9.4a Composition of Parenteral Nutrition: Glutamine Supplementation May 2015

2015 Recommendation: *Based on 31 studies (10 level 1 studies and 21 level 2 studies), when parenteral nutrition is prescribed to critically ill patients, we recommend parenteral supplementation with glutamine NOT be used. There are insufficient data on the use of intravenous glutamine in critically ill patients receiving enteral nutrition but given the safety concerns we also recommend intravenous glutamine not be used in enterally fed critically ill patients.*

2015 Discussion: The committee noted that with the inclusion of 3 new trials (Perez Barcena 2014, Grintescu 2014 and Carrol 2004), the effect on overall mortality and infections did not change since the last update and there is still only a trend for reduction in these outcomes. Of the 6 multicentre studies (Andrews 2011, Wernerman 2011, Ziegler 2012, Grau 2011, Dechelotte 2006, Perez Barcena 2014), 4 failed to show a strong positive effect on mortality or infections. The positive signals for reduction in ICU, hospital LOS and mechanical ventilation were noted to have significant statistical heterogeneity. The use of free glutamine (L-glutamine) vs dipeptides (L-alanyl-L-glutamine) did not alter the effect on mortality, infections or LOS and the same was true for isonitrogenous vs. non-isonitrogenous studies. The committee was concerned about the signals of harm for the use of combined intravenous and enteral glutamine in critically ill patients with shock and organ failure from the REDOXS study and the higher mortality seen in medical patients and an increase in 6 month mortality in patients receiving enteral glutamine in the large van Zanten study. Furthermore, the difficulty in accurately distinguishing the timing when a non septic patient may become septic was acknowledged, It was therefore recommended that intravenous glutamine not be used in the critically ill population. Considering this and the minimal data in burns and trauma patients, the committee chose not to make a recommendation in these specific ICU populations.

2013 Recommendation: *Based on 9 level 1 studies and 19 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine should be considered. However, we strongly recommend that glutamine NOT be used in critically ill patients with shock and multi-organ failure (refer to section 9.4 b Combined Parenteral and Enteral Glutamine. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.*

2013 Discussion:

It was noted that with the addition of 11 new trials (Tian 2006, Zhang 2007, Ozgultekin 2008, Yang 2008, Eroglu 2009, Perez-Barcena 2010, Andrews 2011, Cekman 2011, Grau 2011, Wernerman 2011 & Ziegler 2012), there were weaker signals for a reduction in overall mortality & infectious complications and yet a strong treatment effect of IV supplemented glutamine on hospital mortality and ICU and hospital length of stay remained. It was further noted that a few large scale multicenter randomized trials of IV glutamine had failed to demonstrate a convincing positive effect (Andrews 2011, Wernerman 2011, Ziegler 2012). The committee agreed that the REDOXS study (Heyland 2012), which uses combined EN and PN glutamine supplementation at high doses, should not be included in this section due to its different intervention and patient population (shock and multi-organ failure patients). However, it was felt that the results of this 1200 patient multicentre trial, which suggested a significant safety concern, could not be ignored. Coupled with a diminished signal of benefit and a potential increase in harm, the committee downgraded the recommendation for IV glutamine to “should be considered.”

Semi Quantitative Scoring

Value	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	**1 (infection) 1 (mortality)**	**1 (infection) 1 or 2 (mortality)**
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	**2 (infection) 2 (mortality)**	**2 (infection) 2 (mortality)**
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	**1 (infection) 3 (mortality)**	**1 (infection) 3 (mortality)**
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	**2**	**2**
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	**3**	**2**
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.	**1**	**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	**2**	**2**
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	**0 (available with difficulty)**	**0**
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	**1**	**0**

9.4a Composition of Parenteral Nutrition: Glutamine Supplementation

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 isonitriogenous feeding on outcomes, subgroup analyses were done, Need to add Koskal 2014 RCT in which 1 of 3 groups compared EN Glutamine to EN only and reported on mechanical ventilation only.

