectious complications but has no effect on ventilator associated pneumonia.
3) IV glutamine supplementation may be associated with a reduction in ICU LOS and is associated with a reduction in hospital LOS.
4) There is no difference between IV glutamine supplementation given as free glutamine vs dipeptides or isonitrogenous vs non isonitrogenous feeding.
5) IV glutamine supplementation has no effect on quality of life in the critically ill.

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 glutamine (PN) in critically ill patients

Study	Population	Methods (score)	Intervention Dose of Lglutamine gm/kg/day	Mortality # (%)†		Infections # (%)‡		Length of stay (days)	
				Experimental	Control	Experimental	Control	Experimental	Control
1) Griffiths 1997 & 2002	Single-centre, mixed ICU patients N=84	C.Random: yes ITT: yes Blinding: double (11)	PN and 0.26 IV L-glutamine vs. PN Isocaloric, isonitrogenous	**Hospital** 18/42(43)	**Hospital** 25/42(60)	28/42 (67)	26/42 (62)	**ICU** 10.5 (6-19)*	**ICU** 10.5 (6-24)*
2) Powell-Tuck 1999	Single-centre, mixed ICU/hospital patients N=168	C.Random: yes ITT: yes Blinding: double (8)	0.26 IV free glutamine mixed intoPN vs. PN, isocaloric, non-isonitrogenous.	**Hospital** 14/83(17)	**Hospital** 20/85(24)	NR	NR	**Hospital** 43.4 ± 34.1 (83)	**Hospital** 48.9 ± 38.4 (85)
3) Wischmeyer 2001	Single-centre, critically ill burns N=31	Random: not sure ITT: no Blinding double (8)	0.57 IV L-glutamine and EN orEN+PN vs. AAcids + PN or EN or EN+PN Nonisonitrogenous, isocaloric	**Hospital** 1/12 (8)	**Hospital** 4/14 (29)	7/12 (58)	9/14 (64)	**Hospital** 40 ± 10 (12)	**Hospital** 40 ± 9 (14)
4) Goeters 2002*	Single-centre, surgical ICU patients N=68	C.Random: not sure ITT: no Blinding: no	0.2 IV L-alanyl-L-glutamine + PN or EN or EN+PN vs PN or EN or EN+PN. Non-isonitrogenous.	**ICU** 7/33 (21)* **30-day** 7/33 (21)* **6-month** 11/33 (33)*	**ICU** 10/35 (29)* **30-day** 11/35 (31)* **6-month** 21/35 (60)*	NR	NR	**ICU (avg)** 21.3 ± 13.5 (33)* **Hospital (avg)** 46 ± 49.1 (33)*	**ICU (avg)** 20.8 ± 9.1 (35)* **Hospital (avg)** 39.4 ± 31.1 (35)*
5) Carrol 2004	Single center, N=19	C. Random: no ITT: yes Blinding: no (9)	PN w IV gln (L-glutamine 0.4 g/kg/d) vs standard PN. Isocaloric, non-isonitrogenous.	**Hospital** 0/7 **ICU** 0/7	**Hospital** 0/7 **ICU** 0/7	**NA**	**NA**	**NA**	**NA**

6) Fuentes-Oroczo 2004	Single-centre, secondary peritonitis requiring TPN N=33	C.Random: yes ITT: yes Blinding: double (11)	PNwith added 0.27 L-analyl-L-glutamine vs. PN, isocaloric, isonitrogenous	**Hospital** 2/17 (12)	**Hospital** 3/16 (19)	4/17 (23)	12/16 (75)	**ICU** 7.2 ± 9.2 (17) **Hospital** 16.5 ± 8.9 (17)	**ICU** 7.3 ± 4.5 (16) **Hospital** 16.7 ± 7 (16)
7) Zhou 2004	Severe burns N=30	C.Random: yes ITT: yes Blinding: double (11)	0.35 IV glutamine (given as 0.5 g/kg/d L-alanyl-L-glutamine) + PN vs. PN, isocaloric, isonitrogenous.	NR	NR	3/15 (20)	4/15 (26)	**Hospital** 42 ± 7.0 (15)	**Hospital** 46 ± 6.6 (15)
8) Xian-Li 2004	Single-centre, severe acute pancreatitis N=69	C.Random: yes ITT: no Blinding: no (5)	0.4 IV L-alanyl-L-glutamine + PN vs. PN. Nonisonitrogenous	**Hospital** 0/20 (0)	**Hospital** 3/21 (14)	**# Compl** 4	**# Compl** 11	**Hospital** 25.3 ± 7.6 (20)	**Hospital** 28.6 ± 6.9 (21)
9) Dechelotte 2006	Multi-centre, Multiple trauma, surgery,sepsis, pancreatitis from 16 ICUs N=114	C.Random: NR ITT: yes Blinding: double (N/A)	0.35 IV glutamine (given as 0.5 g/kg/d L-alanyl-L-glutamine) + PN vs. PN + L-alanine and L-proline. isocaloric, isonitrogenous.	**Hospital** 2/58 (3) **6-month** 16/58 (28)	**Hospital** 2/56 (3) **6-month** 9/56 (16)	**All** 23/58 (40) **Pneumonia** 10/58 (17)	**All** 32/56 (58) **Pnemonia** 19/56 (34)	**ICU** 12.5 (1-430) **Hospital** 30 (1-560)	**ICU** 11.5 (3-121) **Hospital** 26 (4-407)
10) Palmese 2006	Single-centre, mixed ICU N=84	C.Random: yes ITT: yes Blinding: outcomes assessors (10)	0.14 IV free glutamine + EN&PN with FOS vs. EN without FOS. Unable to tell if isonitrogenous w glutamine.	**ICU** 6/42 (14)	**ICU** 8/42 (19)	**All** 13/42 (31) **Pneumonia** 2/42 (5)	**All** 21/42 (50) **Pneumonia** 6/42 (14)	**ICU** 12 ± 4.6 (42)	**ICU** 13 ± 3.4 (42)
11) Tian 2006	Single-centre, MODS N=40	C.Random: not sure ITT: yes Blinding: no (6)	PN + 0.27 IV glutamine (given as 0.4 g/kg/d L-alanyl-L-glutamine) vs PN. Nonisonitrogenous.	**Unspecified** 2/20 (10)	**Unspecified** 5/20 (25)	NR	NR	NR	NR

