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 13 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), 1 in elective cardiac surgery patients (Efremov 2017) and the remaining 7 were in mixed ICU patients. One study of mixed ICU patients also reported on the subgroup of trauma patients (van Zanten 2014).

Mortality: When the data from all the 11 trials that reported on 28 day or hospital mortality were aggregated, there was no statistically significant difference in overall hospital mortality between the groups receiving glutamine supplemented EN or not (RR 1.00. 95% CI 0.77, 1.30, p=1.00, test for heterogeneity I^2 = 0%) (figure 1). Subgroup analyses of the 4 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 4 studies of burn patients, patient deaths in hospital were reported in 3 studies (Garrel 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 2 level 2 studies and 2 level 1 studies 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, based on two studies, 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). In one study in mixed ICU patients, there were no statistically significant differences in the incidence of new severe sepsis between the EN glutamine supplemented group (5.6%, 95% CI; 0–13.9%) and the control group (11.8%, 95%CI, 2.8–23.5%; p = 0.309, Shariatpanahi 2019).

Length of Stay: There were 8 level 2 studies and 1 level 1 study that demonstrated a significant reduction in hospital length of stay (LOS) [WMD (weighted mean difference) -4.13, 95% CI -6.95, -1.30, p = 0.004, test for heterogeneity I^2 = 41%] (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 7) 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 8). Enteral glutamine has no effect on ICU LOS (WMD -0.33, 95% CI -2.26, 1.60, p =0.74, test for heterogeneity I^2= 69%) (figure 9) when

all studies were aggregated but was associated with a trend towards a reduction in the subgroup of trauma patients from two studies (WMD -4.66, 95% CI -9.68, 0.36, p = 0.07, test for heterogeneity I^2= 0%) (figure 10).

Mechanical ventilation: Only 4 studies, including one in burn patients (Garrel 2003) 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 -0.19, 95% CI -0.89, 0.51, p =0.60, test for heterogeneity I^2 =0% (figure 11).

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.
4) Glutamine supplemented enteral nutrition has no effect on duration of mechanical ventilation in critically ill 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) or gm/day -Type of feeding	Mortality # (%)†		Infections # (%)‡		Hospital stay (days)		ICU LOS (days)	
				Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control
1) Houdijk 1998	Critically ill trauma (100%) N = 80	C.Random: Yes ITT: No Blinding: Yes (10) Level: 2	> 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) Level: 2	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) Level: 2	0.50 Glutamine supplemented Enteral formula vs. standard formula (Isonitrogenous) Protein given 1.5gm/kg/d	NA	NA	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: double (13) Level: 1	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)*; p=NS	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: double (11) Level: 1	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) Level: 2	0.35 Ensure + glutamine vs. Ensure + amino acids (isonitrogenous)	NA	NA	2/20 (10)	6/20 (30)	67 ± 4 (20)	73 ± 6 (20)	NA	NA

