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 I²=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 I²=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 I²=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 I²=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 I²=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 I²=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 $l^2 = 39\%$; 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 $l^2 = 41\%$; 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 $l^2=0\%$; 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 $l^2=0\%$; 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 $l^2=7\%$; figure 5) or EN fed patients (RR 0.44, 95% CI 0.11, 1.67, p=0.23, heterogeneity $l^2=0\%$; 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 \pm 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 I²=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 I²=89%; figure 6) or EN (WMD -0.47, 95% CI -1.84, 0.90, p = 0.50, heterogeneity I²= 68%; figure 6). The test for subgroup differences

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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 \pm 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 | Intervention Dose of Lglutamine | Mortalit | y # (%)† | Infection | s # (%)‡ | Length of s | stay (days) |
|-----------------------------|---|---|--|---|---|--------------|------------|---|--|
| | | (score) | gm/kg/day | 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. GIn-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 ≥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 \pm (): Mean \pm Standard deviation (number)

NR: Not reported

* 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.

† Hospital mortality unless stated otherwise ‡ Number of patients with infections unless stated otherwise

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, pai Measured at entry into trial and when PN stopped All modalities improved (p<0.0001 for each) but no statistical difference between | | | | | | | | | | | |
| 25) Andrews 2011 | GIn GIn+Se Se Neither SF-12 PCS at 3 months | | | | | | | | | | | |
| | 35.2 <u>+</u> 9.8 (49) 33.3 <u>+</u> 11.1 (50) 33.9 <u>+</u> 9.8 (52) 36.6 <u>+</u> 11. SF-12 PCS at 6 months | 6 (59) | | | | | | | | | | |
| | 35.9 ± 9.3 (45) 35.9 ± 10.9 (43) 36.3 ± 10.0 (46) 39.9 ± 10 SF-12 MCS at 3 months | .5 (53) | | | | | | | | | | |
| | 420 <u>+</u> 11.8 (49) 40.3 <u>+</u> 12.0 (50) 41.9 <u>+</u> 11.9 (52) 42.2 <u>+</u> 12 SF-12 MCS at 6 months | .2 (59) | | | | | | | | | | |
| | 43.4 <u>+</u> 11.9 (45) 44.8 <u>+</u> 11.9 (43) 44.1 <u>+</u> 11.6 (46) 43.3 <u>+</u> 12 EQ-5D at 3 months | 2.1 (53) | | | | | | | | | | |
| | 0.47 <u>+</u> 0.41 (52) 0.51 <u>+</u> 0.35 (52) 0.49 <u>+</u> 0.35 (55) 0.56 <u>+</u> 0 EQ-5D at 6 months | .34 (61 | | | | | | | | | | |
| | 0.53 ± 0.35 (49) 0.60 ± 0.30 (51) 0.53 ± 0.33 (47) 0.63 ± 0.33 | 28 (55) | | | | | | | | | | |

Figure 1. Overall Mortality (EN vs PN)

