4.1c Composition of EN: Glutamine

Question:

Compared to standard care, does glutamine-supplemented enteral nutrition result in improved clinical outcomes in critically ill patients?

Summary of Evidence: There were 9 level 2 studies and 3 level 1 studies, 5 of which were in burn patients (Garrel 2003, Zhou 2003, Peng 2004, Pattanshetti 2009, Iamsirisaengthong 2017), 3 in trauma patients (Houdijk 1998, Brantley 2000 and McQuiggan 2008) and the remaining 4 were in mixed ICU patients.

Mortality: When the data from all the 10 trials that reported on mortality were aggregated, there was no statistically significant difference in mortality between the groups receiving glutamine supplemented EN or not (RR = RR 0.97, 95% CI 0.70, 1.34, p =0.84, test for heterogeneity I^2 = 10%) (figure 1). Subgroup analyses of the 5 studies of trauma patients showed that glutamine supplemented EN had no significant effect on hospital mortality (RR 1.03, 95% CI 0.54, 1.97, p = 0.92, test for heterogeneity I^2 = 0%) (figure 2). In the 5 studies of burn patients, patient deaths in hospital occurred in 4 studies (Garrel 2003, Zhou 2003, Pattanshetti 2009, Iamsirisaungthong 2017) and a significant reduction in hospital mortality was associated with the use of enteral glutamine (RR 0.26, 95% CI 0.08, 0.80, p =0.02, test for heterogeneity I^2 = 0%) (figure 3).

Infections: Of the 3 level 2 studies and 1 level 1 study that reported on the total number of patients with infectious complications, there was no statistically significant difference in infectious complications with glutamine supplemented EN (RR 0.93, 95% CI 0.79, 1.10, p = 0.39, test for heterogeneity I^2 = 0%) (figure 4). In the one study in burn patients that reported on patients with infections (Zhou 2003), glutamine supplemented EN was associated with a significant reduction in infectious complications while in one burn study (Garrel 2003) a significant reduction was seen in the number of positive blood cultures. In the subgroup of trauma patients, there was a trend towards a reduction in infections in the groups that received enteral glutamine (RR 0.85, 95% CI 0.68, 1.06, p =0.15, test for heterogeneity I^2 = 0%) (figure 5).

Length of Stay: There were 7 level 2 studies and 1 level 1 study that demonstrated a significant reduction in length of hospital stay (WMD (weighted mean difference) -4.69, 95% CI -8.19, -1.18, p = 0.009, test for heterogeneity I^2 = 44%) (figure 6). A stronger effect was seen in the subgroup of burn patients (WMD -8.18, 95% CI -12.69, -3.67, p = 0.0004, test for heterogeneity I^2= 30%) (figure 8) but not seen in the subgroup of trauma patients (WMD -0.54 95% CI -4.40, 3.31, p = 0.78, test for heterogeneity I^2= 0%) (figure 7). Enteral glutamine has no effect on ICU LOS (WMD -1.36, 95% CI -5.51, 2.78, p =0.52, test for heterogeneity I^2= 70%) (figure 9) when all studies were aggregated but was associated with a trend towards a reduction in the subgroup of trauma patients (WMD -4.66, 95% CI -9.68, 0.36, p = 0.07, test for heterogeneity I^2= 0%) (figure 10).

Mechanical ventilation: Only 2 studies reported on mechanical ventilation as means and standard deviation and when the data were aggregated, enteral glutamine had no effect on duration of mechanical ventilation (WMD -0.10, 95% CI -0.93, 0.73, p =0.82).

Conclusions:

1) Glutamine supplemented enteral nutrition is associated with a reduction in mortality in burn patients, but inconclusive in other critically ill patients.
2) Glutamine supplemented enteral nutrition may be associated with a reduction in infectious complications in burn and trauma patients.
3) Glutamine supplemented enteral nutrition is associated with a reduction in hospital length of stay in burn and other critically ill patients but not in trauma patients and may be associated with a reduction in ICU LOS in trauma patients.

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 (EN) in critically ill patients

