4.1.c Composition of EN: Glutamine July 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).

Recommendation 2009: *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.*

Discussion 2009: 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 safety, cost and feasibility considerations were favourable despite potential limitations in acquiring the product. 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

	Definition	2009 Score (0,1,2,3)	2013 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	2
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	1
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	3	2

4.1.c Composition of EN: Glutamine July 2013

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

Summary of Evidence: There were 7 level 2 studies and 2 level 1 studies, 3 of which were in burn patients (Garrel 2003, Zhou 2003, Peng 2004), 3 in trauma patients (Houdijk 1998, Brantley 2000 and McQuiggan 2008) and the remaining 3 were in mixed ICU patients.

Mortality: When the data from all the 8 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 0.81, 95% CI 0.48,1.34 p = 0.41) (figure 1). Subgroup analyses of the 3 studies of trauma patients showed that glutamine supplemented EN had no significant effect on mortality (RR= 0.79, 95% CI 0.16, 3.92, p = 0.77, some heterogeneity present, 21%) (figure 2). In the 2 studies of burn patients, patient deaths occurred in only one study (Garrel 2003) and these were significantly lower than the control group (RR 0.19, 95% CI 0.57-0.76, p =0.02).

Infections: There were 3 level 2 studies that demonstrated a trend towards a reduction in infectious complications with glutamine supplemented EN (RR 0.83, 95% CI 0.64-1.08, p = 0.16) (figure 3). In one study in burn patients (Zhou 2003), and one study in trauma patients (Houdijk 1998), glutamine supplemented EN was associated with a significant reduction in infectious complications.

Length of Stay: There were 5 level 2 studies that demonstrated a significant reduction in length of hospital stay (WMD (weighted mean difference) -4.50, 95% CI -7.29, -1.70, p= 0.002) (see figure 4). Two of these studied also reported on ICU LOS but there were no significant differences between the two groups.

Conclusions:
1) Glutamine supplemented enteral nutrition may be 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 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

For overall effect of glutamine supplementation (enteral and parenteral), refer to pages 4.1(c)-6 and 4.1(c)-7.

Table 1. Randomized studies evaluating glutamine (EN) in critically ill patients

Study	Population	Methods (score)	Intervention -Dose (gm/kg/day) -Type of feeding	Mortality # (%)†		Infections # (%)‡		Hospital stay (days)	
				Experimental	Control	Experimental	Control	Experimental	Control
1) Houdijk 1998	Critically ill trauma 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)
2) Jones 1999	Mixed ICU population 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)	10/26 (38.5)	9/24 (37.5)	NA	NA	ICU 11(4-54)*	ICU 16.5 (5-66)*
3) Brantley 2000	Critically ill trauma 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)
4) Hall 2003	Mixed ICU population 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)	27/179 (15)	30/184 (16)	38/179 (21)	43/184 (23)	25 (16-42)*	30 (19-45)*
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) **
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)

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	46.6 ± 12.9 (25)	55.7 ± 17.4 (23)
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	1/12	0 /9	NA	NA	ICU 8.1 ± 0.4 (12)	ICU 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	Hospital 32 ± 13.6 (10) ICU 14.8± 6.7 (10)	Hospital 39.3 ± 33.6 (10) ICU 10.4 ± 6.2 (10)