| | PN GI | | Contr | | | Risk Ratio | | Risk Ratio |
|---|----------------------|-----------|-------------|----------|---------------------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | M-H, Random, 95% Cl |
| .3.1 Patients on PN | | | | | | | | |
| Griffiths | 18 | 42 | 25 | 42 | 12.2% | 0.72 [0.47, 1.11] | | |
| Powell-Tuck | 14 | 83 | 20 | 85 | 6.0% | 0.72 [0.39, 1.32] | 1999 | |
| Nischmeyer | 1 | 12 | 4 | 14 | 0.5% | 0.29 [0.04, 2.27] | 2001 | • |
| (ian-Li | 0 | 20 | 3 | 21 | 0.3% | 0.15 [0.01, 2.73] | 2004 | ← |
| Carroll | 0 | 7 | 0 | 7 | | Not estimable | 2004 | |
| Fuentes-Orozco 2004 | 2 | 17 | 3 | 16 | 0.8% | 0.63 [0.12, 3.28] | 2004 | |
| Dechelotte | 2 | 58 | 2 | 56 | 0.6% | 0.97 [0.14, 6.62] | 2006 | |
| Fian | 2 | 20 | 5 | 20 | 1.0% | 0.40 [0.09, 1.83] | 2006 | |
| Sahin | 2 | 20 | 6 | 20 | 1.0% | 0.33 [0.08, 1.46] | 2007 | |
| Duska | 2 | 10 | 0 | 10 | 0.3% | 5.00 [0.27, 92.62] | 2008 | |
| Fuentes-Orozco 2008 | 2 | 22 | 5 | 22 | 1.0% | 0.40 [0.09, 1.85] | 2008 | |
| /ang 2008 | 1 | 25 | 3 | 25 | 0.5% | 0.33 [0.04, 2.99] | | < |
| Cai | 17 | 55 | 20 | 55 | 8.1% | 0.85 [0.50, 1.44] | | + |
| Estivariz | 1 | 32 | 6 | 31 | 0.5% | 0.16 [0.02, 1.26] | | ← → ↓ |
| Perez-Barcena 2008 | 3 | 15 | Ō | 15 | 0.3% | 7.00 [0.39, 124.83] | | |
| Perez-Barcena 2010 | 4 | 23 | 3 | 20 | 1.2% | 1.16 [0.29, 4.57] | | |
| Nernerman | 14 | 205 | 20 | 208 | 5.2% | 0.71 [0.37, 1.37] | | _ |
| Andrews | 88 | 250 | 80 | 252 | 36.9% | 1.11 [0.87, 1.42] | | _ _ |
| 3rau | 9 | 59 | 13 | 68 | 3.7% | 0.80 [0.37, 1.73] | | |
| Cekman | 3 | 15 | .0 | 15 | 1.6% | 0.50 [0.15, 1.64] | | |
| Ziegler | 11 | 75 | 13 | 75 | 4.2% | 0.85 [0.41, 1.77] | | - |
| Grintescu | 4 | 48 | 4 | 49 | 1.3% | 1.02 [0.27, 3.85] | | |
| Perez-Barcena 2014 | 4 | 71 | 5 | 71 | 1.4% | 0.80 [0.22, 2.86] | | |
| Subtotal (95% CI) | 4 | 1184 | 5 | 1197 | 88.5% | 0.86 [0.74, 1.01] | 2014 | |
| Fotal events | 204 | | 246 | | 001070 | oloo [oli ij ilo i] | | • |
| Heterogeneity: Tau ² = 0. | | - 10 40 | | 0-06 | (c) (Z = 0.0) | Ĺ | | |
| Fest for overall effect: Z = | | | | r – 0.5 | 0),1 = 03 | 0 | | |
| | | , | | | | | | |
| 2.3.2 Patients on EN | | | | | | | | |
| Palmese | 6 | 42 | 8 | 42 | 2.4% | 0.75 [0.28, 1.97] | 2006 | |
| Ozgultekin | 12 | 20 | 12 | 20 | 8.8% | 1.00 [0.60, 1.66] | 2008 | |
| _uo | 0 | 11 | 0 | 9 | | Not estimable | 2008 | |
| Eroglu | 1 | 20 | 1 | 20 | 0.3% | 1.00 [0.07, 14.90] | 2009 | |
| Subtotal (95% CI) | | 93 | | 91 | 11.5% | 0.94 [0.61, 1.47] | | - |
| Fotal events | 19 | | 21 | | | | | |
| Heterogeneity: Tau ² = 0. | .00; Chi * = | = 0.30, i | df = 2 (P = | = 0.86); | I ² = 0% | | | |
| Fest for overall effect: Z = | = 0.27 (P | = 0.79) | i - | | | | | |
| Fotal (95% CI) | | 1277 | | 1200 | 100.0% | 0.87 [0.75, 1.01] | | |
| | | 1211 | 207 | 1200 | 100.0% | 0.07 [0.75, 1.01] | | • |
| Fotal events | 223 | 40.0- | 267 | | | , | | |
| | | | - of - 247 | e – n 7 | un: P≚ – 00 | 6 | | |
| Heterogeneity: Tau ² = 0. | | | | i = 0.r | 0),1 = 0 / | • | | |
| leterogeneity: Tau² = 0. 'est for overall effect: Z = 'est for subgroup differe | = 1.80 (P | = 0.07) | | | | | | 0.1 0.2 0.5 1 2 5 10 Favours PN GLN Favours control |

