4.1.c Composition of EN: Glutamine May 2015

2015 Recommendation: ***Based on 3 level 1 and 8 level 2 studies, we recommend that enteral glutamine NOT be used in critically ill patients.***

2015 Discussion: The committee reviewed the aggregated results with the inclusion of 1 new small study in burns (Pattenshetti 2014) and a large study in mixed ICU patients including trauma patients in which the glutamine was given in addition to antioxidants and fish oils (van Zanten 2014). It was noted that there was no effect on hospital mortality, except in the small subgroup of burn patients in which enteral glutamine was associated with a significant reduction in mortality and a trend towards a reduction in infections. Since the data on trauma patients was not available from some studies, it was hard to elucidate a treatment effect in this subgroup. There was a significant reduction in hospital length of stay data overall and in burn patients but the data points were sparse with large confidence intervals. The cost and feasibility considerations were favourable despite potential limitations in acquiring the product. However, the committee was concerned about the higher mortality seen in patients receiving EN glutamine in the large van Zanten study, particularly in the subgroup of medical patients. It was also noted in our meta analyses that much of the benefit of enteral glutamine may be attributed to "small-study effects (1). Given this and the previously mentioned harm associated with glutamine in patients with shock and multi-organ failure in the REDOXS study, it was decided to downgrade the recommendation to enteral glutamine NOT being used in all critically ill patients. We noted the positive treatment effect in the studies of burns patients; however, the committee did not want to not make a separate recommendation in burn patients until the results of the multicentre RE-ENERGIZE Study in burns patients are available.

(1) Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000 Nov;53(11):1119-29.

2013:

There were no new randomized controlled trials since the 2009 update but a caution against the use of any glutamine in patients with shock and MOF was added given the possibility of harm as demonstrated by the results of the REDOXS study of combined enteral and parenteral glutamine.

Recommendation 2013: ***Based on 2 level 1 and 7 level 2 studies, enteral glutamine should be considered in burn and trauma patients. There are insufficient data to support the routine use of enteral glutamine in other critically ill patients. In addition, we strongly recommend that any 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).***

Discussion 2013: In examining the results of the meta-analysis of enteral glutamine supplementation, the committee noted the modest treatment effect with wide confidence intervals and the presence of heterogeneity across the studies. The largest effect on mortality was attributable to one study in burn patients with high internal validity (Garrel). On the other hand, a large well-designed trial in a heterogenous group of ICU patients showed no beneficial effect with glutamine enriched EN (Hall). With respect to infectious complications, the committee noted that the largest treatment effect was attributed to one study in burn patients (Zhou) and one large

study in trauma patients (Houdijk). There was a large treatment effect with respect to a reduced length in hospital stay however the data was quite skewed. Given that all studies were single centre trials, the likelihood of results being replicated in other settings is low. The cost and feasibility considerations were favourable despite potential limitations in acquiring the product. Given the results of the REDOXS study and harm associated with glutamine in patients with shock and multi-organ failure, we considered it unsafe to administer even EN glutamine to burns/trauma patients with shock and multi-organ failure. It is not known what the optimal dose of enteral glutamine supplementation is. In the studies reviewed, the dose of glutamine varied from 0.16-0.5 gm/kg/day (see table 1). The committee decided that a dose of 0.3 to 0.5 gm/kg/day would be reasonable. The effect of parenteral glutamine is discussed separately (section 9-4).

Semi Quantitative Scoring

Values	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	**2**	**all 0 Burns 3**
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	**1**	**all 1 Burns 2**
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**	**1**
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	**3**	**3**
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	**2**	**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**	**1**
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	**3**	**3**
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	**3**	**3**
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	**2**	**2**