7) Peng 2004	Severe Burns TBSA > 30 % N = 48	C.Random: Not sure ITT: yes Blinding: no (7) Level: 2	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 2008* **	Medical Surgical N=44	C.Random: not sure ITT: no Blinding: double (9) Level: 2	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) Level: 2	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)	39.3 ±33.6 (10)	4.8 ±- 6.7 (10)	10.4 ±6.2 (10)
10) Pattanshetti 2009	Burn ICU patients N=30	C.Random: Not sure ITT: yes Blinding: single (outcomes) (8) Level: 2	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) Level: 1	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 N=120	C.Random: yes ITT: other Blinding: single (outcomes) (9) Level: 2	30 g/day EN glutamine (Glutamine resource, Nestle) + EN vs EN, no placebo, no supplemental glutamine	NA	NA	NA	NA	NA	NA	NA	NA
13) Iamsirisaengthong 2017	Major burn patients (>20% TBSA) N=20	C.Random: no ITT: no Blinding: no (3) Level: 2	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
14) Efremov 2017	Mechanically ventilated, critically ill patients undergoing elective cardiac surgery N=40	C.Random: yes ITT: yes Blinding: no (10) Level: 2	25 gm/day glutamine (Nutricomp immune-high calorie 1.33 Kcal/mL,6.7 gm/L protein, 0.2 gm/100 mL omega 3) vs.standard EN (Nutricomp standard-1 Kcal/mL, 3.8 gm/lL protein, 0.26 gm/100 mL omega 3). PN used to supplement. Non-isocaloric, non-isonitrogenous	**Hospital** 6/20 (30%)	**Hospital** 4/20 (20%)	**NA**	**NA**	**Hospital** 30 (25-33)*	**Hospital** 26 (19-21)*	**ICU** 11 (7-23)*	**ICU** 9 (7-11)*
15) Shariatpanahi 2019	Mix ICU adult patients Medical (32) Surgical (24) Trauma (14)	C.Random: no ITT: no Blinding: no (6) Level: 2	Glutamine (0.3 grams/kg/d) + EN vs. placebo (maltodextrin) + EN; both 3 times per day	**ICU** 7/36 19% (95% CI:8-33%)	**ICU** 4/34 12% (95% CI:3-24%)	**New sepsis** 5.6% (95% CI; 0–13.9%)	**New sepsis** 11.8% (95% CI, 2.8–23.5%	NA	NA	10 (8-20)*	13 (7-29)*
16) Nakamura 2020	Mix ICU population Sepsis (42); Cardiac (20); Stroke (23); Cardiopulmonary arrest (6); Post surgery (13); Respiratory failure (23); trauma (2)	C.Random: Yes ITT: Yes Blinding: single (12) Level: 2	Daily 3grams HMB+14 grams arginine+14 grams of glutamine vs. standard EN	**28 days** 8.7% (4/45)	**28 days** 13.6% (6/43)	NA	NA	21.9 ±8.8	24.3 ±7.8	5.4 ±3.5	5.8 ±3.8
	Final Femoral Muscle subgroup analysis SOC (24) vs. Intervention (26)			**30-day** mortality rate 16.8%	**30-day** mortality rate 19.3%	NA	NA	20.4 ±10.7	19.8 ±12.5	9.1 ±4.4	8.6 ±5.2
	Femoral Muscle Volume by SOFA subgroup SOFA <10 (31) vs. SOFA >10 (19)			SOFA<10: 0% SOFA>10: 26.5%	SOFA <10: 0% SOFA>10: 25.8%	NA	NA	**SOFA<10** 22.7 ±13.1 **SOFA>10** 17.3 ±7.1	**SOFA<10** 19.6 ±9.9 **SOFA>10** 20.1 ±13.4	**SOFA<10** 10.0 ±4.4 **SOFA>10** 7.9 ±4.4	**SOFA<10** 7.3 ±3.7 **SOFA>10** 11.3 ±6.9

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-analyses
** data from a subgroup, hence not included in meta-analyses
*** data from PN glutamine group not shown here, appears in PN glutamine section
****Reports on mechanical ventilation
28 or 30 day hospital mortality were aggregated as Overall Mortality
NA: Not available or not reported

Figure 1. Overall Hospital Mortality

Study or Subgroup	EN glutamine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Houdijk	4	41	3	39	3.4%	1.27 [0.30, 5.31]	1998
Jones	10	26	9	24	13.7%	1.03 [0.50, 2.08]	1999
Garrel	2	21	12	24	3.6%	0.19 [0.05, 0.76]	2003
Hall	24	179	23	184	24.2%	1.07 [0.63, 1.83]	2003
Lou	1	12	0	9	0.7%	2.31 [0.10, 50.85]	2007
McQuiggan	0	10	2	10	0.8%	0.20 [0.01, 3.70]	2008
Pattanshetti	0	15	2	15	0.8%	0.20 [0.01, 3.85]	2009
van Zanten	38	152	33	149	41.4%	1.13 [0.75, 1.70]	2014
Efremov	6	20	4	20	5.7%	1.50 [0.50, 4.52]	2017
Iamsirisaengthong	1	10	1	10	1.0%	1.00 [0.07, 13.87]	2017
Nakamura	4	45	6	43	4.8%	0.64 [0.19, 2.10]	2020
Total (95% CI)		**531**		**527**	**100.0%**	**1.00 [0.77, 1.30]**	
Total events	90		95				

Heterogeneity: Tau² = 0.00; Chi² = 9.93, df = 10 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