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. 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 were on 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). In the 15 studies that reported hospital mortality, a significant reduction in hospital mortality was seen when they were aggregated (RR 0.70, 95% ci 0.53, 0.92, P = 0.01, heterogeneity I^2=0%; figure 2). 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 3). 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 3). 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 3). 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 4). 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 4) or EN fed patients (RR 0.44, 95% CI 0.11, 1.67, p=0.23, heterogeneity I^2=0%; figure 4). 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 5). 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 5) or EN (WMD -0.47, 95% CI -1.84, 0.90, p = 0.50, heterogeneity I^2= 68%; figure 5). 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 6). 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 7)

Conclusions:

1) IV glutamine supplementation is associated with a trend towards a reduction in overall mortality and a significant reduction in hospital mortality.
2) IV glutamine supplementation is associated with a trend towards a reduction in infectious complications but no effect on ventilator associated pneumonia.
3) IV glutamine supplementation is associated with a trend in reduction in ICU LOS and a significant 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.

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.

Figure 1. Overall Mortality (EN vs PN)

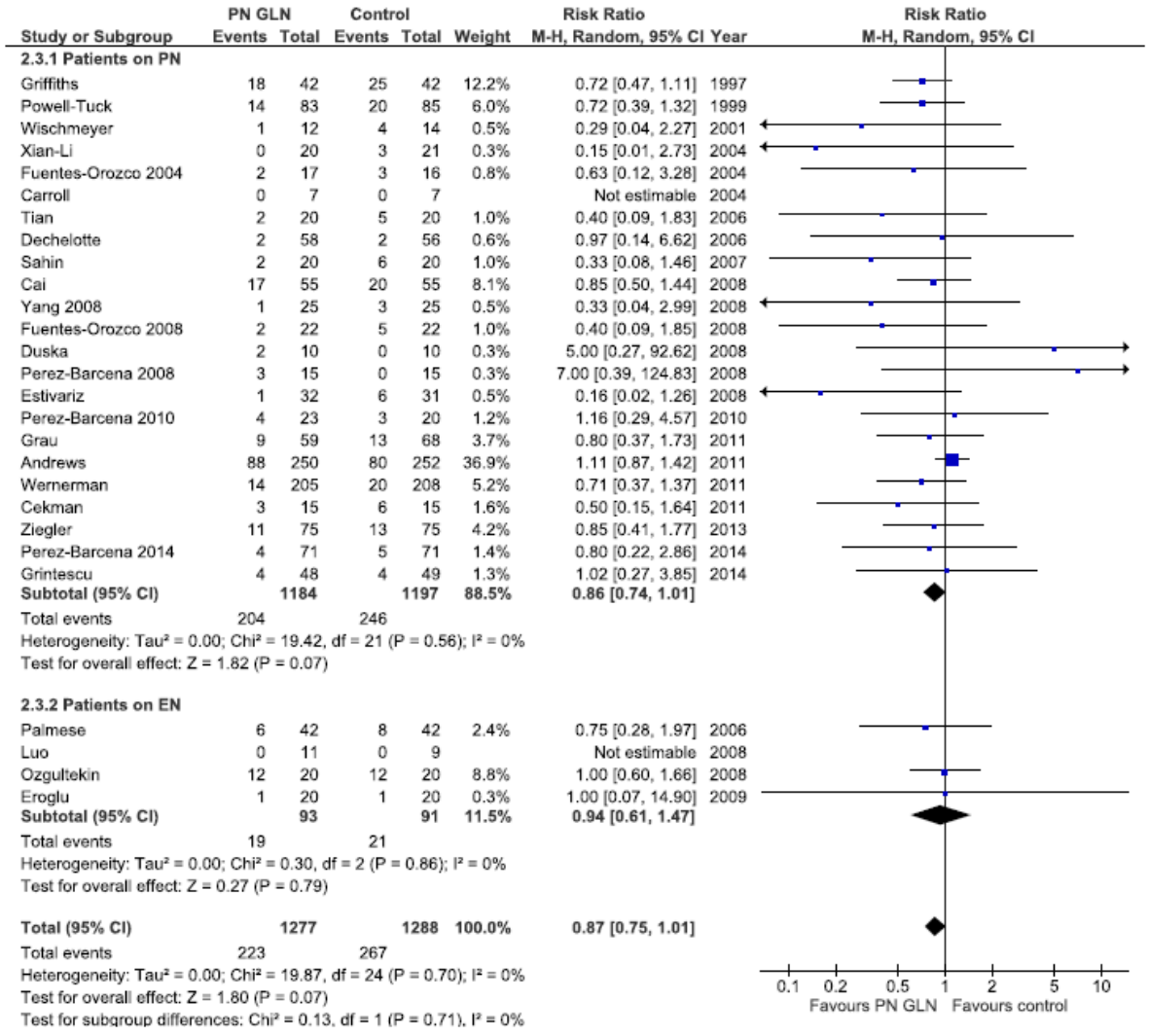


Figure 2. Hospital Mortality

Study or Subgroup	PN GLN Events	PN GLN Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Griffiths	18	42	25	42	41.4%	0.72 [0.47, 1.11]	1997
Powell-Tuck	14	83	20	85	20.3%	0.72 [0.39, 1.32]	1999
Wischmeyer	1	12	4	14	1.8%	0.29 [0.04, 2.27]	2001
Carroll	0	7	0	7		Not estimable	2004
Xian-Li	0	20	3	21	0.9%	0.15 [0.01, 2.73]	2004
Fuentes-Orozco 2004	2	17	3	16	2.8%	0.63 [0.12, 3.28]	2004
Dechelotte	2	58	2	56	2.1%	0.97 [0.14, 6.62]	2006
Sahin	2	20	6	20	3.5%	0.33 [0.08, 1.46]	2007
Perez-Barcena 2008	3	15	0	15	0.9%	7.00 [0.39, 124.83]	2008
Yang 2008	1	25	3	25	1.6%	0.33 [0.04, 2.99]	2008
Luo	0	11	0	9		Not estimable	2008
Estivariz	1	32	6	31	1.8%	0.16 [0.02, 1.26]	2008
Perez-Barcena 2010	4	23	3	20	4.1%	1.16 [0.29, 4.57]	2010
Ziegler	11	75	13	75	14.1%	0.85 [0.41, 1.77]	2013
Perez-Barcena 2014	4	71	5	71	4.7%	0.80 [0.22, 2.86]	2014
Total (95% CI)		**511**		**507**	**100.0%**	**0.70 [0.53, 0.92]**	
Total events	63		93				

Heterogeneity: Tau² = 0.00; Chi² = 8.60, df = 12 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.53 (P = 0.01)