Figure 2. Overall Mortality (Single vs Multi Centre)

| | PN Gluta | | Contr | | | Risk Ratio | | Risk Ratio |
|--------------------------------------|---------------------------|----------|-------------------|-----------------------|-------------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | M-H, Random, 95% Cl |
| I.4.1 Single-centre stud | dies | | | | | | | |
| Griffiths | 18 | 42 | 25 | 42 | 12.2% | 0.72 [0.47, 1.11] | 1997 | |
| Powell-Tuck | 14 | 83 | 20 | 85 | 6.0% | 0.72 [0.39, 1.32] | 1999 | |
| Nischmeyer | 1 | 12 | 4 | 14 | 0.5% | 0.29 [0.04, 2.27] | 2001 | |
| Fuentes-Orozco 2004 | 2 | 17 | 3 | 16 | 0.8% | 0.63 [0.12, 3.28] | 2004 | |
| Carroll | 0 | 7 | 0 | 7 | | Not estimable | 2004 | |
| ≺ian-Li | 0 | 20 | 3 | 21 | 0.3% | 0.15 [0.01, 2.73] | 2004 | ← |
| Palmese | 6 | 42 | 8 | 42 | 2.4% | 0.75 [0.28, 1.97] | | |
| Tian | 2 | 20 | 5 | 20 | 1.0% | 0.40 [0.09, 1.83] | | |
| Bahin | 2 | 20 | 6 | 20 | 1.0% | 0.33 [0.08, 1.46] | | |
| _uo | 0 | 11 | 0 | 9 | | Not estimable | | |
| Estivariz | 1 | 32 | 6 | 31 | 0.5% | 0.16 [0.02, 1.26] | | |
| Fuentes-Orozco 2008 | 2 | 22 | 5 | 22 | 1.0% | 0.40 [0.09, 1.85] | | |
| Duska | 2 | 10 | Ŭ | 10 | 0.3% | 5.00 [0.27, 92.62] | | |
| Yang 2008 | 1 | 25 | 3 | 25 | 0.5% | 0.33 [0.04, 2.99] | | |
| Cai | 17 | 55 | 20 | 55 | 8.1% | 0.85 [0.50, 1.44] | | |
| Ozgultekin | 12 | 20 | 12 | 20 | 8.8% | 1.00 [0.60, 1.66] | | |
| Perez-Barcena 2008 | 3 | 15 | 0 | 15 | 0.3% | 7.00 [0.39, 124.83] | | |
| Eroglu | 1 | 20 | 1 | 20 | 0.3% | 1.00 [0.07, 14.90] | | |
| Perez-Barcena 2010 | 4 | 23 | 3 | 20 | 1.2% | 1.16 [0.29, 4.57] | | |
| Cekman | 3 | 15 | 6 | 15 | 1.6% | 0.50 [0.15, 1.64] | | |
| Grintescu | 4 | 48 | 4 | 49 | 1.3% | 1.02 [0.27, 3.85] | | |
| Subtotal (95% CI) | 4 | 559 | 4 | 558 | 48.0% | 0.75 [0.60, 0.93] | 2014 | • |
| Total events | 95 | | 134 | | | | | • |
| Heterogeneity: Tau² = 0. | | 13.00 4 | | - 0.743 | · IZ = 0.96 | | | |
| Test for overall effect: Z: | | | n = 10 (i | - 0.74, | ,1 - 0 /0 | | | |
| restion overall effect. 2 - | - 2.02 (1 - | . 0.003) | | | | | | |
| 1.4.2 Multi-centre studi | es | | | | | | | |
| Dechelotte | 2 | 58 | 2 | 56 | 0.6% | 0.97 [0.14, 6.62] | 2006 | |
| Vernerman | 14 | 205 | 20 | 208 | 5.2% | 0.71 [0.37, 1.37] | | |
| Andrews | 88 | 250 | 80 | 252 | 36.9% | 1.11 [0.87, 1.42] | | _ |
| Grau | 9 | 250 | 13 | 68 | 3.7% | 0.80 [0.37, 1.73] | | _ |
| Ziegler | 11 | 75 | 13 | 75 | 4.2% | 0.85 [0.41, 1.77] | | |
| Perez-Barcena 2014 | 4 | 75 | 5 | 71 | 4.2 % | 0.80 [0.22, 2.86] | | |
| Subtotal (95% CI) | 4 | 718 | 5 | 730 | 52.0% | 1.00 [0.81, 1.23] | 2014 | |
| Total events | 128 | | 133 | | | | | Ţ |
| Heterogeneity: Tau ² = 0. | | 2.41 df | | n 791 [,] 18 | = 0% | | | |
| Test for overall effect: Z : | | | | 5.1 57,1 | - 0 /0 | | | |
| i con overall ellett. Z - | - 0.00 (F - | 0.30) | | | | | | |
| | | 1277 | | 1288 | 100.0% | 0.87 [0.75, 1.01] | | • |
| Total (95% CI) | | | | | | | | • |
| Fotal (95% CI) Fotal events | 223 | | 767 | | | | | |
| Total events | 223 00: Chi ≧ = | 19.87 ल | 267 If = 24 (P | = 0.70 | 1² = 0% | | | |
| | 00; Chi²= | | | = 0.70) | ; I² = 0% | | | 0.01 0.1 1 10 10 Favours PN Glutamine Favours control |