12) Sahin 2007	Single-centre, acute pancreatitis N=40	C.Random: not sure ITT: yes Blinding: not sure (9)	0.3 L-alanyl-L-glutamine PN vs. PN, Non-isonitrogenous.	**Hospital** 2/20 (10)	**Hospital** 6/20 (30)	NR	NR	**Hospital** 14.2 ± 4.4 (20)	**Hospital** 16.4 ± 3.9 (20)
13) Yang 2007α	Single-centre, Brain injury Neurosurgical ICU N=46	C.Random: not sure ITT: yes Blinding: no (6)	0.002 IV glutamine dipeptide + PN vs. PN. Unable to tell if isonitrogenous.	**Hospital** 5/23 (22)	**Hospital** 9/23 (39)	NR	NR	**ICU** 10 ± 3.5 (23)	**ICU** 18 ± 5.6 (23)
14) Zhang 2007	Single centre Emergency and neurosurgical ICU, pts requiring PN for >7 days N=44	C.Random: not sure ITT: yes Blinding: no (6)	EN and PN + IV glutamine (Chinese article, unable to tell form) 0.4 g/kg/day vs EN and PN alone. Unable to tell if isonitrogenous	NR	NR	NR	NR	**ICU** 11.73 ±6.57 (22)	**ICU** 13.39 ±5.08 (22)
15) Cai 2008	Single-centre, elderly, severe sepsis N=110	C.Random: not sure ITT: yes Blinding: no (10)	PN or PN&EN with0.19 IV L-alanyl-L-glutamine (10 g/d) Patients received vs PN or EN + PN non-isonitrogenous	**28-day** 17/55 (31)	**28-day** 20/55 (36)	NR	NR	**ICU** 22.1 ± 4.9 (55)	**ICU** 23.8 ± 5.1 (55)
16) Duska 2008 ∂	Single-centre, trauma N=30	C.Random: not sure ITT: yes Blinding: HCPs (8)	EN or EN&PN + 0.3 IV L-alanyl-Lglutamine vs. EN or EN+PN w normal saline + non-isonitrogenous	**ICU** 2/10 (20)	**ICU** 0/10 (0)	NR	NR	**ICU** 23 (median)	**ICU** 24 (median)
17) Estivariz 2008	Single-centre, pancreatic and non pancreatic surgery N=63	C.Random: not sure ITT: no** Blinding: double (9)	0.5 L-alanyl-L-glutamine containing PN vs. Gln-free PN. isocaloric, isonitrogenous	**Hospital** 1/32 (3)	**Hospital** 6/31 (19)	**Pneumonia** 13/30 (43)	**Pneumonia** 16/29 (55)	**ICU** 12 ± 2 (32) **Hospital** 20 ± 2 (32)	**ICU** 23 ± 6 (31) **Hospital** 30 ± 6 (31)

18) Fuentes-Oroczo 2008	Single-centre, Acute pancreatitis requiring admission N=44	C.Random: not sure ITT: yes Blinding: double (12)	0.4 g/kg/d L-alanyl-L-glutamine in PN vs. PN isocaloric, isonitrogenous	**ICU** 2/22 (9)	**ICU** 5/22 (23)	9/22 (41)	16/22 (73)	**ICU** 11 ± 11.7 (22) **Hospital** 30.18 ± 10.42 (22)	**ICU** 11.14 ± 7.41 (22) **Hospital** 26.59 ± 13.3 (22)
19) Luo 2008* **	Single-centre, medical surgical N=44	C.Random: not sure ITT: no Blinding: double (9)	0.50 g/kg/d IV L-alanyl-L-glutamine + EN vs. IV 15% Clinisol (placebo) +EN isocaloric, isonitrogenous	**Hospital** 0/11 (0)	**Hospital** 0/9 (0)	NR	NR	**ICU** 7.6 ± 0.7 (14)	**ICU** 6.9 ± 0.9 (9)
20) Perez-Barcena 2008	Single-centre, mixed ICU N=30	C.Random: not sure ITT: yes Blinding: outcomes assessors (10)	0.35 IV gln (given as 0.5 g/kg/d L-alanyl-L-glutamine) + PN vs. PN isocaloric, isonitrogenous	**Hospital** 3/15 (20)	**Hospital** 0/15 (0)	11/15 (73)	13/15 (87)	**ICU** 22.9 ± 20.6 (15) **Hospital** 35.5 ± 33.6 (15)	**ICU** 20.5 ± 16.0 (15) **Hospital** 42.9 ± 28.8 (15)
21) Ozgultekin 2008	Single-centre, CHI & GCS pts, ventilated, sedated, mean APACHE II 18-19 N=60	C.Random: not sure ITT: no Blinding: none (4)	EN + 0.2-0.4g/kg/d IV gln (given as 20 g L-alanyl-L-glutamine) vs. EN. Nonisonitrogenous	**30-day** 12/20 (60)	**30-day** 12/20 (60)	NR	NR	**ICU** 11.8 ± 5.9 (20)	**ICU** 17.3 ± 16.4 (20)
22) Yang 2008	Single-centre, severe pancreatitis N=61	C.Random: not sure ITT: no Blinding: single (4)	PN + IV L-alanyl-L-glutamine (dose unknown) vs PN + saline (Chinese article, unable to get further info)	**Hospital** 1/25 (4)	**Hospital** 3/25 (12)	NR	NR	**Hospital** 13.48 ± 1.42 (25)	**Hospital** 15.18 ± 1.14 (25)
23) Eroglu 2009	Single-centre, severe trauma, ISS>20 N=40	C.Random: yes ITT: yes Blinding: double (12)	EN + 0.5 g/kg/d IV L-alanyl-L-glutamine vs EN, saline. Nonisonitrogenous, nonisocaloric.	**ICU** 1/20 (5)	**ICU** 1/20 (5)	**Overall** 8/20 (40) **VAP** 1/20 (5)	**Overall** 10/20 (50) **VAP** 1/20 (5)	**ICU** 14 ± 2 (20)	**ICU** 15 ± 2 (20)