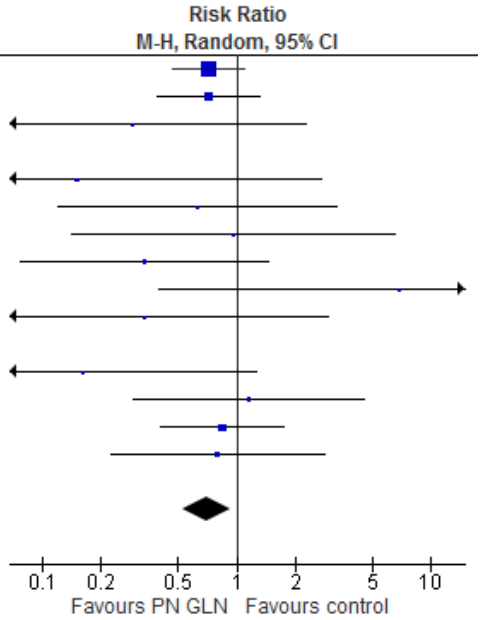


Figure 3. Infectious Complications

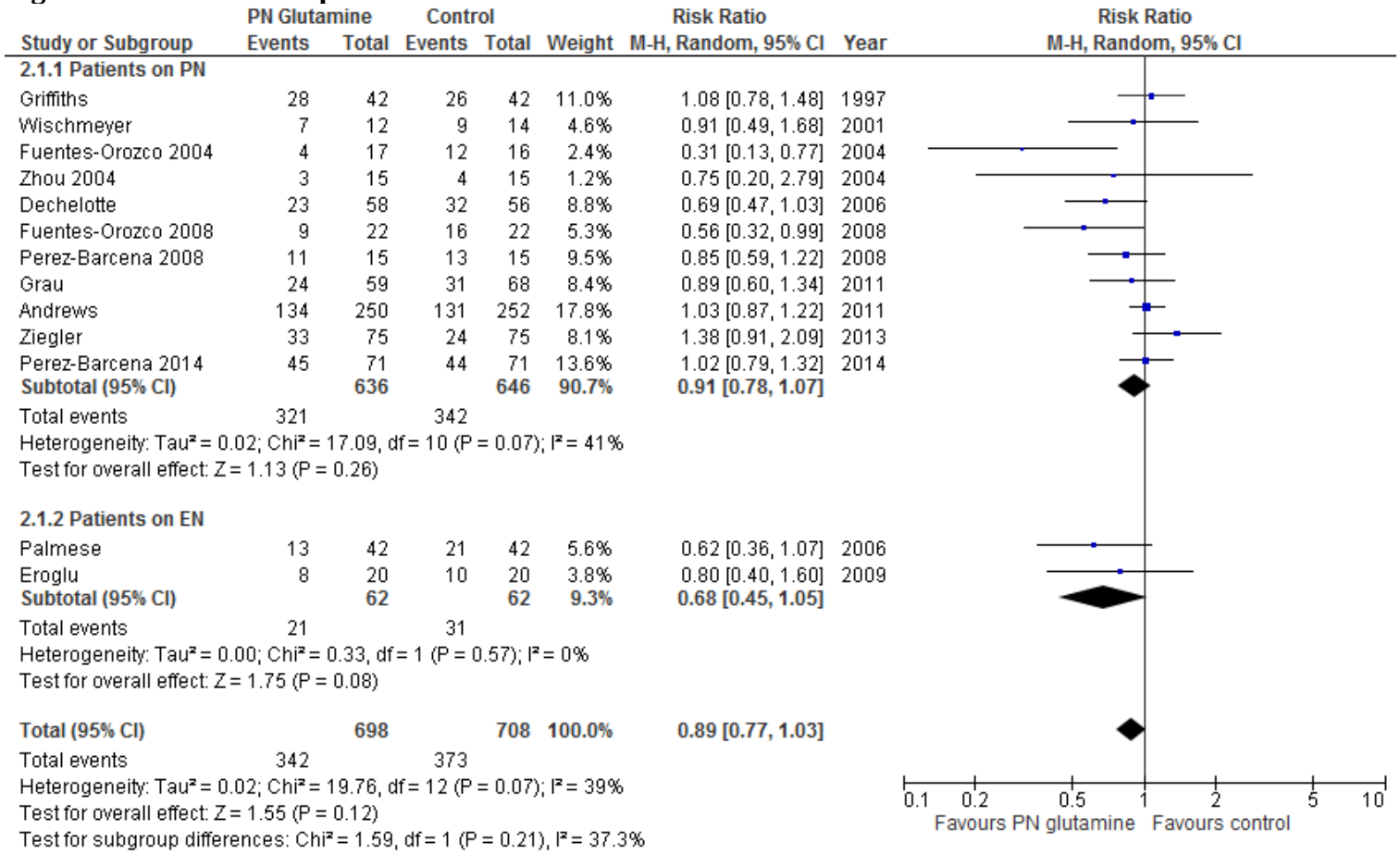


Figure 4. Ventilator Associated Pneumonia