Study	Population	Methods (score)	Intervention -Dose (gm/kg/day) -Type of feeding	Mortality # (%)† Experimental	Mortality # (%)† Control	Infections # (%)‡ Experimental	Infections # (%)‡ Control	Hospital stay (days) Experimental	Hospital stay (days) Control	ICU LOS (days) Exp	ICU LOS (days) control
1) Houdijk 1998	Critically ill trauma (100%) N = 80	C.Random: Yes ITT: No Blinding: Yes (10)	> 0.25 Altira Q (glutamine enriched formula) vs. isonitrogenous control (added amino acids) Same volume of feeding received in both groups	4/41 (9.8)	3/39 (7.7)	20/35 (57.1)	26/37 (70.2)	32.7±17.1 (35)	33.0±23.8 (37)	NA	NA
2) Jones 1999	Mixed ICU Population (6 burns, 6 trauma, no subgroup analysis) N = 78	C.Random: Yes ITT: No Blinding: Yes (8)	0.16 Protina MP + Glutamine (10-15 gm Nitrogen/day) vs. Isonitrogenous Control (11-14 gm Nitrogen/day)	Hospital 10/26 (38.5) ICU 9/26 (35) 6 month 12/26 (46)	Hospital 9/24 (37.5) ICU 9/24 (38) 6 month 10/24 (42)	NA	NA	NA	NA	11 (4–54)	16.5(5–66)
3) Brantley 2000	Critically ill trauma (100%) N = 72	C.Random: Not sure ITT: No Blinding: No (4)	0.50 Glutamine supplemented Enteral formula vs. standard formula (Isonitrogenous) Protein given 1.5gm/kg/d	0/31 (0.0)	0/41 (0.0)	NA	NA	19.5+/-8.8 (31)	20.8±11.5 (41)	11.4	11.1
4) Hall 2003	Mixed ICU Population (mostly trauma, 7 burns) N = 363	C.Random: yes ITT: Yes Blinding: Yes (13)	0.27 Isocal + glutamine (66 gms protein/day) vs. isonitrogenous formula, Isocal + glycine (64 gms protein/day)	6 months 27/179 (15) 30 days 26/179 (15) ICU 16/179 (9) Hospital 24/179 (13)	6 months 30/184 (16) 30 days 25/184 (14) ICU 14/184 (8) Hospital 23/184 (13)	38/179 (21)	43/184 (23)	25 (16-42)*	30 (19-45)*	11(7-19) (excluding deaths)	13 (8-19) (excluding deaths)
	Trauma subgroup			7/76 (9)	6/78 (8)	Sepsis 7/76 (9)	Sepsis 11/78 (14)	NA	NA	NA	NA
5) Garrel 2003	Burns N = 45	C.Random: yes ITT: yes Blinding: yes (11)	0.28 Sandosource + glutamine (2.15 gm/kg/d protein) vs. Sandosource + amino acids (isonitrogenous), 1.97 gm/kg/day protein	2/21 (10)	12/24 (50)	Positive blood cultures 7/19 (37)	Positive blood cultures 10/22 (45)	33 ± 17 (16) **	29 ± 17 (19) **	NA	NA
6) Zhou 2003	Severe Burns TSBA 50-80 % N = 41	C.Random: yes ITT: no Blinding: double (8)	0.35 Ensure + glutamine vs. Ensure + amino acids (isonitrogenous)	0/20	0/20	2/20 (10)	6/20 (30)	67 ± 4 (20) *Mean and SD*	73 ± 6 (20) *Mean and SD*	NA	NA

7) Peng 2004	Severe Burns TBSA > 30 % N = 48	C.Random: Not sure ITT: yes Blinding: no (7)	0.5 oral glutamine granules vs. placebo (isocaoric, isonitrogenous) 2.0 gm/kg/d protein	NA	NA	NA	NA	46.59 ± 12.98 (25)	55.68 ± 17.36 (23)	NA	NA
8) Luo 2007***	Medical Surgical N=44	C.Random: not sure ITT: no Blinding: double (9)	0.32 glutamine + IV saline + vs. Nutren + 15% Clinisol (placebo) (isocaoric, isonitrogenous) 1.7 gm/kg/d protein	28 day 1/12 ICU 1/12	28 day 0 /9 ICU 0 /9	NA	NA	NA	NA	8.1 ± 0.4 (12)	6.9 ±0.9 (9)
9) McQuiggan 2008	Shock trauma patients N = 20	C.Random: Not sure ITT: yes Blinding: no (10)	0.5 (actual 0.4) Impact + glutasolve via NJ tube (1.3 gm/kg/day protein), bolus with H20 vs. Impact + protein supplements {isonitrogenous,isocaloric, 0.85 gm/kg/day protein}	0/10	2/10 (20)	NA	NA	32 ± 13.6 (10) *Mean and SD*	39.3 ± 33.6 (10) *Mean and SD*	4.8 ± 6.7 (10) *Mean and SD*	10.4 ± 6.2 (10) *Mean and SD*
10) Pattanshetti 2009	Burn ICU patients N=30	C.Random: Not sure ITT: yes Blinding: single (outcomes) (8)	Enteral isonitrogenous mixture + 0.5 g/kg/d EN glutamine supplement + 'regular' nutrition vs Enteral isonitrogenous mixture + 'regular' nutrition	0/15	2/15	NA	NA	22.73 ± 9.13	39.73 ± 18.27	NA	NA
11) van Zanten 2014	Mixed, N= 301	C Random: Yes ITT: Yes Blinding: double (12)	Glutamine,omega-3, aox enriched EN (experimental product, Nutriciar) vs high-protein EN (Nutrison Advanced Protison-Nutricia)	Hospital 38/152 (25) ICU 30/152 (20) 28 day 31/152 (20) 6 month 53/152 (35)	Hospital 33/149 (22) ICU 29/149 (20) 28 day 25/149 (17) 6 month 42/149 (29)	80/152 (53)	78/149 (52)	38.2 ± 28.9	37.7 ± 27.5	23.7 ± 22.4 (152)	25.6 ± 24.0 (149)
	Trauma subgroup			Hospital 6/55 (11) ICU 5/55 (9) 28 day 4/55 (7) 6 month 8/55 (15)	Hospital 6/54 (11) ICU 6/54 (11) 28 day 2/54 (4) 6 month 59/54 (17)	32/55 (58)	36/54 (67)	44.4 ± 31.2	39.8 ± 25.3	31.3 ± 30.3	32.5 ± 27.5
12) Koksal 2014****	Septic, malnourished ICU patients	C.Random: yes ITT: other Blinding: single	30 g/day EN glutamine (Glutamine resource, Nestle) + EN vs EN, no	NA	NA	NA	NA	NA	NA	NA	NA