24) Perez-Barcena 2010	Single-centre, trauma pt ISS >12, requires PN based on ASPEN N=43	C.Random: not sure ITT: yes Blinding:Outcomes assessors (6)	PN, 0.35 g/kg/d IV glutamine (given as 0.5 g/kg/d L-alanyl-L-glutamine) vs PN. Isocaloric, isonitrogenous	**ICU** 4/23 (17) **Hospital** 4/23 (0)	**ICU** 2/20 (10) **Hospital** 3/20 (5)	**Pneumonia** 11/23 (48)	**Pneumonia** 8/20 (40)	**ICU** 21 (17-25) **Hospital** 31 (19-42)	**ICU** 21 (14-47) **Hospital** 40 (24-80)
25) Andrews 2011	Multi-centre, critically ill adults, 25% medical pts, from 10 centres N=502	C. Random: yes ITT: yes Blinding: double (13)	PN containing 0.2-0.4 g/kg/day (20.2 g/day x 7 days) vs.PN isocaloric, isonitrogenous (unknown gln form)	**ICU** 88/250 (35) **6-month** 115/250 (46)	**ICU** 80/252 (32) **6-month** 106/252 (42)	134/250 (54)	131/252 (52)	**ICU** 15 (7.9-28.4) **Hospital** 32.5 (14.7-55.6)	**ICU** 13.4(8.2-23.9) **Hospital** 28.2 (15.1-52.4)
26) Cekman 2011	Single-centre, mixed surgical ICU, ISS $\geq$ 10, APACHE II >10 N=30	C.Random: yes ITT: yes Blinding: double (10)	PN containing 0.5 g/kg/d L-alanyl-L-glutamine vs PN (nonisonitrogenous)	**ICU (presumed)** 3/15 (20)	**ICU (presumed)** 6/15 (40)	NR	NR	**ICU** 19.2 ± 12 (15)	**ICU** 27.4 ± 12 (15)
27) Grau 2011	Multi-centre, mechanically ventilated, APACHE II >12, need TPN N=127	C.Random: not sure ITT: yes Blinding: double (11)	PN, 0.5 g/kg/d L-alanyl-L-glutamine IV glutamine vs PN. Isonitrogenous, isocaloric.	**ICU** 9/59 (15) **6-month** 16/59 (27)	**ICU** 13/68 (19) **6-month** 23/68 (34)	**All** 24/59 (41) **Surgical** 13/59 (22) **Pneu (#/1000 vent days)** 13.5 **# infect/pt** 1.5	**All** 31/68 (46) **Surgical** 17/68 (25) **Pneu (#/1000 vent days)** 27.2 **# infect/pt** 2.4	**ICU** 12 (7-22) **Hospital** 35 (23-56)	**ICU** 12 (7-24) **Hospital** 31 (20-58)
28) Wernerman 2011	Multi-centre, mixed ICU, APACHE II $\geq$10 N=413	C.Random: yes ITT: yes Blinding: double (11)	EN or PN, 0.28 g/kg/day IV glutamine (given as L-alanyl-L-glutamine) vs EN or PN, normal saline IV. Nonisocaloric, nonisonitrogenous	**ICU** 8/205 (4) **28-day** 14/205 (7)	**ICU** 11/208 (5) **28-day** 20/208 (10)	NR	NR	NR	NR

29) Grintescu 2014	Single center, trauma pts N=97	C. Random: yes ITT: no Blinding: no (7)	EN + PN, L-alanyl-L-glutamine dipeptide (0.5 g/kg/day) vs EN + PN w standard amino acid solution (0.5 g/kg/day as Aminoven 10%; Fresenius Kabi). Isonitrogenous, isocaloric.	**ICU** 4/48 (8)	**ICU** 4/49 (8)	**All after 6 days** 10/41 (24)	**All after 6 days** 14/41 (34)	**NA**	**NA**
30) Koskal 2014* **	Septic, malnourished ICU patients N=120	C.Random: yes ITT: other Blinding: single (outcomes) (9)	30 g/day parenteral glutamine + EN vs EN, no placebo, no supplemental glutamine	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
31) Perez-Barcena 2014	Multi-center, trauma ICU N=142	C. Random: yes ITT: yes Blinding: double (13)	EN or PN, L-alanyl-L-glutamine dipeptide (0.5 g/kg/d = 0.35 g of L-glutamine/kg /d) vs EN or PN w placebo. Non-isonitrogenous, non-isocaloric.	**Hospital** 4/71 (6) **ICU** 3/71 (4)	**Hospital** 5/71 (7) **ICU** 3/71 (4)	**Any** 45/71 (63) **Respiratory** 37/71 (52) **Pneumonia** 23/71 (32)	**Any** 44/71 (62) **Respiratory** 33/71 (47) **Pneumonia** 21/71 (30)	**ICU** 14 (8-28) **Hospital** 29 (17-47)	**ICU** 14 (7-24) **Hospital** 27 (16-46)
32) Ziegler 2016	Multi-center, N=150	C. Random: yes ITT: yes Blinding: double (12)	PN containing 0.5 gm/kg/day L-alanyl-L-glutamine vs. PN, isocaloric. Isonitrogenous.	**Hospital** 11/75 (15)	**Hospital** 13/75 (17)	**Any** 33/75 (44) **Pneumonia** 10/75 (13)	**Any** 24/75 (32) **Pneumonia** 12/75 (16)	**ICU** 17.5 ± 14.6 (75) **Hospital** 33.6 ± 28 (75)	**ICU** 13.6 ± 10 (75) **Hospital** 29.7 ± 20.7 (75)

C.Random: Concealed randomization median (range)
ITT: Intent to treat
NA: not applicable
EN: Enteral nutrition; TPN Total parenteral nutrition
± ( ) : Mean ± Standard deviation (number)
NR: Not reported
† Hospital mortality unless stated otherwise
‡ Number of patients with infections unless stated otherwise

* Data from a sub group, hence not included in meta-analysis
** Data for mortality is ITT, infections is non-ITT.
*** Data from EN glutamine group not shown here, appears in EN glutamine section
α Unable to confirm the low dose from authors (0.002 gm/kg/day) hence data not included in the meta-analyses
∂ Data from growth hormone group not shown here
Δ Data not shown as awaiting publication

Ozgultekin 2008: data presented here only pertains to glutamine supplemented group and standard group, refer to section 9.1 Branched Chain Amino Acids (BCAA) for data pertaining to BCAA vs standard.