4.1.c 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 were8 level 2 studies and 3 level 1 studies, 4 of which were in burn patients (Garrel 2003, Zhou 2003, Peng 2004, Pattanshetti 2009), 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 0.94, 95% CI 0.65, 1.36, p =0.74, test for heterogeneity I^2 = 21%) (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 3 studies of burn patients, patient deaths in hospital occurred in 2 studies (Garrel 2003, Pattanshetti 2009) and a significant reduction in hospital mortality was associated with the use of enteral glutamine (RR 0.19, 95% CI 0.06, 0.67, p =0.010, 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 6 level 2 studies and 1 level 1 study that demonstrated a significant reduction in length of hospital stay (WMD (weighted mean difference) -4.73, 95% CI -8.56, -0.90, p = 0.02, test for heterogeneity I^2 = 52%) (see figure 6). A stronger effect was seen in the subgroup of burn patients (WMD -9.16m 95% CI -15.06, -3.26, p = 0.002, test for heterogeneity I^2= 52%) (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 (WND -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 significant 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)	73 ± 6 (20)	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)	39.3 □3.6 (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)	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**	**Hospital** 33/149 (22) **ICU** 29/149 (20) **28 day** 25/149 (17) **6 month**	80/152 (53)	78/149 (52)	38.2 ± 28.9	37.7 ± 27.5	23.7 ± 22.4 (152)	25.6 ± 24.0 (149)

				53/152 (35)	42/149 (29)						
	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)	30 g/day EN glutamine (Glutamine resource, Nestle) + EN vs EN, no placebo, no supplemental glutamine	NA	NA	NA	NA	NA	NA	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