	N=120	(outcomes) (9)	placebo, no supplemental glutamine								
13) Iamsirisaengthong 2017	Major burn patients (≥20% TBSA) N=20	C.Random: no ITT: no Blinding: no (3)	Neomune (25% protein, gln and arg containing) vs blenderized diet (17% protein). Isocaloric, non-isonitrogenous.	Hospital 1/10 (10%)	Hospital 1/10 (10%)	Septic complications 4/10 (40%) Wound Healing (days) 32.3 ± 14.3	Septic complications 7/10 (70%) Wound Healing (days) 38.3 ± 14.9	35.4 ± 15.2	40.4 ± 15.2	NA	NA

C.Random: concealed randomization median (range) EN: enteral nutrition NA: not available
ITT: intent to treat TPN: Total parenteral nutrition
± ( ) : mean ± Standard deviation (number) † hospital mortality unless otherwise stated
* median and range hence not included in meta analysis (Hall 2003 p = NS)
** data from a subgroup, hence not included in meta-analysis
*** data from PN glutamine group not shown here, appears in PN glutamine section
****Reports on mechanical ventilation

Figure 1. Overall Mortality

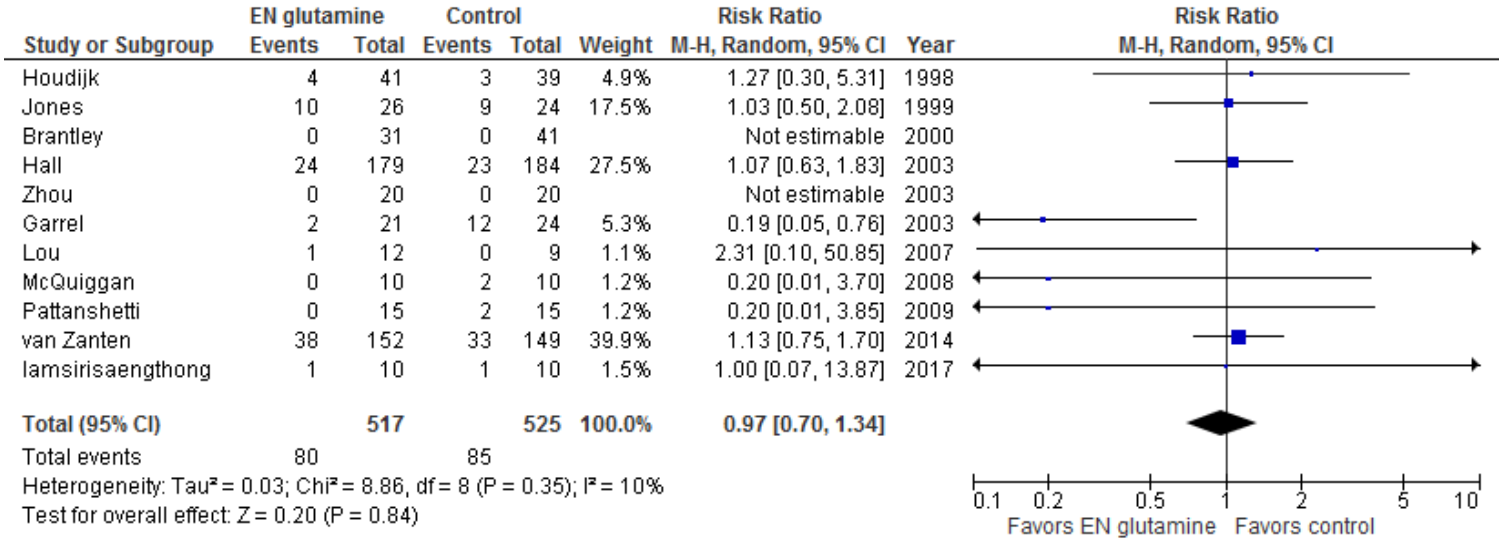