Figure 3. Hospital Mortality (Single vs Multi Centre)

| | PN Gluta | mine | Contr | ol | | Risk Ratio | | Risk Ratio |
|---|---|--|--|---|---|---|------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year | M-H, Random, 95% Cl |
| 1.2.1 Single Centre stu | dies | | | | | | | |
| 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 | |
| Fuentes-Orozco 2004 | 2 | 17 | 3 | 16 | 2.8% | 0.63 [0.12, 3.28] | 2004 | |
| Xian-Li | 0 | 20 | 3 | 21 | 0.9% | 0.15 [0.01, 2.73] | 2004 | • • • • |
| Carroll | 0 | 7 | 0 | 7 | | Not estimable | 2004 | |
| Sahin | 2 | 20 | 6 | 20 | 3.5% | 0.33 [0.08, 1.46] | 2007 | |
| Luo | 0 | 11 | 0 | 9 | | Not estimable | 2008 | |
| Yang 2008 | 1 | 25 | 3 | 25 | 1.6% | 0.33 [0.04, 2.99] | 2008 | |
| Perez-Barcena 2008 | 3 | 15 | 0 | 15 | 0.9% | 7.00 [0.39, 124.83] | 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 | |
| Subtotal (95% CI) | | 307 | | 305 | 79.2% | 0.67 [0.49, 0.91] | | \bullet |
| Suprotal (35% Ci) | | | | | | | | |
| Total events | 46 | | 73 | | | | | |
| Total events Heterogeneity: Tau² = 0 | .00; Chi² = | | |).52); P | ²= 0% | | | |
| Total events | .00; Chi² = | | |).52); P | ²= 0% | | | |
| Total events Heterogeneity: Tau² = 0 | .00; Chi ² = = 2.56 (P = | | |).52); P | ²= 0% | | | |
| Total events Heterogeneity: Tau² = 0 Test for overall effect: Z | .00; Chi ² = = 2.56 (P = | | |).52); lª 56 | ²= 0% 2.1% | 0.97 [0.14, 6.62] | 2006 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center stud | .00; Chi ² = = 2.56 (P = ies | 0.01) | = 9 (P = 1 | | | 0.97 [0.14, 6.62] 0.85 [0.41, 1.77] | | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center stud Dechelotte | .00; Chi ² = = 2.56 (P = ies 2 | 0.01) 58 | = 9 (P = 1 | 56 | 2.1% | • • • | 2013 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center stud Dechelotte Ziegler | .00; Chi ² = = 2.56 (P = ies 2 11 | 0.01) 58 75 | = 9 (P = 1 2 13 | 56 75 | 2.1% 14.1% | 0.85 [0.41, 1.77] | 2013 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center stud i Dechelotte Ziegler Perez-Barcena 2014 | .00; Chi ² = = 2.56 (P = ies 2 11 | 0.01) 58 75 71 | = 9 (P = 1 2 13 | 56 75 71 | 2.1% 14.1% 4.7% | 0.85 [0.41, 1.77] 0.80 [0.22, 2.86] | 2013 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center studi Dechelotte Ziegler Perez-Barcena 