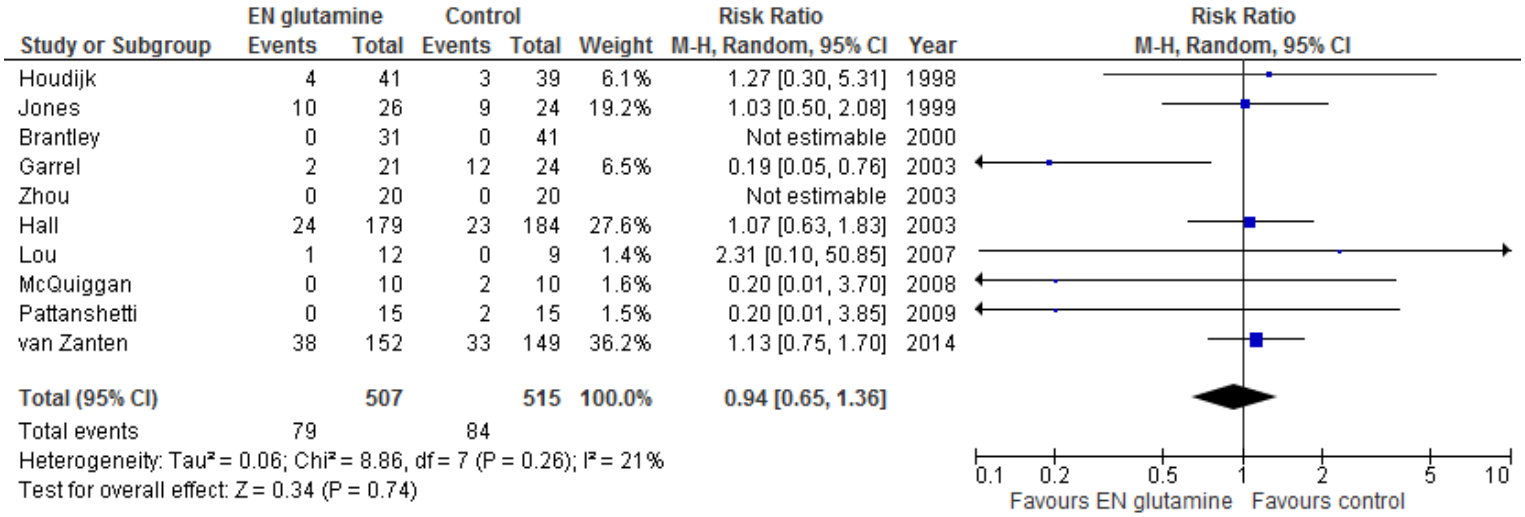

Figure 2. Hospital Mortality, trauma subgroup analysis

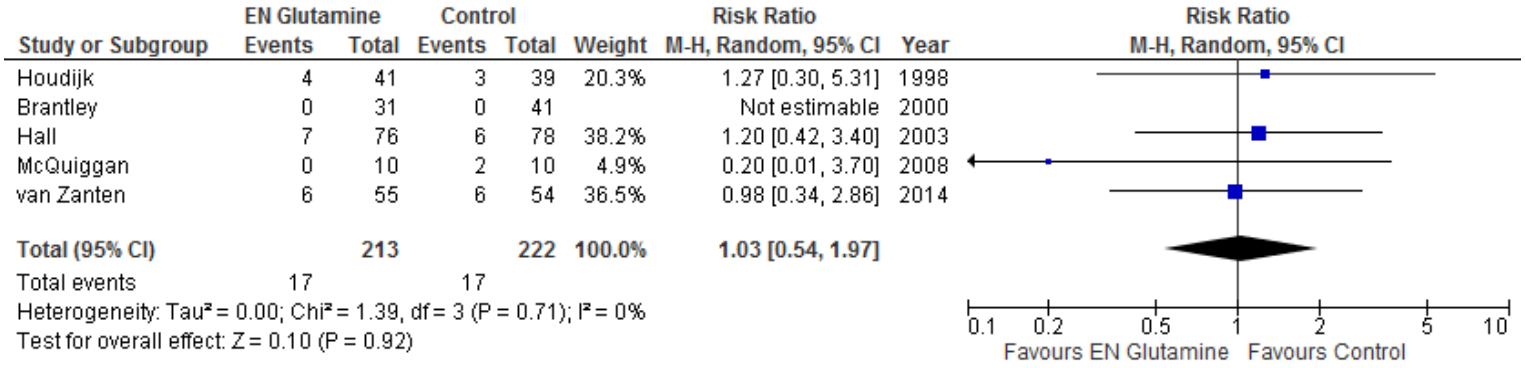

Figure 3. Hospital Mortality, burns subgroup

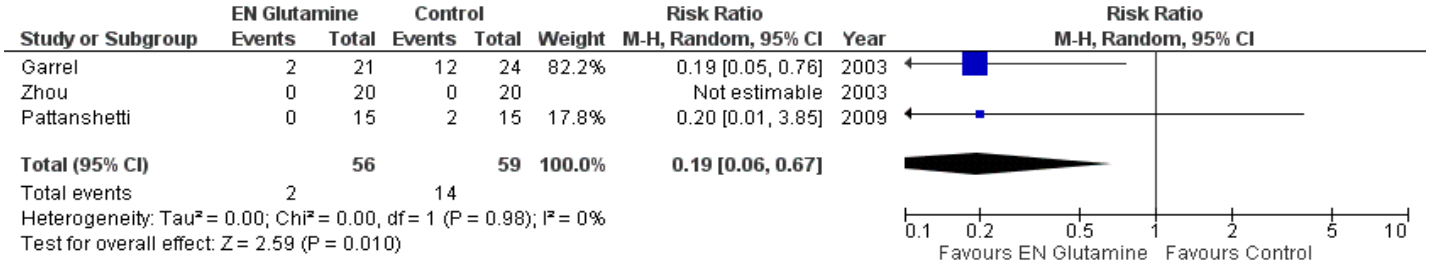

Figure 4. Infectious Complications