Figure 2. Hospital Mortality, trauma subgroup analysis

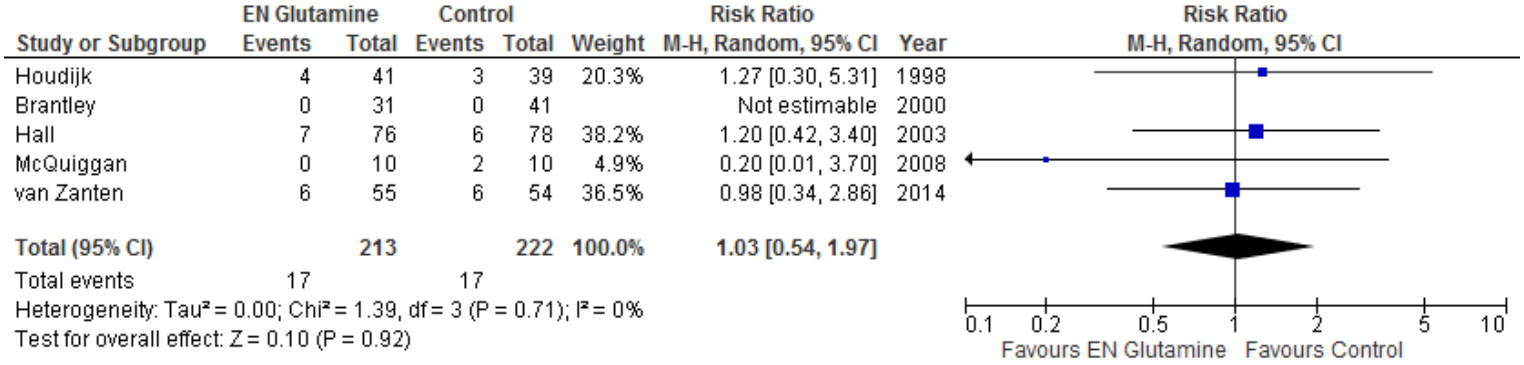

Figure 3. Hospital Mortality, burns subgroup

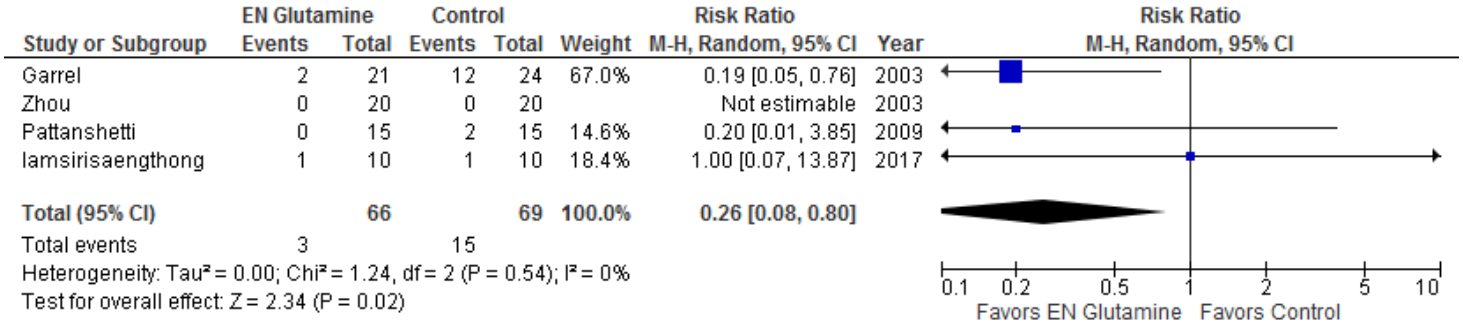

Figure 4. Infectious Complications

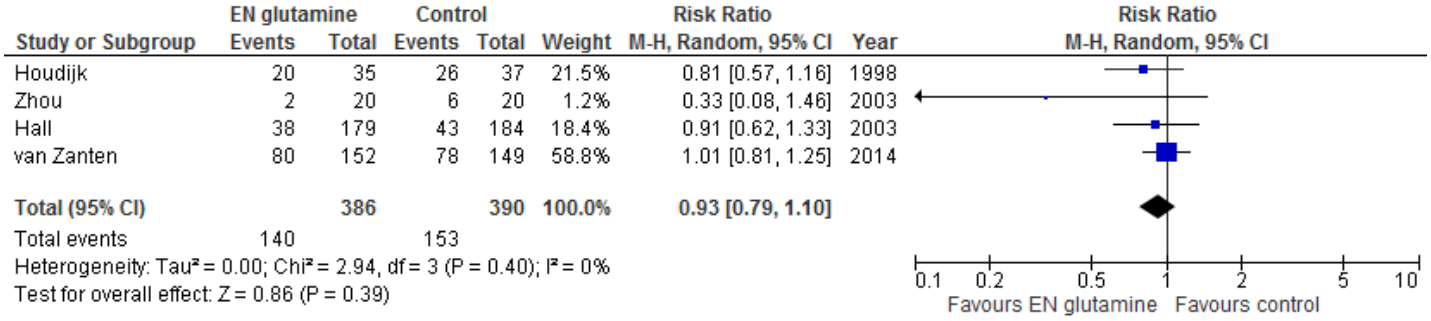

Figure 5. Infectious Complications: trauma

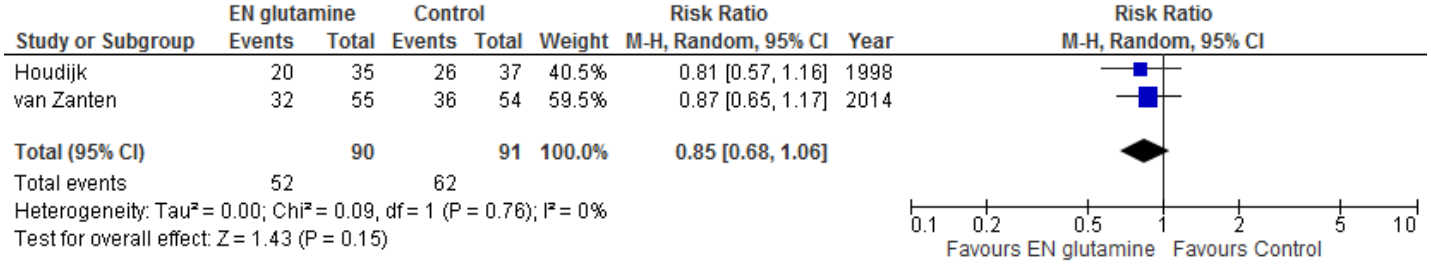

Figure 6: Hospital LOS

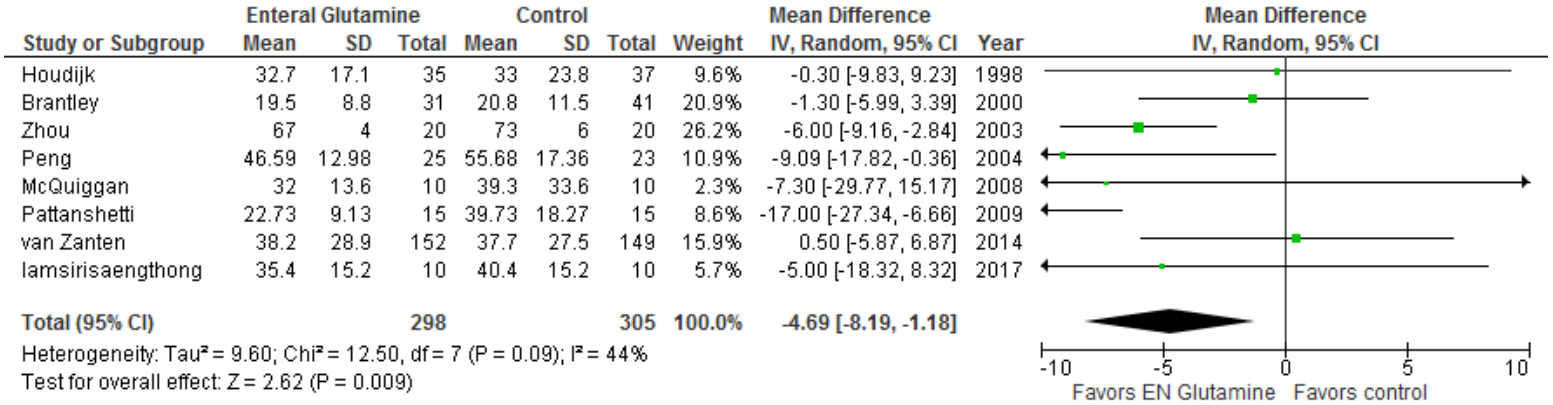

Figure 7. Hospital LOS, trauma subgroup analysis

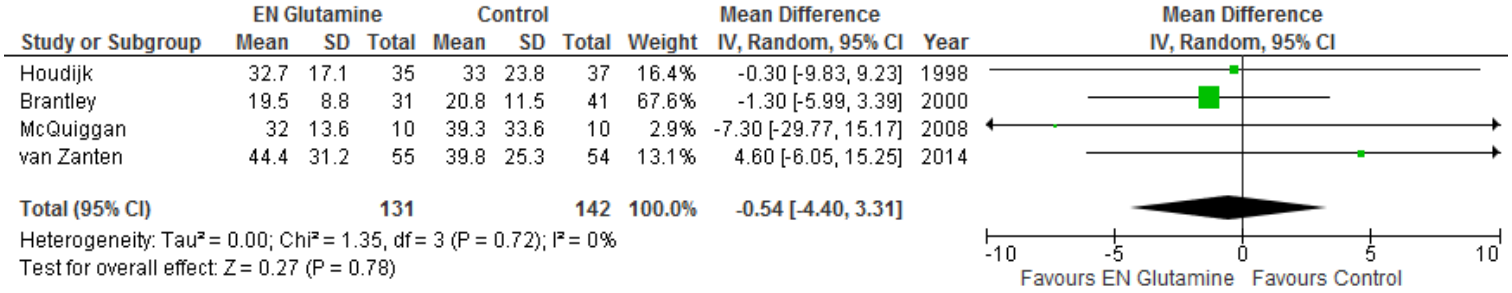

Figure 8. Hospital LOS, burns subgroup analysis

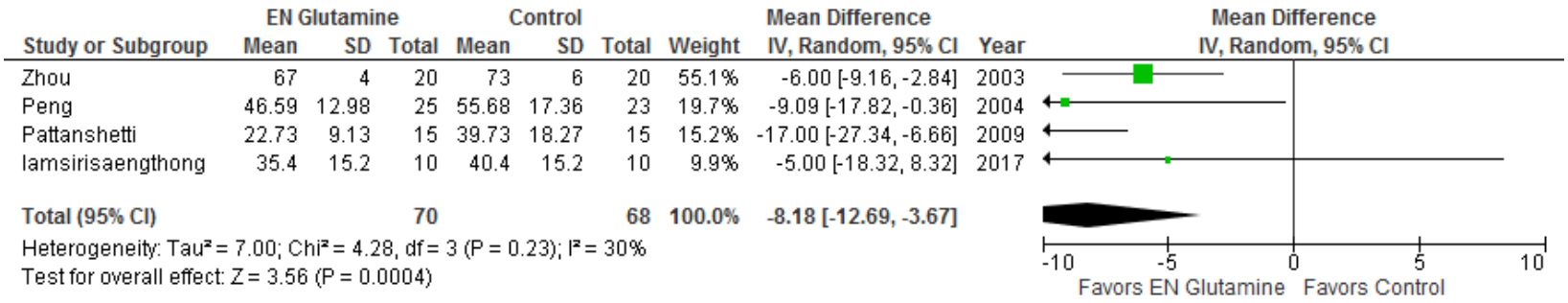

Figure 9. ICU LOS, all studies

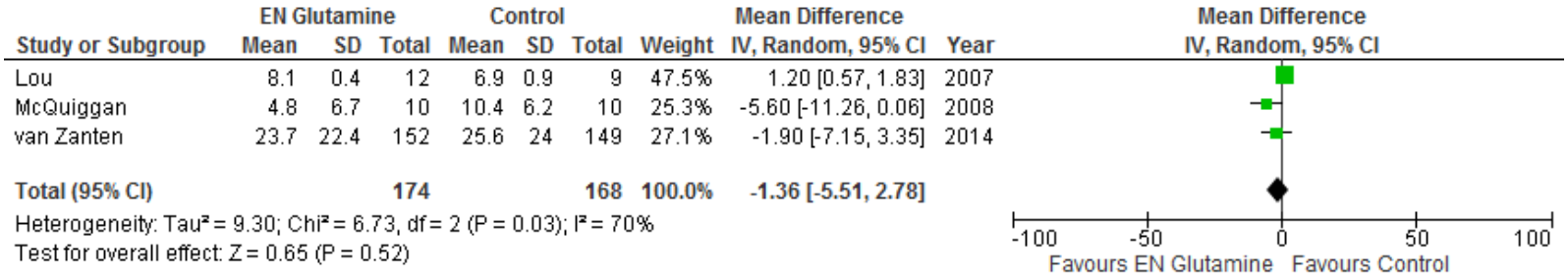

Figure 10. ICU LOS, trauma subgroup analysis

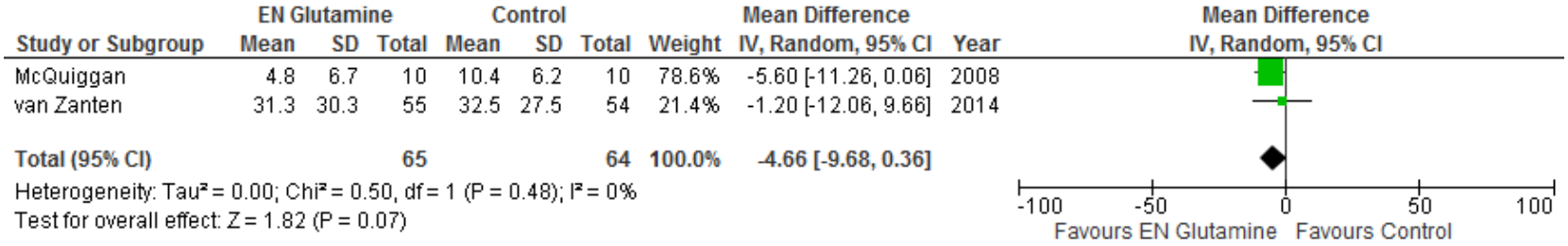

Table 2. Excluded Articles

#	Reason excluded	Citation
1	Transplant/elective surgery pts	Jebb SA, Marcus R, Elia M. A pilot study of oral glutamine supplementation in patients receiving bone marrow transplants. Clin Nutr. 1995 Jun;14(3):162-5.