2014 Subtotal (95% CI) | .00; Chi ² = = 2.56 (P = ies 2 11 4 17 | : 0.01) 58 75 71 204 | = 9 (P = 1 2 13 5 20 | 56 75 71 202 | 2.1% 14.1% 4.7% 20.8% | 0.85 [0.41, 1.77] 0.80 [0.22, 2.86] | 2013 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center stud Dechelotte Ziegler Perez-Barcena 2014 Subtotal (95% CI) Total events | .00; Chi ² = = 2.56 (P = ies 2 11 4 .00; Chi ² = | : 0.01) 58 75 71 204 0.03, df | = 9 (P = 1 2 13 5 20 | 56 75 71 202 | 2.1% 14.1% 4.7% 20.8% | 0.85 [0.41, 1.77] 0.80 [0.22, 2.86] | 2013 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center studi Dechelotte Ziegler Perez-Barcena 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 | .00; Chi ² = = 2.56 (P = ies 2 11 4 .00; Chi ² = | : 0.01) 58 75 71 204 0.03, df | = 9 (P = 1 2 13 5 20 | 56 75 71 202).99); P | 2.1% 14.1% 4.7% 20.8% | 0.85 [0.41, 1.77] 0.80 [0.22, 2.86] | 2013 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center studi Dechelotte Ziegler Perez-Barcena 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Total (95% CI) | .00; Chi ² = = 2.56 (P = ies 2 11 4 .00; Chi ² = = 0.54 (P = | : 0.01) 58 75 71 204 0.03, df : 0.59) | 2 (P = 1 13 5 20 = 2 (P = 1 | 56 75 71 202).99); P | 2.1% 14.1% 4.7% 20.8% ⁵ =0% | 0.85 (0.41, 1.77) 0.80 (0.22, 2.86) 0.85 (0.46, 1.55) | 2013 | • |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center studi Dechelotte Ziegler Perez-Barcena 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Total (95% CI) Total events | .00; Chi ² = = 2.56 (P = 2 11 4 .00; Chi ² = = 0.54 (P = 63 | : 0.01) 58 75 71 204 0.03, df : 0.59) 511 | = 9 (P = 1 2 13 5 20 = 2 (P = 1 93 | 56 75 71 202 0.99); I ^a 507 | 2.1% 14.1% 4.7% 20.8% ² = 0% | 0.85 (0.41, 1.77) 0.80 (0.22, 2.86) 0.85 (0.46, 1.55) | 2013 | |
| Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.2.2 Multi-center studi Dechelotte Ziegler Perez-Barcena 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Total (95% CI) | .00; Chi ² = = 2.56 (P = 2 11 4 .00; Chi ² = = 0.54 (P = 63 .00; Chi ² = | : 0.01) 58 75 71 204 0.03, df : 0.59) 511 8.60, df | = 9 (P = 1 2 13 5 20 = 2 (P = 1 93 | 56 75 71 202 0.99); I ^a 507 | 2.1% 14.1% 4.7% 20.8% ² = 0% | 0.85 (0.41, 1.77) 0.80 (0.22, 2.86) 0.85 (0.46, 1.55) | 2013 | 0.01 0.1 10 100 Favours PN Glutamine Favours control |