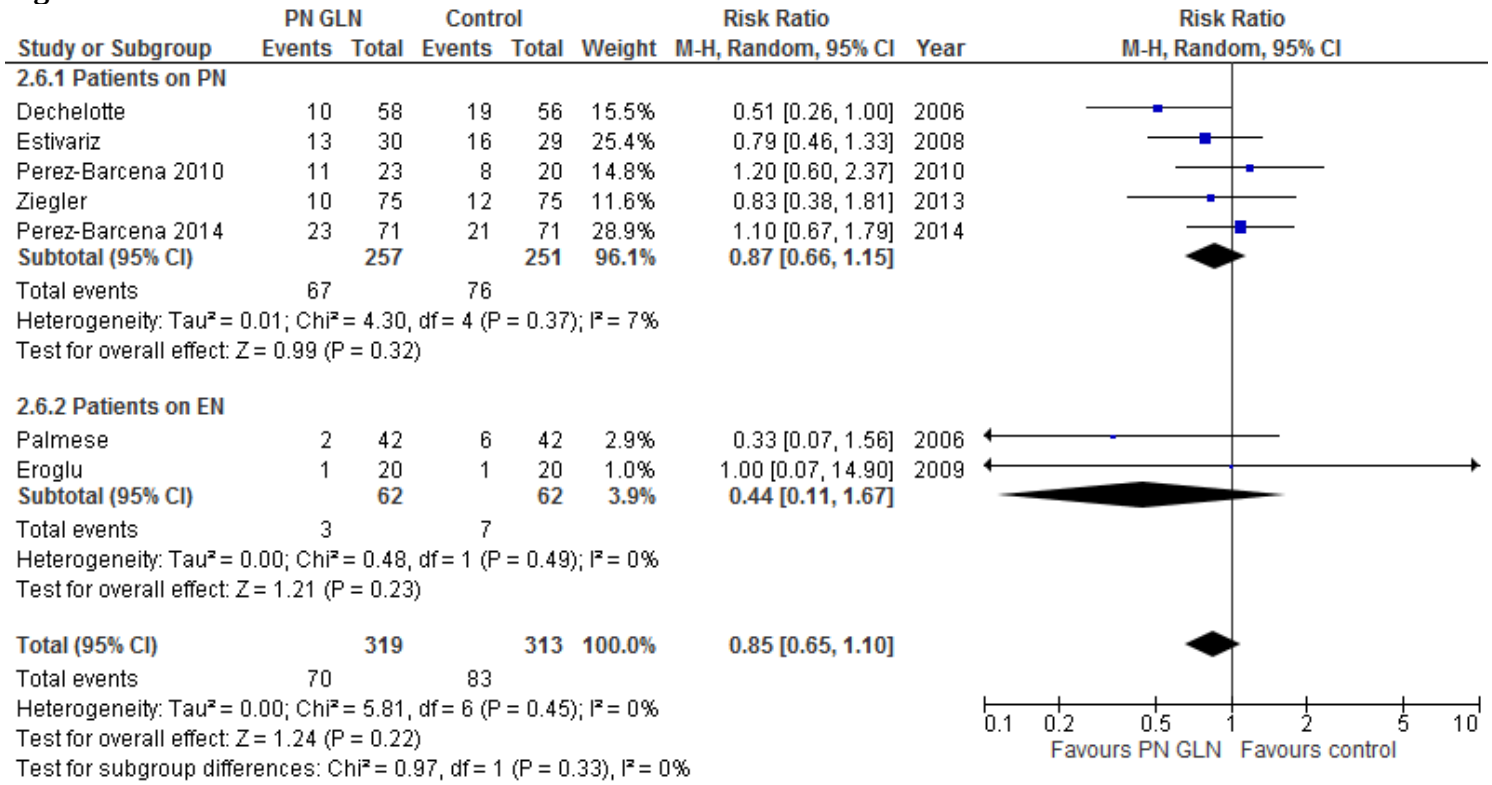


Figure 5 ICU LOS

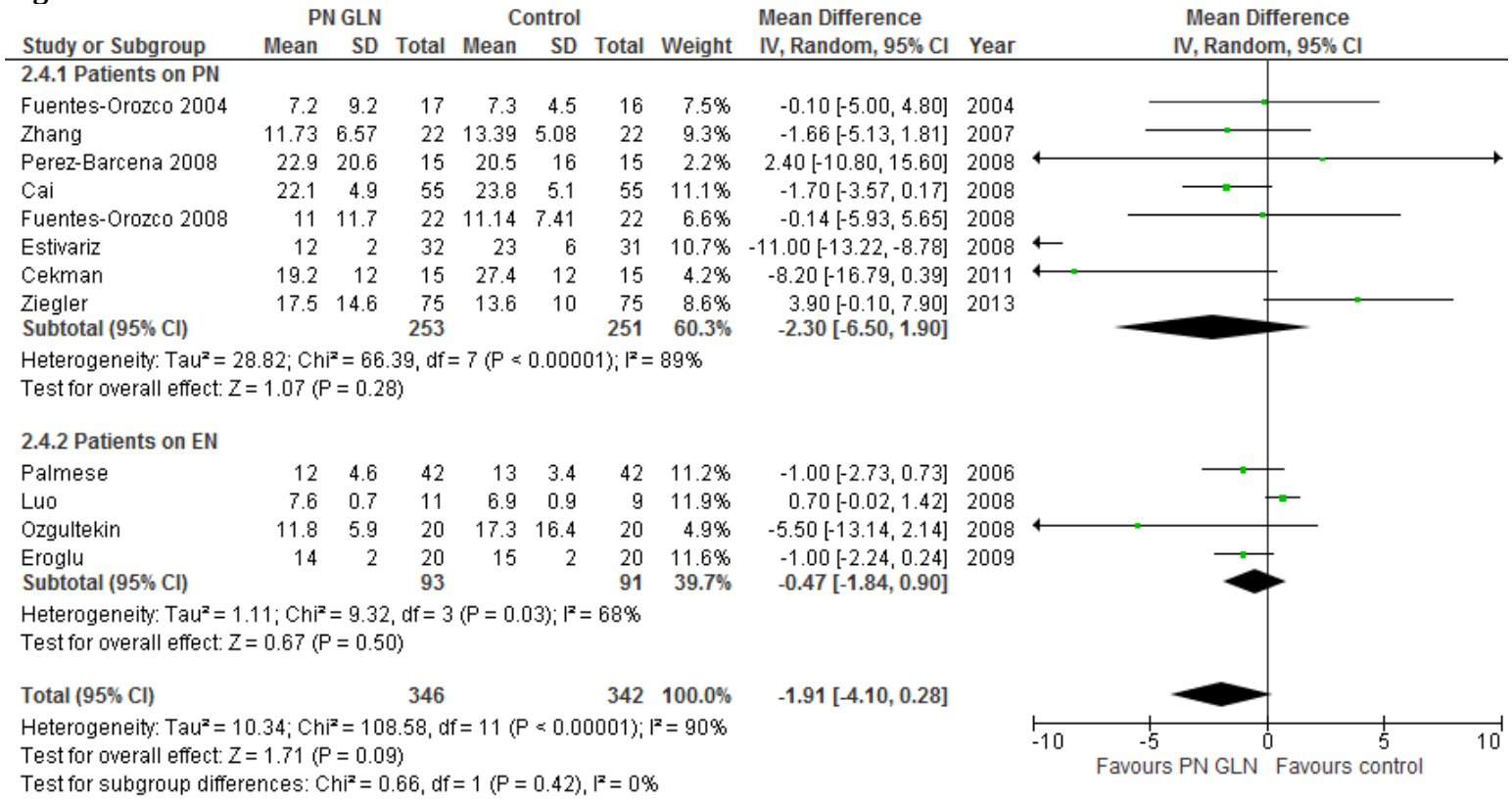


Figure 6 Hospital LOS

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)