2	No clinical outcomes	Long CL, Nelson KM, DiRienzo DB, Weis JK, Stahl RD, Broussard TD, Theus WL,Clark JA, Pinson TW, Geiger JW, et al. Glutamine supplementation of enteral nutrition: impact on whole body protein kinetics and glucose metabolism in critically ill patients.J Parenter Enteral Nutr. 1995 Nov-Dec;19(6):470-6.
3	No clinical outcomes	Jensen GL, Miller RH, Talabiska DG, Fish J, Gianferante L. A double-blind, prospective, randomized study of glutamine-enriched compared with standard peptide-based feeding in critically ill patients. Am J Clin Nutr 1996;64(4):615-21.
4	Cancer pts	Fish J, Sporay G, Beyer K, Jones J, Kihara T, Kennedy A, Apovian C, Jensen GL. A prospective randomized study of glutamine-enriched parenteral compared with enteral feeding in postoperative patients. Am J Clin Nutr. 1997 Apr;65(4):977-83.
5	Crossover design	Scolapio JS, Camilleri M, Fleming CR, Oenning LV, Burton DD, Sebo TJ, Batts KP, Kelly DG. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: a randomized, controlled study. Gastroenterology. 1997 Oct;113(4):1074-81. Comment in: Gastroenterology. 1997 Oct;113(4):1402-5.