Figure 4. Infectious Complications

| 0 | PN Gluta | mine | Contr | ol | | Risk Ratio | | Risk Ratio |
|--|---------------------------------------|-----------|------------|-----------------------|--------------|---------------------|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | M-H, Random, 95% Cl |
| 2.1.1 Patients on PN | | | | | | | | |
| Griffiths | 28 | 42 | 26 | 42 | 11.0% | 1.08 [0.78, 1.48] | 1997 | _ |
| Wischmeyer | 7 | 12 | 9 | 14 | 4.6% | 0.91 [0.49, 1.68] | 2001 | |
| Fuentes-Orozco 2004 | 4 | 17 | 12 | 16 | 2.4% | 0.31 [0.13, 0.77] | 2004 | |
| Zhou 2004 | 3 | 15 | 4 | 15 | 1.2% | 0.75 [0.20, 2.79] | 2004 | |
| Dechelotte | 23 | 58 | 32 | 56 | 8.8% | 0.69 [0.47, 1.03] | 2006 | |
| Fuentes-Orozco 2008 | 9 | 22 | 16 | 22 | 5.3% | 0.56 [0.32, 0.99] | 2008 | |
| Perez-Barcena 2008 | 11 | 15 | 13 | 15 | 9.5% | 0.85 [0.59, 1.22] | 2008 | |
| Grau | 24 | 59 | 31 | 68 | 8.4% | 0.89 [0.60, 1.34] | 2011 | |
| Andrews | 134 | 250 | 131 | 252 | 17.8% | 1.03 [0.87, 1.22] | 2011 | + |
| Ziegler | 33 | 75 | 24 | 75 | 8.1% | 1.38 [0.91, 2.09] | 2013 | |
| Perez-Barcena 2014 | 45 | 71 636 | 44 | 71 | 13.6% | 1.02 [0.79, 1.32] | 2014 | |
| Subtotal (95% CI) | | 020 | | 646 | 90.7% | 0.91 [0.78, 1.07] | | - |
| Total events | 321 | | 342 | ~ ~ ~ | | | | |
| Heterogeneity: Tau² = 0.1 Test for overall effect: Z = | | | IT = 10 (P | = 0.07) | i; i* = 41 % |) | | |
| 2.1.2 Patients on EN | | | | | | | | |
| Palmese | 13 | 42 | 21 | 42 | 5.6% | 0.62 [0.36, 1.07] | 2006 | |
| Eroglu | 8 | 20 | 10 | 20 | 3.8% | 0.80 [0.40, 1.60] | 2009 | |
| Subtotal (95% CI) | | 62 | | 62 | 9.3% | 0.68 [0.45, 1.05] | | - |
| Total events | 21 | | 31 | | | | | |
| Heterogeneity: Tau ² = 0.1 | 00; Chi ² = 1 | 0.33, df | = 1 (P = 0 | 0.57); I [≥] | = 0% | | | |
| Test for overall effect: Z = | = 1.75 (P = | 0.08) | | | | | | |
| Total (95% CI) | | 698 | | 708 | 100.0% | 0.89 [0.77, 1.03] | | • |
| Total events | 342 | | 373 | | | | | - |
| Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Test for subgroup differe | 02; Chi ^z = = 1.55 (P = | 0.12) | lf=12 (P | | | | | 0.1 0.2 0.5 1 2 5 10 Favours PN glutamine Favours control |