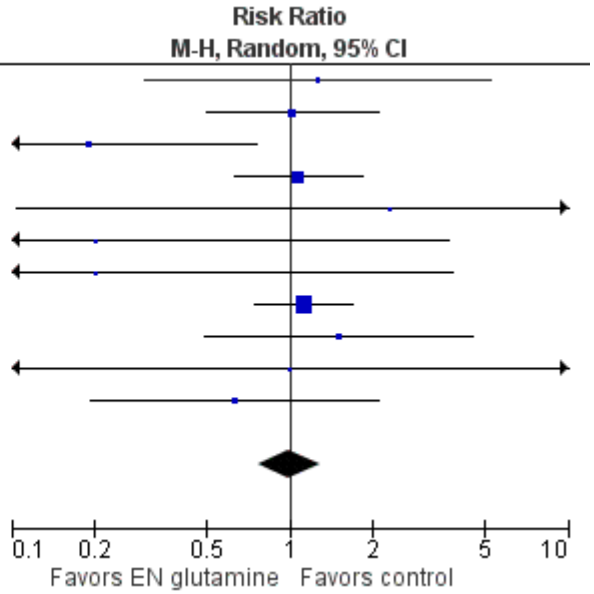


Figure 2. Hospital Mortality, trauma subgroup analysis

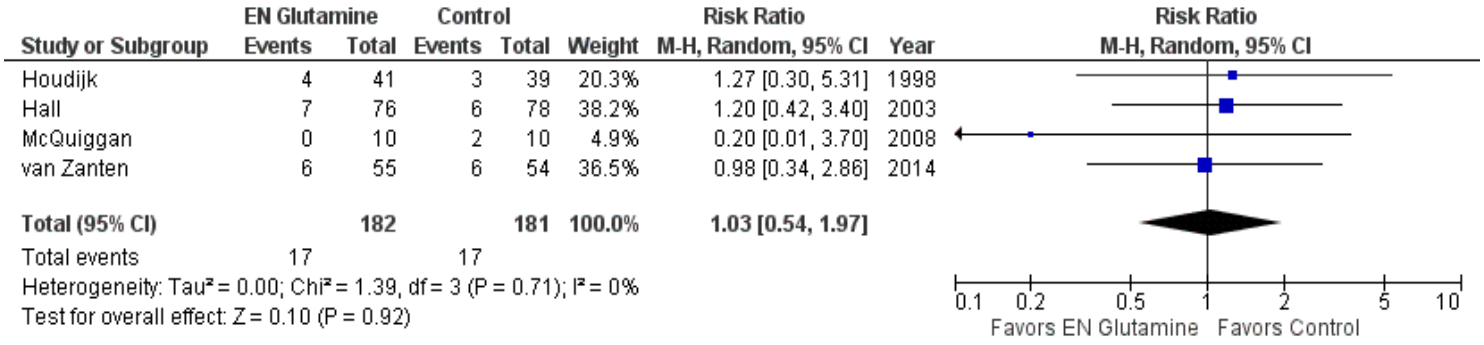


Figure 3. Hospital Mortality, burns subgroup

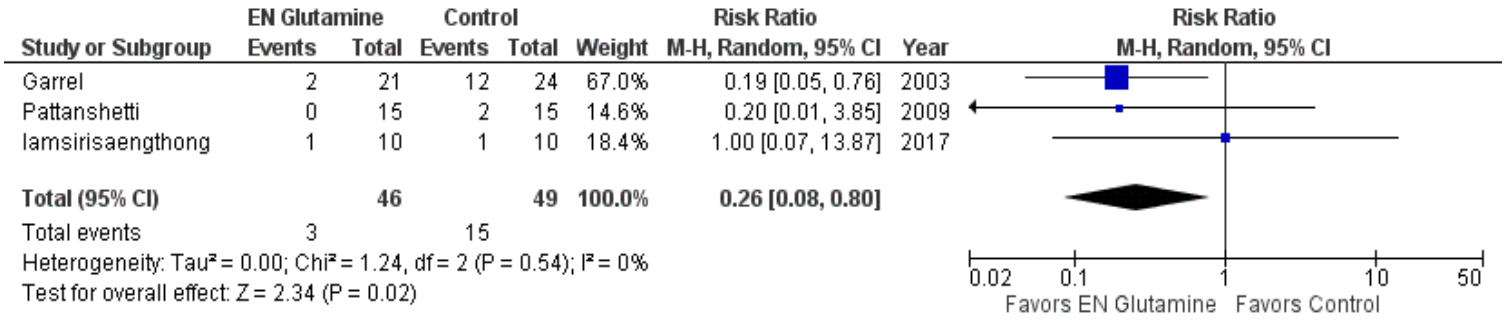


Figure 4. Infectious Complications

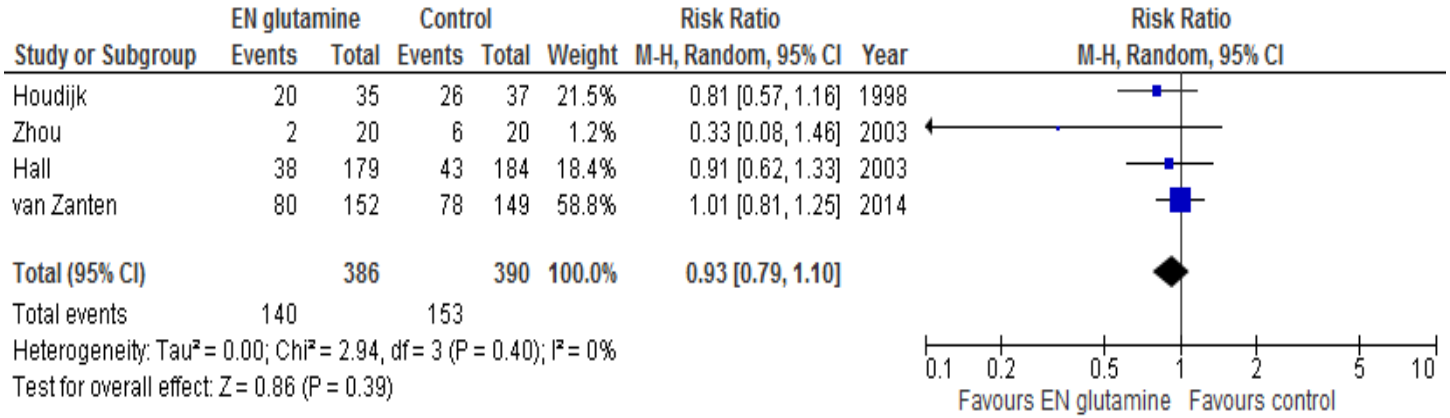


Figure 5. Infectious Complications: trauma

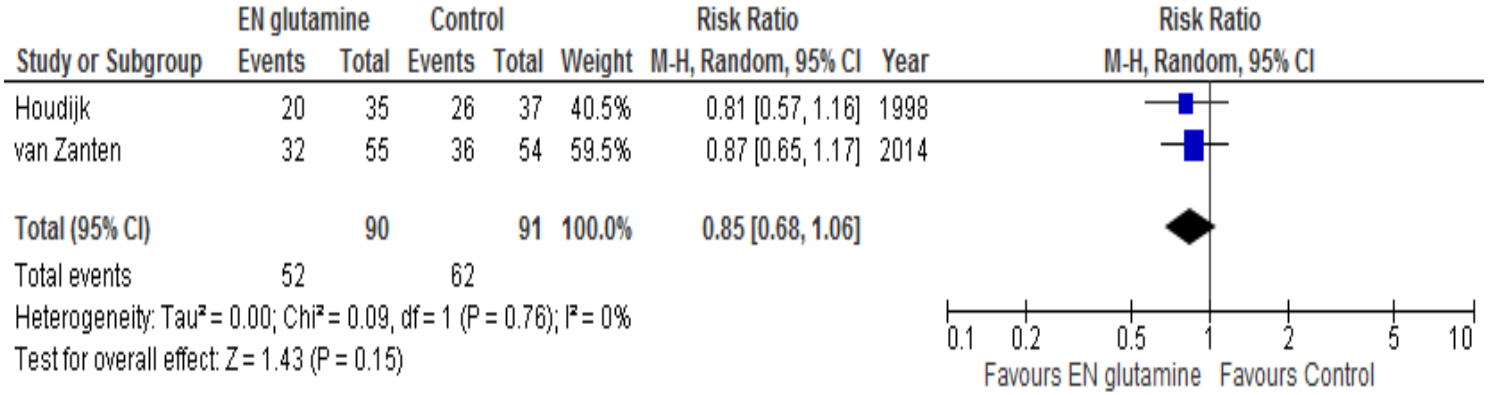


Figure 6: Hospital LOS

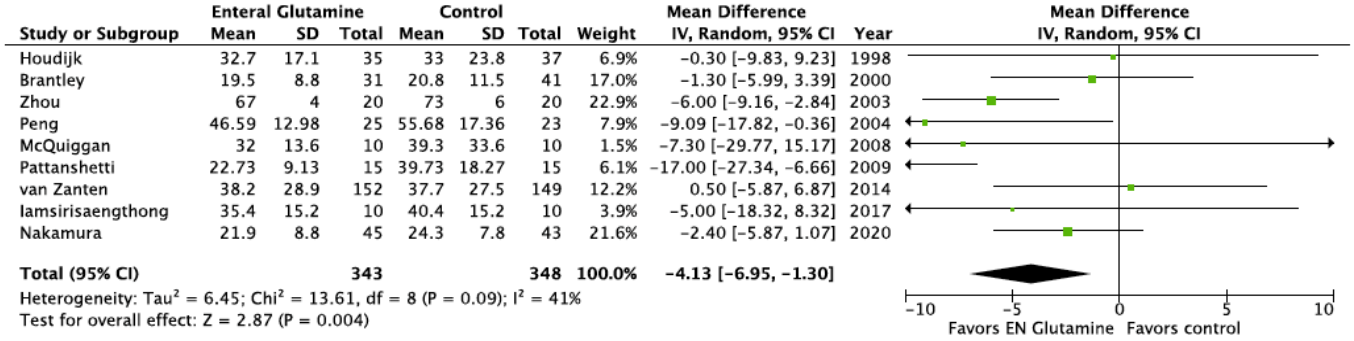


Figure 7. Hospital LOS, burns subgroup analysis