6	Surgical pts	Anderson PM, Ramsay NK, Shu XO, Rydholm N, Rogosheske J, Nicklow R, Weisdorf DJ, Skubitz KM. Effect of low-dose oral glutamine on painful stomatitis during bone marrow transplantation. Bone Marrow Transplant. 1998 Aug;22(4):339-44.
7	Pediatric cancer pts	Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer. 1998 Oct 1;83(7):1433-9.
8	Not ICU pts	Den Hond E, Hiele M, Peeters M, Ghoos Y, Rutgeerts P. Effect of long-term oral glutamine supplements on small intestinal permeability in patients with Crohn's disease JPEN J Parenter Enteral Nutr. 1999 Jan-Feb;23(1):7-11.
9	Cancer/surgery pts	Schloerb PR, Skikne BS. Oral and parenteral glutamine in bone marrow transplantation: a randomized, double-blind study. JPEN J Parenter Enteral Nutr. 1999 May-Jun;23(3):117-22.
10	Crossover design	Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. JPEN J Parenter Enteral Nutr. 1999 Nov-Dec;23(6):309-12; discussion 312-3.
11	Earlier study of 2003 RCT already included	Zhou Y, Jiang Z, Sun Y. Gu an zuo an shuang zuo gai shan zhong du shao shang huan zhe chang zhan mo tong tou xing de yan jiu. National Medical Journal of China. 1999;79(11):825.
12	Surgery patients, No clinical outcomes	Jackson NC, Carroll PV, Russell-Jones DL, Sönksen PH, Treacher DF, Umpleby AM. Effects of glutamine supplementation, GH, and IGF-I on glutamine metabolism in critically ill patients. Am J Physiol Endocrinol Metab. 2000 Feb;278(2):E226-33.
13	Crossover design	Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. Gut. 2000 Aug;47(2):199-205.
14	No clinical outcomes	Chen G, Xie W, Jiang H. [Clinical observation of the protective effect of oral feeding of glutamine granules on intestinal mucous membrane]. Zhonghua Shao Shang Za Zhi. 2001 Aug;17(4):210-1. Chinese.
15	Crossover design	Scolapio JS, McGreevy K, Tennyson GS, Burnett OL. Effect of glutamine in short-bowel syndrome. Clin Nutr. 2001 Aug;20(4):319-23.