Figure 5. Ventilator Associated Pneumonia

| J | PN GI | N | Contr | ol | | Risk Ratio | | Risk Ratio |
|---|------------------------|------------------|-------------|------------------|------------------------------------|---|------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | Year | M-H, Random, 95% Cl |
| 2.6.1 Patients on PN | | | | | | | | |
| Dechelotte | 10 | 58 | 19 | 56 | 15.5% | 0.51 [0.26, 1.00] | 2006 | |
| Estivariz | 13 | 30 | 16 | 29 | 25.4% | 0.79 [0.46, 1.33] | 2008 | |
| Perez-Barcena 2010 | 11 | 23 | 8 | 20 | 14.8% | 1.20 [0.60, 2.37] | 2010 | |
| Ziegler | 10 | 75 | 12 | 75 | 11.6% | 0.83 [0.38, 1.81] | 2013 | |
| Perez-Barcena 2014 Subtotal (95% CI) | 23 | 71 257 | 21 | 71 251 | 28.9% 96.1% | 1.10 [0.67, 1.79] 0.87 [0.66, 1.15] | 2014 | • |
| Total events | 67 | | 76 | | | | | |
| Heterogeneity: Tau ² = 0 |).01; Chi ^z | = 4.30 | , df = 4 (P | = 0.37 |); l ^z = 7% | | | |
| Test for overall effect: Z | = 0.99 (F | P = 0.32 | 2) | | | | | |
| 2.6.2 Patients on EN | | | | | | | | |
| Palmese | 2 | 42 | 6 | 42 | 2.9% | 0.33 [0.07, 1.56] | 2006 | · |
| Eroglu Subtotal (95% CI) | 1 | 20 62 | 1 | 20 62 | 1.0% 3.9% | 1.00 [0.07, 14.90] 0.44 [0.11, 1.67] | 2009 | ← → |
| Total events | 3 | | 7 | | 01070 | 5111[5111, 1151] | | |
| Heterogeneity: Tau ² = 0 | | = 0.48 | | = 0.49 |) [,] I ² = 0% | | | |
| Test for overall effect: Z | | | | - 0.40 | ,,, = 0,0 | | | |
| Total (95% CI) | | 319 | | 313 | 100.0% | 0.85 [0.65, 1.10] | | • |
| Total events | 70 | | 83 | | | | | |
| Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ | = 1.24 (F | P = 0.22 | 2) | | | | | 0.1 0.2 0.5 1 2 5 10 Favours PN GLN Favours control |
| reerier cabgroup amer | 0.1000.0 | = 0 | .or ar = 1 | V. – 0 | | | | |

Figure 6. ICU LOS

| | PI | N GLN | | C | ontrol | | | Mean Difference | | Mean Difference |
|---|-----------|---------|-----------------------|----------|-----------|-----------------|-----------------------|--|------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 2.4.1 Patients on PN | | | | | | | | | | |
| Fuentes-Orozco 2004 | 7.2 | 9.2 | 17 | 7.3 | 4.5 | 16 | 7.5% | -0.10 [-5.00, 4.80] | 2004 | |
| Zhang | 11.73 | 6.57 | 22 | 13.39 | 5.08 | 22 | 9.3% | -1.66 [-5.13, 1.81] | 2007 | |
| Perez-Barcena 2008 | 22.9 | 20.6 | 15 | 20.5 | 16 | 15 | 2.2% | 2.40 [-10.80, 15.60] | 2008 | · |
| Cai | 22.1 | 4.9 | 55 | 23.8 | 5.1 | 55 | 11.1% | -1.70 [-3.57, 0.17] | 2008 | |
| Fuentes-Orozco 2008 | 11 | 11.7 | 22 | 11.14 | 7.41 | 22 | 6.6% | -0.14 [-5.93, 5.65] | 2008 | |
| Estivariz | 12 | 2 | 32 | 23 | 6 | 31 | 10.7% | -11.00 [-13.22, -8.78] | 2008 | ← |
| Cekman | 19.2 | 12 | 15 | 27.4 | 12 | 15 | 4.2% | -8.20 [-16.79, 0.39] | 2011 | ← |
| Ziegler Subtotal (95% CI) | 17.5 | 14.6 | 75 253 | 13.6 | 10 | 75 251 | 8.6% 60.3% | 3.90 [-0.10, 7.90] - 2.30 [-6.50, 1.90] | 2013 | |
| Heterogeneity: Tau ² = 28 Test for overall effect: Z = 2.4.2 Patients on EN | | | | = / (P < | 0.000 | U1); | : 89% | | | |
| Palmese | 12 | 4.6 | 42 | 13 | 3.4 | 42 | 11.2% | -1.00 [-2.73, 0.73] | 2006 | _ _ |
| Luo | 7.6 | 0.7 | 11 | 6.9 | 0.9 | 9 | 11.9% | 0.70 [-0.02, 1.42] | 2008 | |
| Ozgultekin | 11.8 | 5.9 | 20 | 17.3 | 16.4 | 20 | 4.9% | -5.50 [-13.14, 2.14] | 2008 | < |
| Eroglu Subtotal (95% CI) | 14 | 2 | 20 <mark>93</mark> | 15 | 2 | 20 91 | 11.6% 39.7% | -1.00 [-2.24, 0.24] - 0.47 [-1.84, 0.90] | 2009 | |
| Heterogeneity: Tau ² = 1. ⁻ Test for overall effect: Z = | | | • | (P = 0.0 | 03); I² : | = 68% | | | | |
| Total (95% CI) | | | 346 | | | 342 | 100.0% | -1.91 [-4.10, 0.28] | | |
| Heterogeneity: Tau ² = 10 Test for overall effect: Z = Test for subgroup differe | = 1.71 (F | ° = 0.0 | 9) | | | | | | | -10 -5 0 5 10 Favours PN GLN Favours control |