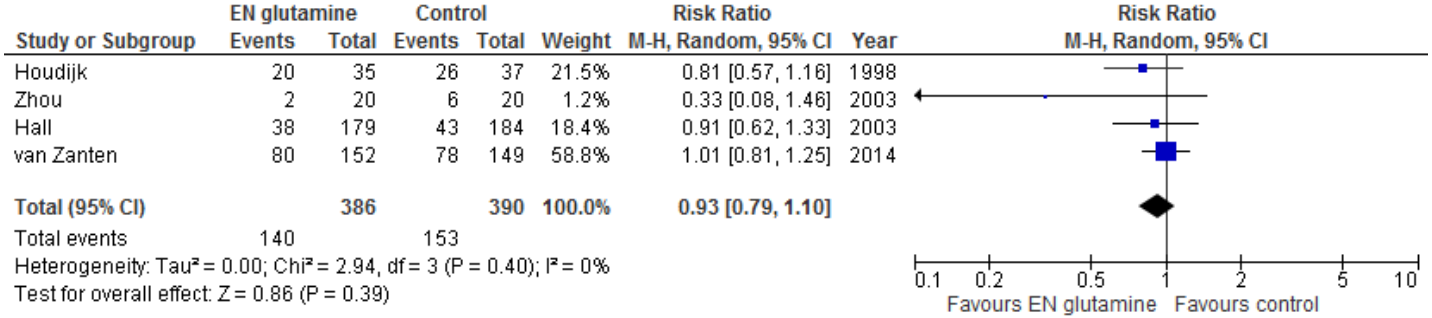

Figure 5. Infectious Complications: trauma

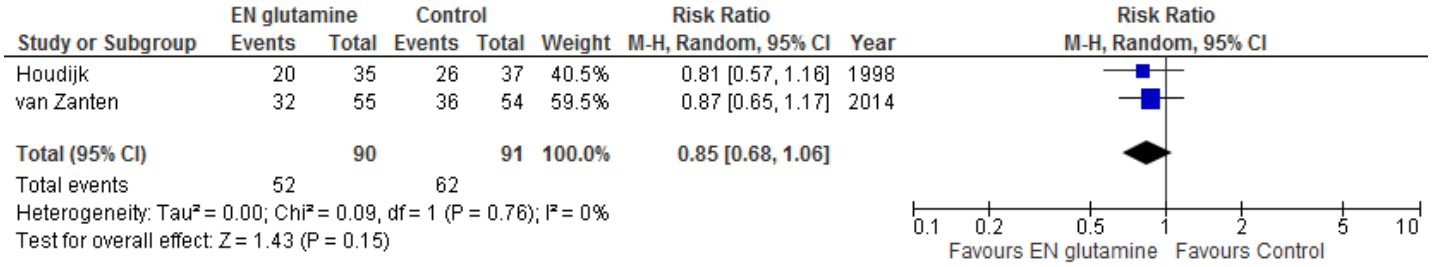

Figure 6: Hospital LOS

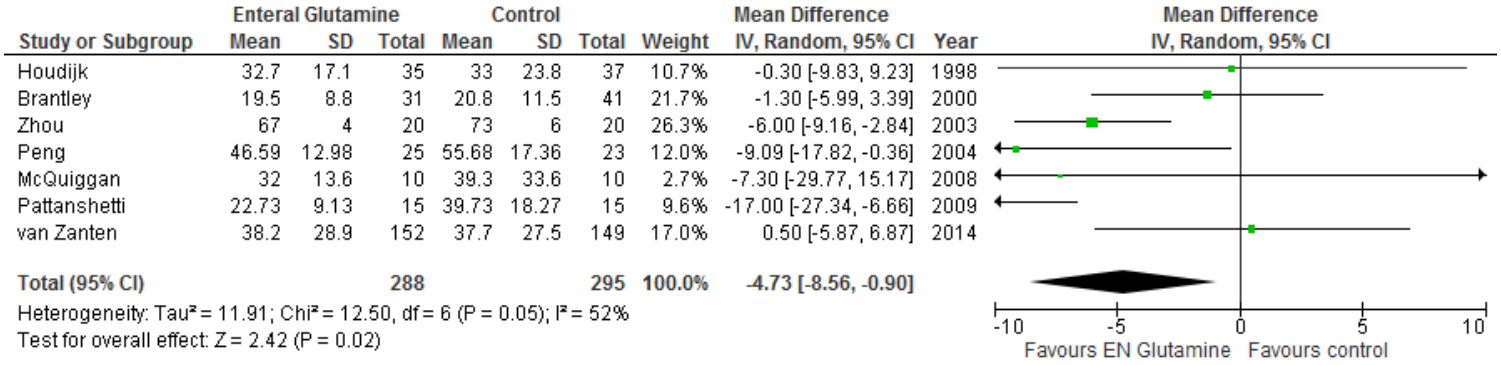

Figure 7. Hospital LOS, trauma subgroup analysis