Table 2. QOL Outcomes

Study	QOL Outcomes
2) Powell Tuck 1999	**Perceived morbidity/quality of life scores – patients were asked to score mood, sleep, energy, appetite, pain and mobilisation on a 10 point scale** **Measured at entry into trial and when PN stopped** All modalities improved (p<0.0001 for each) but no statistical difference between groups.
25) Andrews 2011	**Gln** / **Gln+Se** / **Se** / **Neither** **SF-12 PCS at 3 months** 35.2 ± 9.8 (49) / 33.3 ± 11.1 (50) / 33.9 ± 9.8 (52) / 36.6 ± 11.6 (59) **SF-12 PCS at 6 months** 35.9 ± 9.3 (45) / 35.9 ± 10.9 (43) / 36.3 ± 10.0 (46) / 39.9 ± 10.5 (53) **SF-12 MCS at 3 months** 420 ± 11.8 (49) / 40.3 ± 12.0 (50) / 41.9 ± 11.9 (52) / 42.2 ± 12.2 (59) **SF-12 MCS at 6 months** 43.4 ± 11.9 (45) / 44.8 ± 11.9 (43) / 44.1 ± 11.6 (46) / 43.3 ± 12.1 (53) **EQ-5D at 3 months** 0.47 ± 0.41 (52) / 0.51 ± 0.35 (52) / 0.49 ± 0.35 (55) / 0.56 ± 0.34 (61 **EQ-5D at 6 months** 0.53 ± 0.35 (49) / 0.60 ± 0.30 (51) / 0.53 ± 0.33 (47) / 0.63 ± 0.28 (55)

Figure 1. Overall Mortality (EN vs PN)

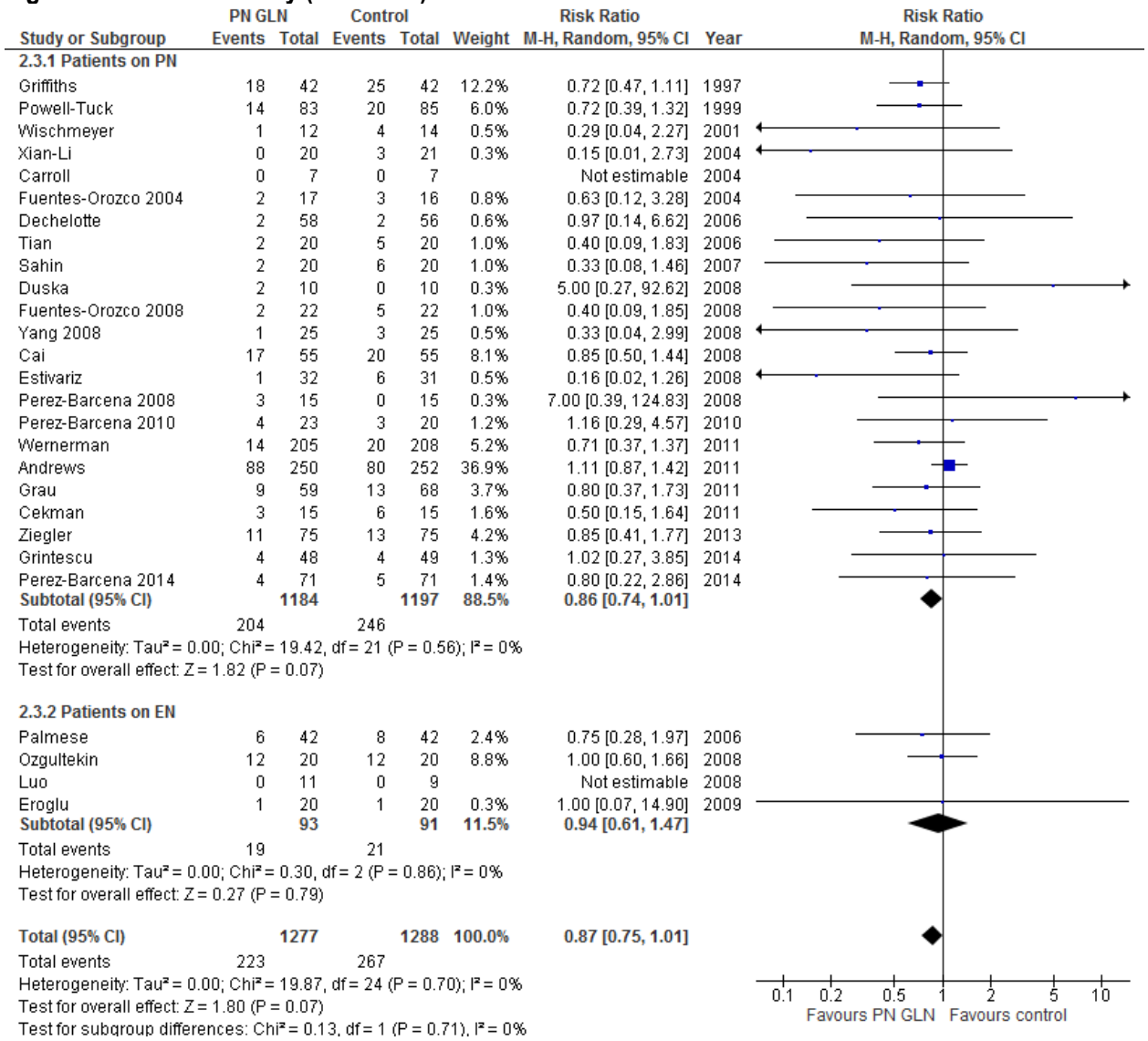


Figure 2. Overall Mortality (Single vs Multi Centre)