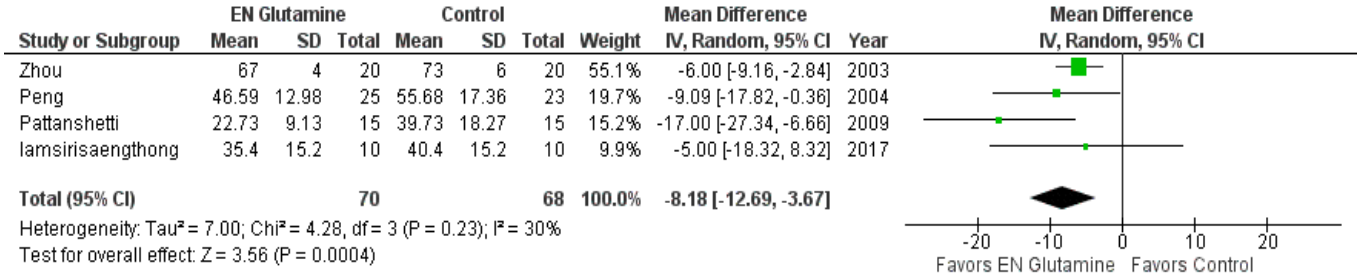


Figure 8. Hospital LOS, trauma subgroup analysis

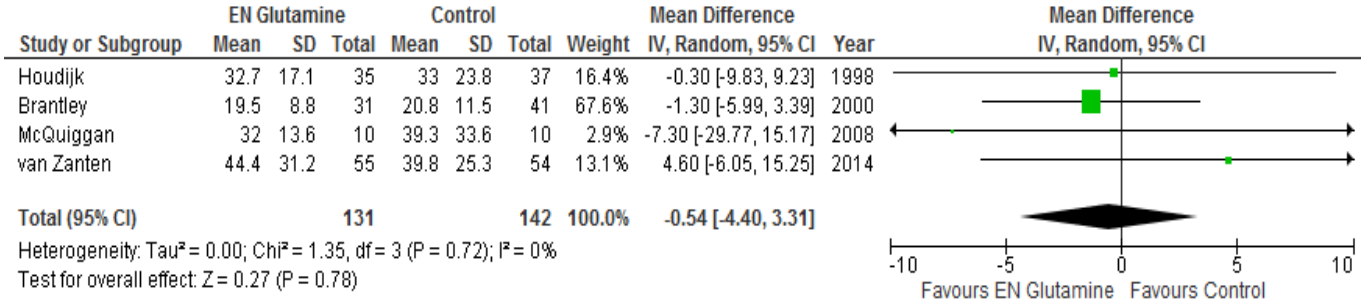


Figure 9. ICU LOS, all studies

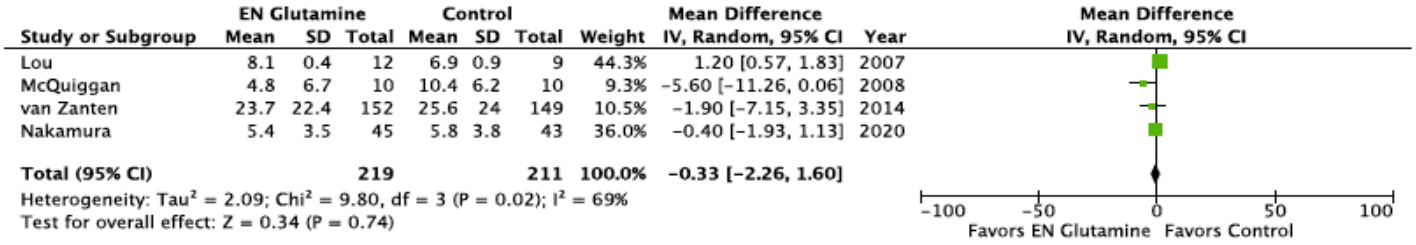


Figure 10. ICU LOS, trauma subgroup analysis

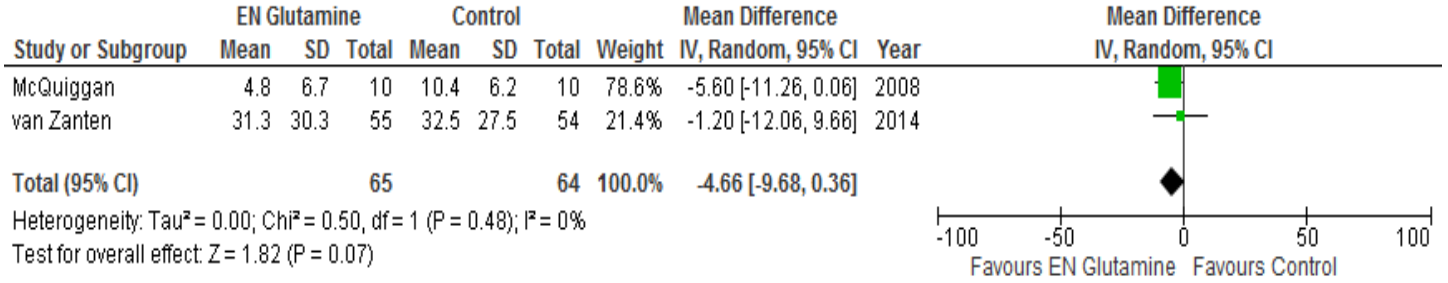
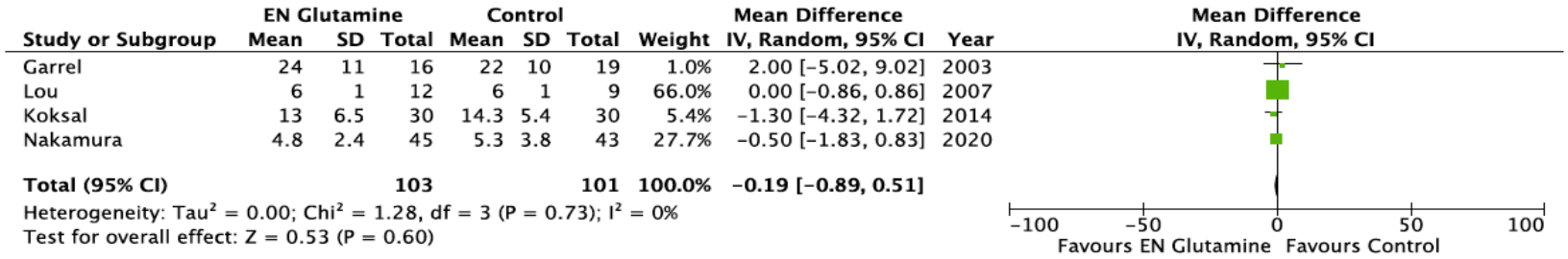


Figure 11. Mechanical Ventilation Days



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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.	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.	No clinical outcomes
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.	Surgical patients
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.	Crossover design
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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.	Pediatric patients
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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.	No clinical outcomes

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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.	Post hoc analysis, no new relevant outcomes
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	Surgical patients
Shariatpanahi M, Raghunath M, Deepika G, Jakkampudi A, Murthy HVV, Rao GV, Reddy DN, Talukdar R. Efficacy of enteral glutamine supplementation in patients with severe and predicted severe acute pancreatitis- A randomized controlled trial. Indian J Gastroenterol. 2019 Aug;38(4):338-347. doi: 10.1007/s12664-019-00962-7. Epub 2019 Oct 14. PMID: 31612309.	Not ICU patients