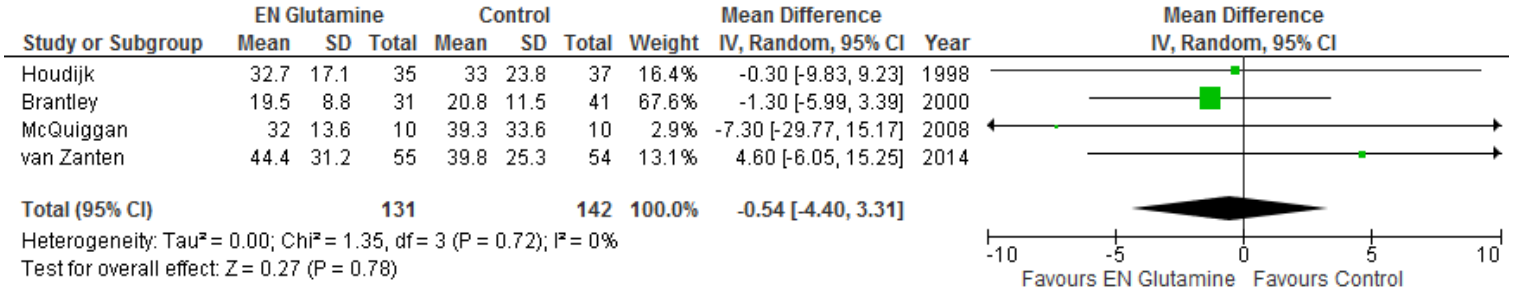

Figure 8. Hospital LOS, burns subgroup analysis

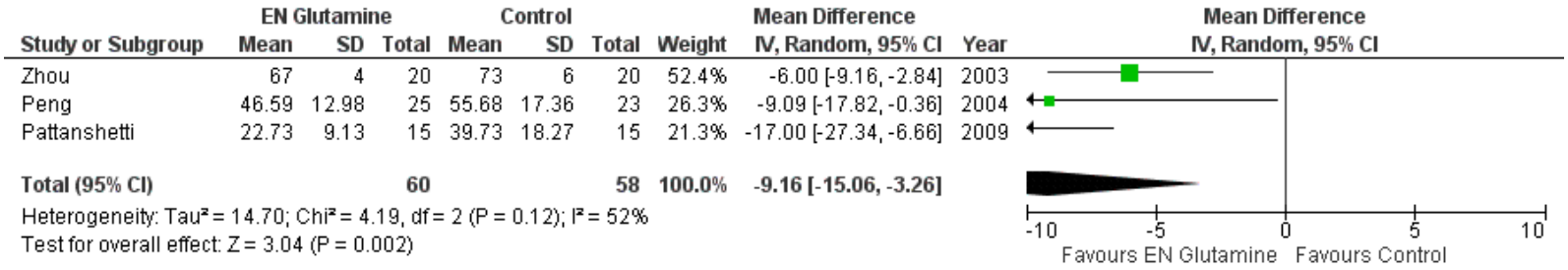

Figure 9. ICU LOS, all studies

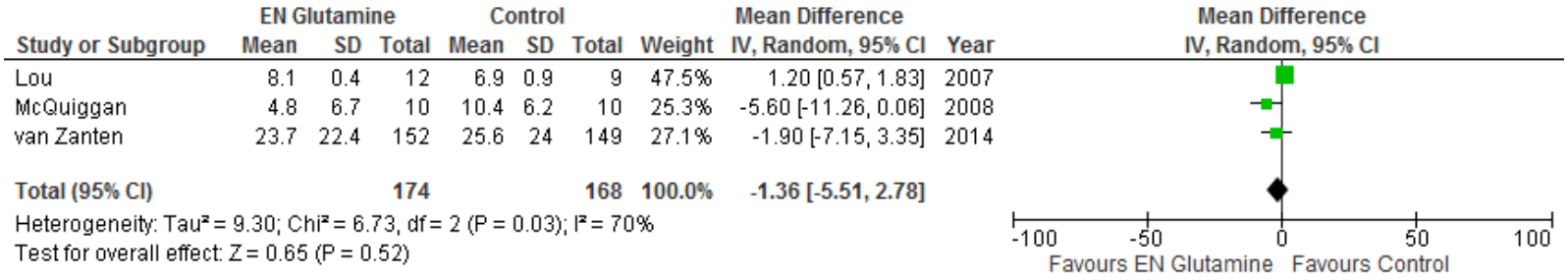

Figure 10. ICU LOS, trauma subgroup analysis