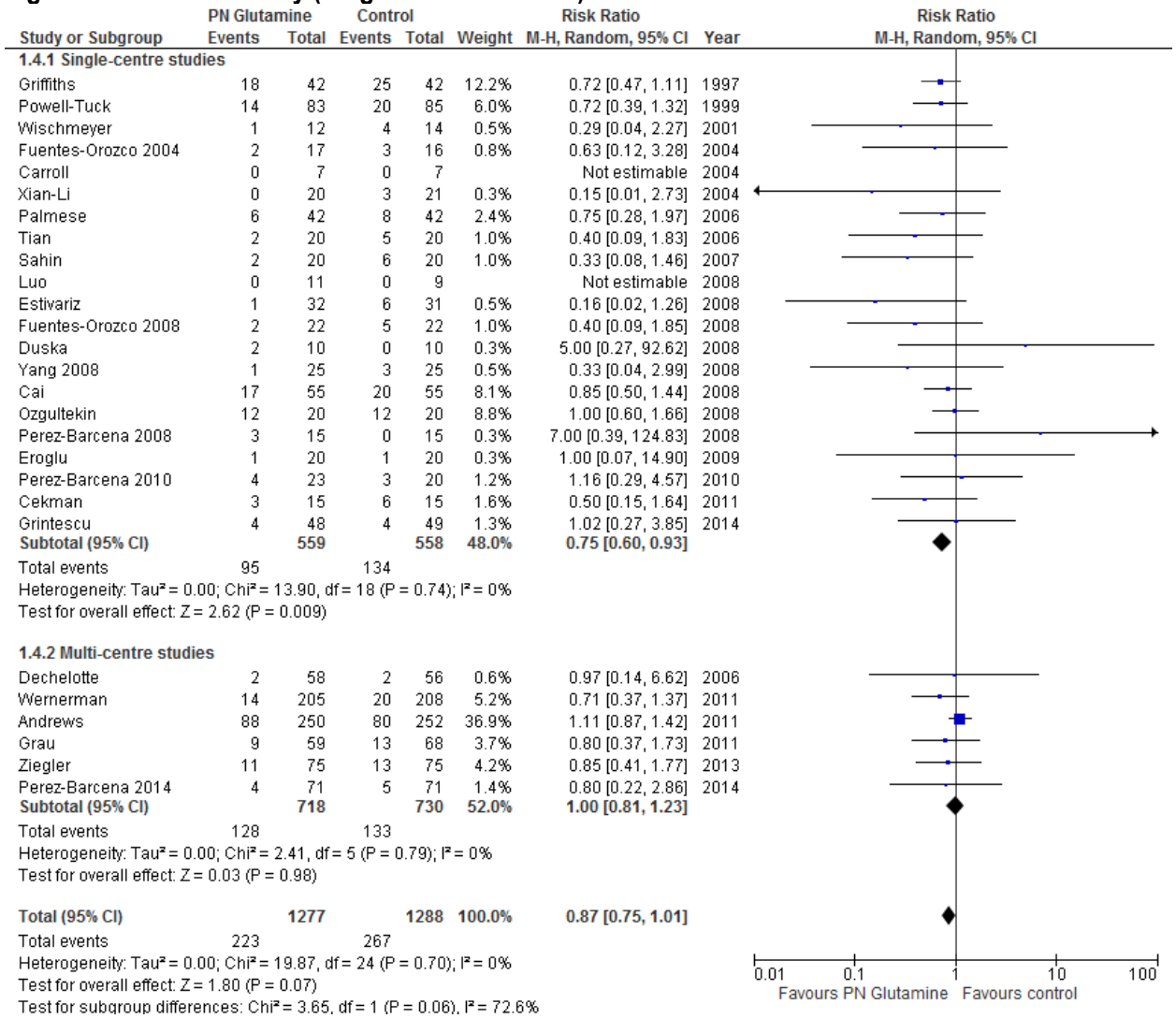


Figure 3. Hospital Mortality (Single vs Multi Centre)