Figure 7. Hospital LOS

| | PN Glutamine | | | Control | | | Mean Difference | | | Mean Difference | | |
|--|--------------------|---------|-----------|----------|---------|----------------------|-----------------|------------------------|------|---|--|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% Cl | | |
| 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: Tau ² = 5 | .92; Chi ² | = 27.15 | i, df = 1 | 0 (P = 0 |).002); | l ^z = 63' | % | | | -10 -5 0 5 10 | | |
| Test for overall effect: Z = 2.34 (P = 0.02) | | | | | | | | | | Favours PN Glutamine Favours control | | |

Figure 8. Mechanical Ventilation

| Ŭ | | PN G | lutami | ne | C | ontrol | | | Mean Difference | | Mean Difference |
|------|---------------------------|-----------|----------|-------|---------|--------|-----------|--------|------------------------|------|--------------------------------------|
| Stud | dy or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| Fue | ntes-Orozco 2004 | 4.88 | 8.2 | 17 | 4.47 | 4.4 | 16 | 7.2% | 0.41 [-4.04, 4.86] | 2004 | + |
| Palr | mese | 6 | 1.7 | 42 | 5 | 2.5 | 42 | 13.2% | 1.00 [0.09, 1.91] | 2006 | + |
| Zha | ng | 5.27 | 1.78 | 22 | 7.18 | 2.76 | 22 | 12.6% | -1.91 [-3.28, -0.54] | 2007 | - |
| Pere | ez-Barcena 2008 | 14 | 10 | 15 | 14 | 10 | 15 | 4.1% | 0.00 [-7.16, 7.16] | 2008 | |
| Ozg | ultekin | 10.1 | 4.4 | 20 | 14.4 | 14 | 20 | 4.7% | -4.30 [-10.73, 2.13] | 2008 | + |
| Esti | variz | 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 | • |
| Erog | glu | 8 | 3 | 20 | 9 | 3 | 20 | 11.9% | -1.00 [-2.86, 0.86] | 2009 | 4 |
| Pere | ez-Barcena 2010 | 15.2 | 8.2 | 23 | 18.9 | 11.1 | 20 | 5.3% | -3.70 [-9.61, 2.21] | 2010 | |
| Kok | sal | 13 | 12.2 | 30 | 14.3 | 5.4 | 30 | 6.7% | -1.30 [-6.07, 3.47] | 2014 | |
| Tota | al (95% CI) | | | 273 | | | 261 | 100.0% | -2.16 [-3.89, -0.43] | | * |
| | erogeneity: Tau² = 5. | | | | 10 (P < | 0.000 | 01); I² = | 86% | | | -100 -50 0 50 100 |
| (es) | t for overall effect: Z = | = 2.45 (H | ' = 0.0' | 1) | | | | | | | Favours PN glutamine Favours control |

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9.4a Composition of Parenteral Nutrition: Glutamine Supplementation

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

| Isonitrogenous | Ν | Nonisonitrogenous | Ν |
|-----------------------|------|--------------------|------|
| 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 | Ν | Glutamine Dipeptide | Ν |
|-----------------------|-----|---|-------------------|
| 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 2007 α | 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 |
| | | Cekman 2011 Grau 2011 | 30 127 |
| | | | |
| | | Grau 2011 | 127 |
| | | Grau 2011 Wernerman 2011 | 127 413 |
| | | Grau 2011 Wernerman 2011 Ziegler 2012 | 127 413 150 |

Unknown: Zhang 2007