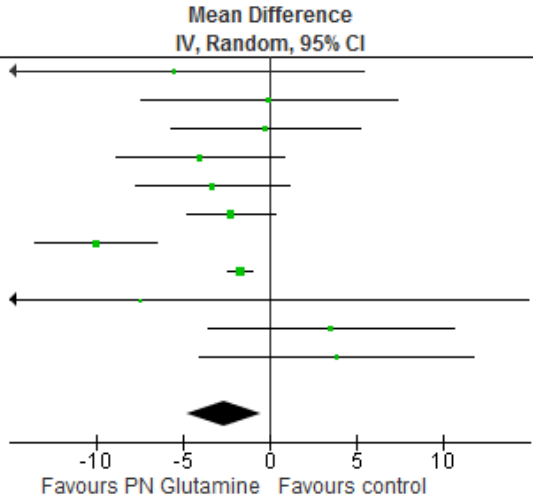
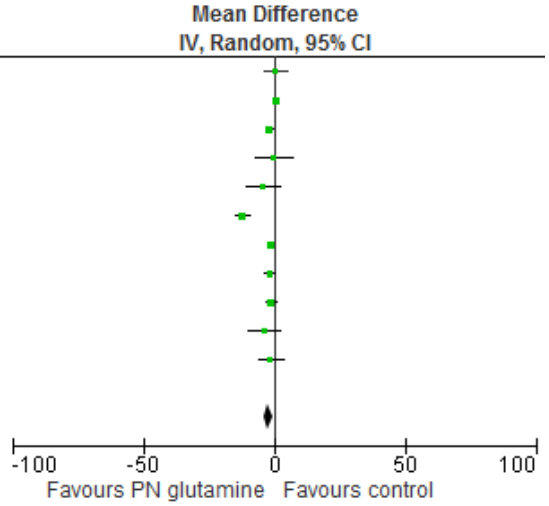


Figure 7. Mechanical Ventilation

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