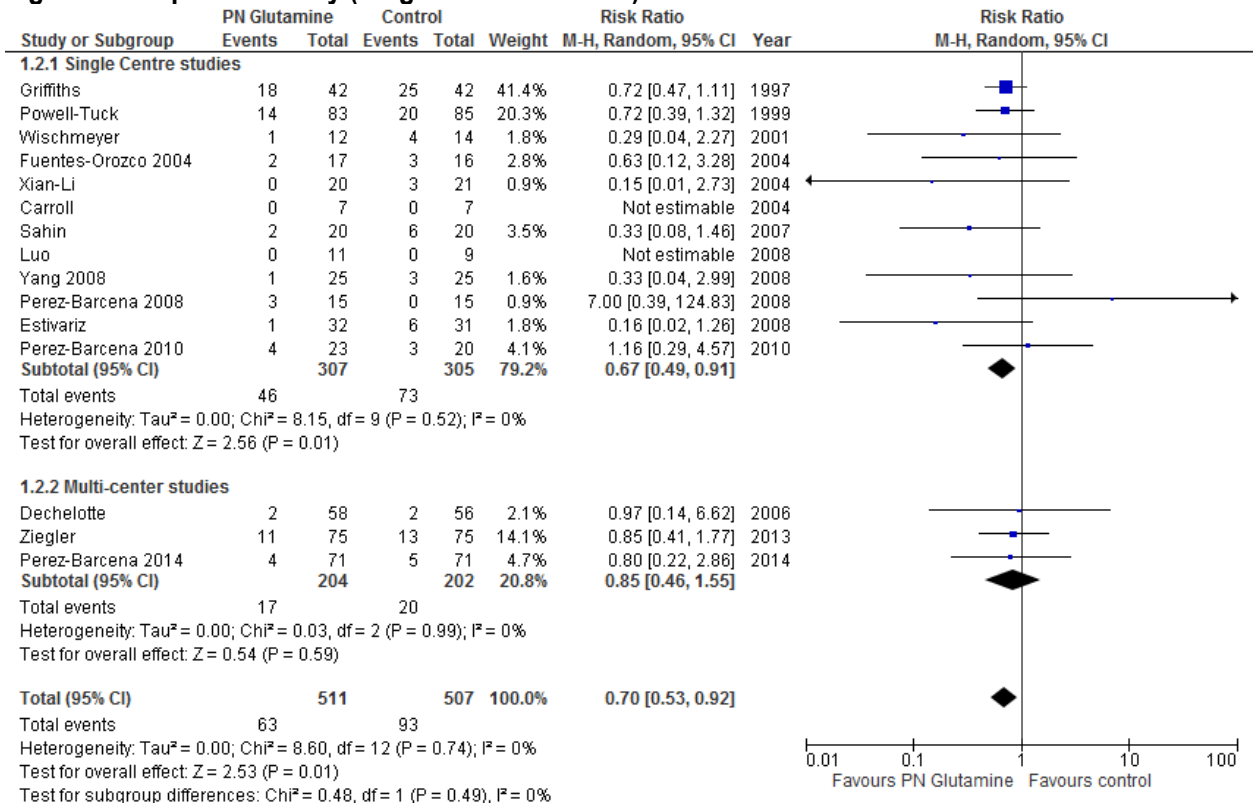


Figure 4. Infectious Complications

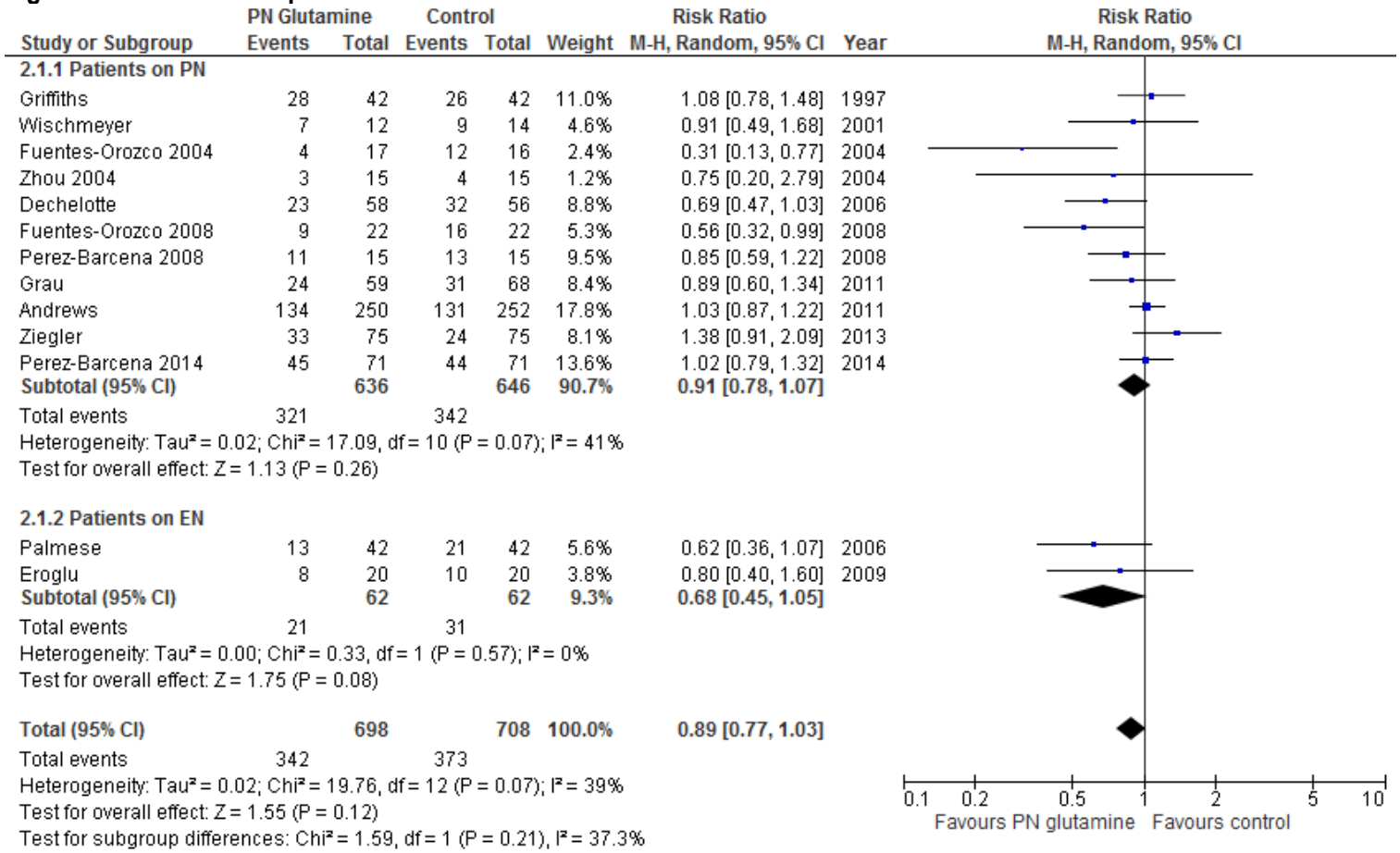


Figure 5. Ventilator Associated Pneumonia

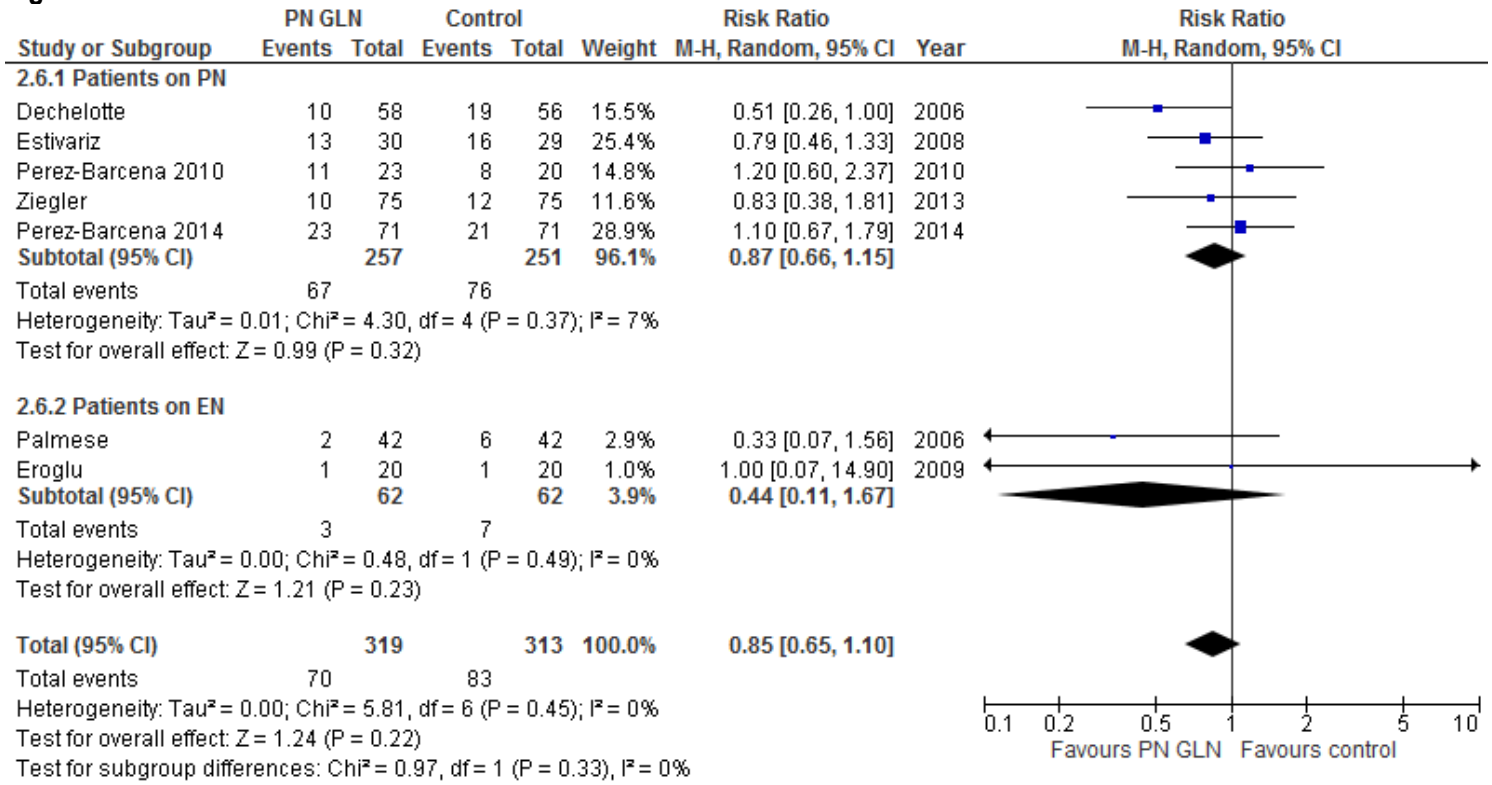


Figure 6. ICU LOS

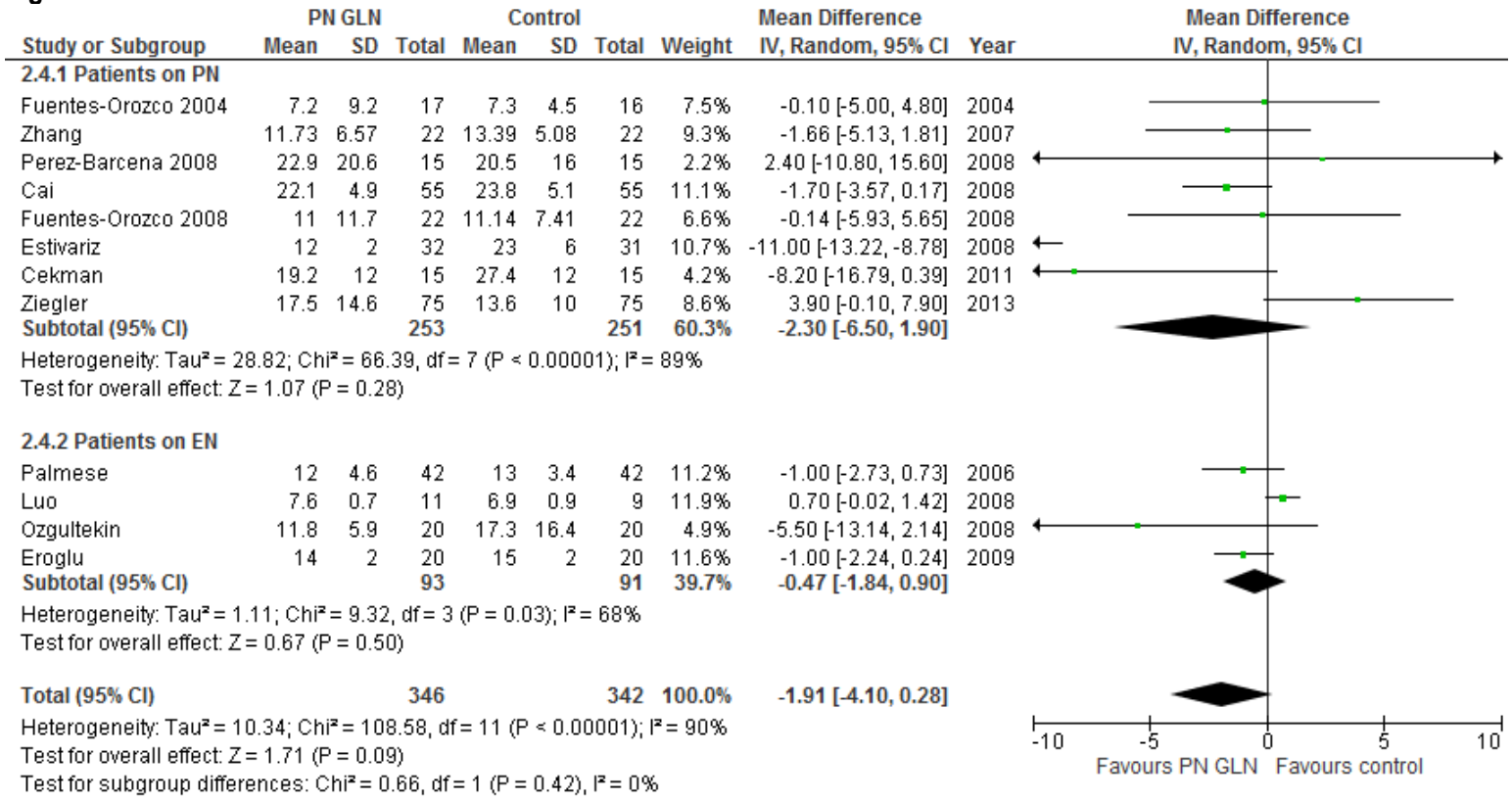


Figure 7. Hospital LOS

Study or Subgroup	PN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Powell-Tuck	43.4	34.1	83	48.9	38.4	85	3.2%	-5.50 [-16.48, 5.48]	1999
Wischmeyer	40	10	12	40	9	14	6.0%	0.00 [-7.36, 7.36]	2001
Fuentes-Orozco 2004	16.5	8.9	17	16.7	7	16	8.8%	-0.20 [-5.65, 5.25]	2004
Zhou 2004	42	7	15	46	6.6	15	9.9%	-4.00 [-8.87, 0.87]	2004
Xian-Li	25.3	7.6	20	28.6	6.9	21	10.8%	-3.30 [-7.75, 1.15]	2004
Sahin	14.2	4.4	20	16.4	3.9	20	15.7%	-2.20 [-4.78, 0.38]	2007
Estivariz	20	2	15	30	6	12	13.1%	-10.00 [-13.54, -6.46]	2008
Yang 2008	13.48	1.42	25	15.18	1.14	25	19.8%	-1.70 [-2.41, -0.99]	2008
Perez-Barcena 2008	35.5	33.6	15	42.9	28.8	15	0.9%	-7.40 [-29.80, 15.00]	2008
Fuentes-Orozco 2008	30.18	10.42	22	26.59	13.3	22	6.4%	3.59 [-3.47, 10.65]	2008
Ziegler	33.6	28	75	29.7	20.7	75	5.4%	3.90 [-3.98, 11.78]	2013
Total (95% CI)			**319**			**320**	**100.0%**	**-2.56 [-4.71, -0.42]**	