16	No clinical outcomes, Duplicate of Houdjik	Velasco N, Hernandez G, Wainstein C et al. Influence of polymeric enteral nutrition supplemented with different doses of glutamine on gut permeability in critically ill patients. Nutrition 2001;17:907-11.
17	No clinical outcomes	Boelens PG, Houdijk AP, Fonk JC et al. Glutamine-Enriched Enteral Nutrition Increases HLA-DR Expression on Monocytes of Trauma Patients. J Nutr 2002:2580-6.
18	Systematic Review	Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the Evidence. Crit Care Med. 2002 Sep;30(9):2022-9. Review.
19	Elective surgery pts	Fläring UB, Rooyackers OE, Wernerman J, Hammarqvist F. Glutamine attenuates post-traumatic glutathione depletion in human muscle. Clin Sci (Lond). 2003 Mar;104(3):275-82
20	Systematic review, Individuals studies looked at	García-de-Lorenzo A, Zarazaga A, García-Luna PP, Gonzalez-Huix F, López-Martínez J, Miján A, Quecedo L, Casimiro C, Usán L, del Llano J. Clinical evidence for enteral nutritional support with glutamine: a systematic review.Nutrition. 2003 Sep;19(9):805-11.
21	Duplicate of Houdijk study	Boelens PG, Houdijk AP, Fonk JC, Puyana JC, Haarman HJ, von Blomberg-van der Flier ME, van Leeuwen PA. Glutamine-enriched enteral nutrition increases in vitro interferon-gamma production but does not influence the in vivo specific antibody response to KLH after severe trauma. A prospective, double blind, randomized clinical study. Clin Nutr. 2004 Jun;23(3):391-400.
22	Includes probiotics	Falcao de Arruda IS, de Aguilar-Nascimento JE. Benefits of early enteral nutrition with glutamine and probiotics in brain injury patients. Clin Sci (Lond) 2004;106(3):287-92.
23	Duplicate study of earlier publication already included	Peng X, Yan H, You Z, Wang P, Wang S. Clinical and protein metabolic efficacy of glutamine granules-supplemented enteral nutrition in severely burned patients. Burns 2005;31(3):342-6.
24	Duplicate of previous 2004 study	Peng X, Yan H, You Z, Wang P, Wang S. Glutamine granule-supplemented enteral nutrition maintains immunological function in severely burned patients. Burns. 2006 Aug;32(5):589-93. Epub 2006 May 24.
25	No clinical outcomes	Guo GH, Deng ZY, Wang YX, Xing JJ, Peng Y, Li GH. [Effects of glutamine enriched enteral feeding on immunoregulation in burn patients]. Zhonghua Shao Shang Za Zhi. 2007 Dec;23(6):406-8. Chinese.
26	Too many interventions	Kuhls DA, Rathmacher JA, Musngi MD, Frisch DA, Nielson J, Barber A, MacIntyre AD, Coates JE, Fildes JJ. Beta-hydroxy-beta-methylbutyrate supplementation in critically ill trauma patients. J Trauma. 2007 Jan;62(1):125-31; discussion 131-2.
27	Too many interventions	Spindler-Vesel A, Bengmark S, Vovk I, Cerovic O, Kompan L. Synbiotics, prebiotics, glutamine, or peptide in early enteral nutrition: a randomized study in trauma patients. JPEN J Parenter Enteral Nutr. 2007 Mar-Apr;31(2):119-26.
28	Too many interventions	Beale RJ, Sherry T, Lei K, Campbell-Stephen L, McCook J, Smith J, Venetz W, Alteheld B, Stehle P, Schneider H. Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. Crit Care Med 2008;36(1):131-44.
29	Systematic review	Jiang H, Chen W, Hu W, Cai B, Liao RJ. [The impact of glutamine-enhanced enteral nutrition on clinical outcome of patients with critical illness: a systematic review of randomized controlled trials]. Zhonghua Shao Shang Za Zhi. 2009 Oct;25(5):325-30. Review. Chinese.
30	Elective surgery pts	Han YY, Lai SL, Ko WJ, Chou CH, Lai HS. Effects of fish oil on inflammatory modulation in surgical intensive care unit patients. Nutr Clin Pract. 2012 Feb;27(1):91-8. Epub 2012 Jan 6.

31	No clinical outcomes, crossover design	Cavalcante AA, Campelo MW, de Vasconcelos MP, Ferreira CM, Guimarães SB,Garcia JH, de Vasconcelos PR. Enteral nutrition supplemented with l-glutamine in patients with systemic inflammatory response syndrome due to pulmonary infection. Nutrition. 2012 Apr;28(4):397-402. Epub 2011 Nov 4.
32	Meta-analyses, individual RCTs were reviewed	Wang X, Dong Y, Han X, Qi X-Q, Huang C-G, Hou L. (2013) Nutritional Support for Patients Sustaining Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prospective Studies. PLoS ONE. 8(3): e58838.
33	No clinical outcomes	Han W. Sun J. Han R. Wang Y. Yi Q. Hua L. Tian F. Application of enteral nutrition support with different doses of glutamine in elderly critically ill patients. Chin J Clin Nutr 2014;22(3):149-153.
34	Posthoc analysis, no new relevant outcomes	Hofman Z, Swinkels S, van Zanten ARH. Glutamine, fish oil and antioxidants in critical illness: MetaPlus trial post hoc safety analysis. Ann Int Care. 2016:6;119.
35	Not critically ill; surgery patients	Vijey Aanandhi M.; John M.R. Enteral/oral glutamine supplementation in patients following surgery and accidental injury. Asian J Pharm and Clin Res. 2017 March;10(3):477-479
36	Not critically ill	Azman M, Mohd Yunus MR, Sulaiman S, Syed Omar SN. Enteral glutamine supplementation in surgical patients with head and neck malignancy: A randomized controlled trial. Head Neck. 2015 Dec;37(12):1799-807.
37	No clinically important outcomes	Kibor DK, Nyaim OE, Wanjeri K. Effects of enteral glutamine supplementation on reduction of infection in adult patients with severe burns. East Afr Med J. 2014 Jan;91(1):33-6.
38	No clinically important outcomes	Han W., Sun J., Han R., Wang Y., Yi Q., Hua L., Tian F. Application of enteral nutrition support with different doses of glutamine in elderly critically ill patients. Chinese Journal of Clinical Nutrition. 2014 Jun;22(3):149-153, 2014.