Heterogeneity: Tau² = 5.92; Chi² = 27.15, df = 10 (P = 0.002); I² = 63%
Test for overall effect: Z = 2.34 (P = 0.02)

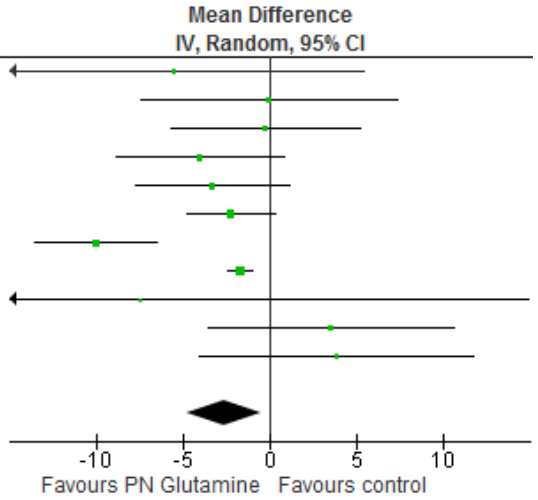
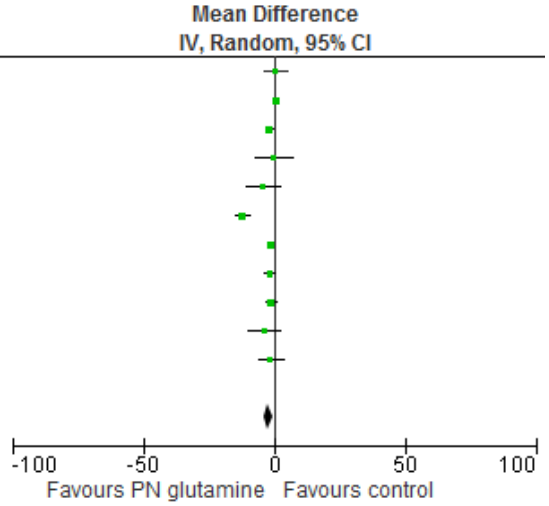


Figure 8. Mechanical Ventilation

Study or Subgroup	PN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Fuentes-Orozco 2004	4.88	8.2	17	4.47	4.4	16	7.2%	0.41 [-4.04, 4.86]	2004
Palmese	6	1.7	42	5	2.5	42	13.2%	1.00 [0.09, 1.91]	2006
Zhang	5.27	1.78	22	7.18	2.76	22	12.6%	-1.91 [-3.28, -0.54]	2007
Perez-Barcena 2008	14	10	15	14	10	15	4.1%	0.00 [-7.16, 7.16]	2008
Ozgultekin	10.1	4.4	20	14.4	14	20	4.7%	-4.30 [-10.73, 2.13]	2008
Estivariz	9	2	15	21	5	12	9.7%	-12.00 [-15.00, -9.00]	2008
Luo	5	1	14	6	1	9	13.3%	-1.00 [-1.84, -0.16]	2008
Cai	15.6	5.7	55	17.2	5.9	55	11.3%	-1.60 [-3.77, 0.57]	2008
Eroglu	8	3	20	9	3	20	11.9%	-1.00 [-2.86, 0.86]	2009
Perez-Barcena 2010	15.2	8.2	23	18.9	11.1	20	5.3%	-3.70 [-9.61, 2.21]	2010
Koksal	13	12.2	30	14.3	5.4	30	6.7%	-1.30 [-6.07, 3.47]	2014
Total (95% CI)			**273**			**261**	**100.0%**	**-2.16 [-3.89, -0.43]**	

Heterogeneity: Tau² = 5.65; Chi² = 73.91, df = 10 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.45 (P = 0.01)



9.4a Composition of Parenteral Nutrition: Glutamine Supplementation

Note: isonitrogenous refers to nitrogen provided from all sources (nutrition support **and** study intervention drug).

Isonitrogenous	N	Nonisonitrogenous	N
Griffiths 1997 & 2002	84	Powell-Tuck 1999	168
Fuentes-Oroczo 2004	33	Wischmeyer 2001	31
Zhou 2004	30	Goeters 2002	68
Dechelotte 2006	114	Carrol 2004	19
Estivariz 2008	63	Xian-Li 2004	69
Fuentes-Oroczo 2008	44	Tian 2006	40
Luo 2008	44	Sahin 2007	40
Perez- Barcena 2008	30	Cai 2008	110
Perez-Barcena 2010	43	Duska 2008	30
Andrews 2011	502	Ozgultekin 2008	60
Grau 2011	127	Eroglu 2009	40
Ziegler 2012	150	Wernerman 2011	413
Grintescu 2014	97	Cekman 2011	30
		Perez-Barcena 2014	142
TOTAL	1361	TOTAL	1260

Unknown: Palmese 2006, Yang 2007, Zhang 2007, Yang 2008

Glutamine	N	Glutamine Dipeptide	N
Griffiths 1997 & 2002	84	Goeters 2002	68
Powell-Tuck 1999	168	Fuentes-Oroczo 2004	33
Wischmeyer 2001	31	Zhou 2004	30
Carrol 2004	19	Xian-Li 2004	69
Palmese2006	84	Dechelotte 2006	114
Andrews 2011	502	Tian 2006	40
		Sahin 2007	40
		Yang 2007α	46
		Cai 2008	110
		Duska 2008	30
		Estivariz 2008	63
		Fuentes-Oroczo 2008	44
		Luo 2008	44
		Perez- Barcena 2008	30
		Ozgultekin 2008	60
		Yang 2008	61
		Eroglu 2009	40
		Perez-Barcena 2010	43
		Cekman 2011	30
		Grau 2011	127
		Wernerman 2011	413
		Ziegler 2012	150
		Perez-Barcena 2014	142
		Grintescu 2014	97
TOTAL	888	TOTAL	1924

Unknown: Zhang 2007