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

Figure 1. Mortality

Review:
Comparison: 01 Enteral Glutamine vs Control
Outcome: 03 Mortality

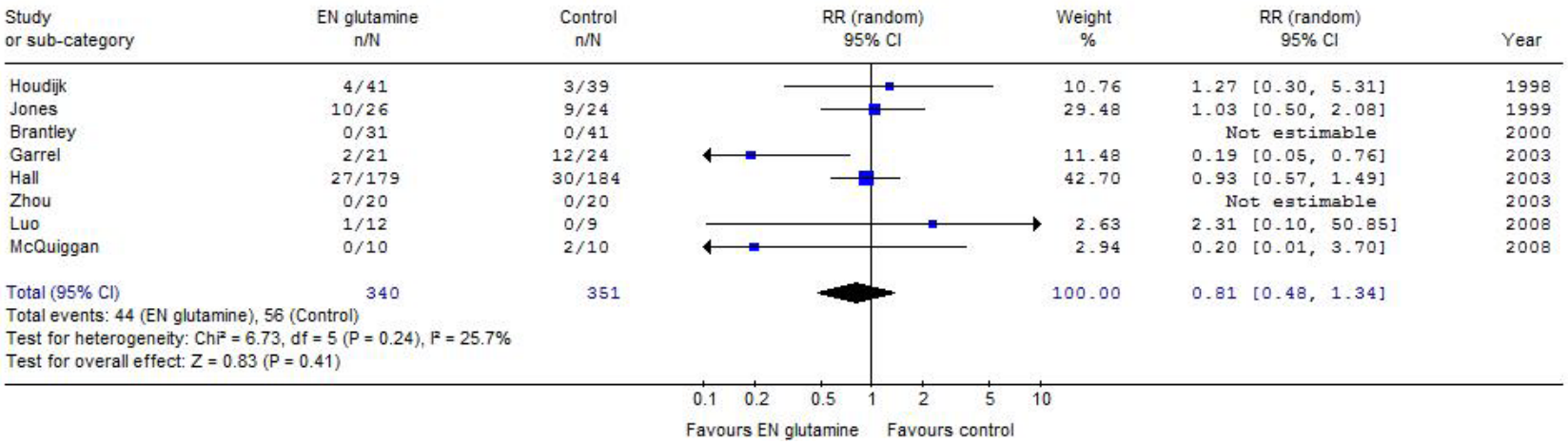


Figure 2. Subgroup analysis of studies of Trauma patients

Review: glutamine New review
Comparison: 01 Enteral Glutamine vs Control
Outcome: 03 Mortality

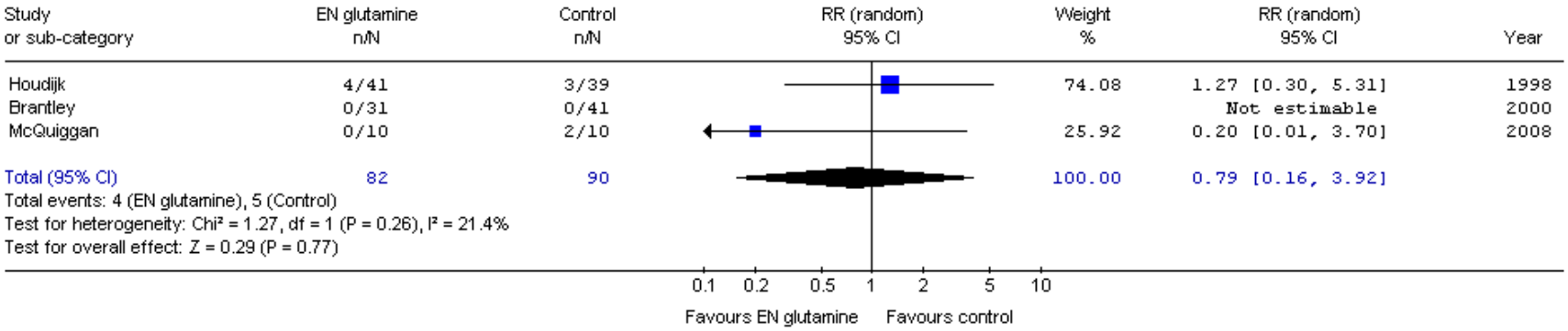


Figure 3. Infections

Review: glutamine New review
Comparison: 01 Enteral Glutamine vs Control
Outcome: 01 Infectious complications

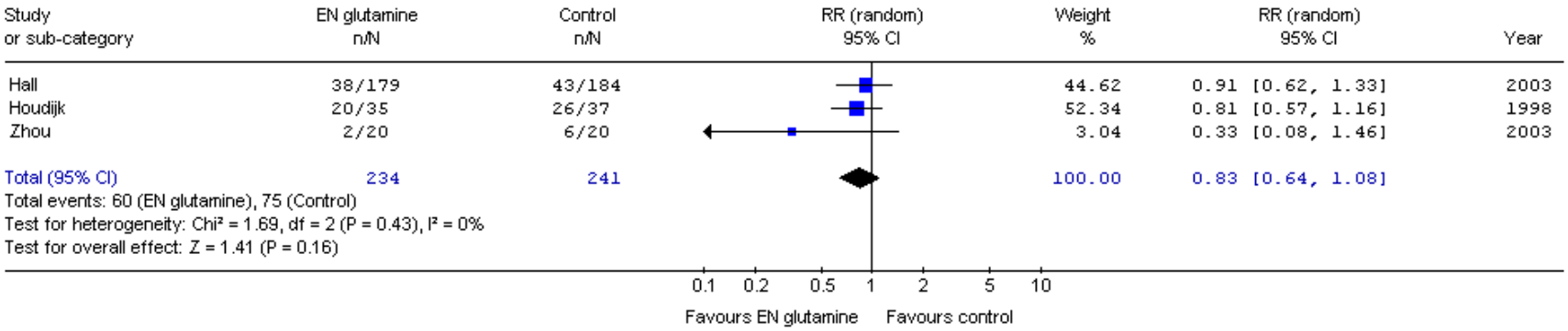
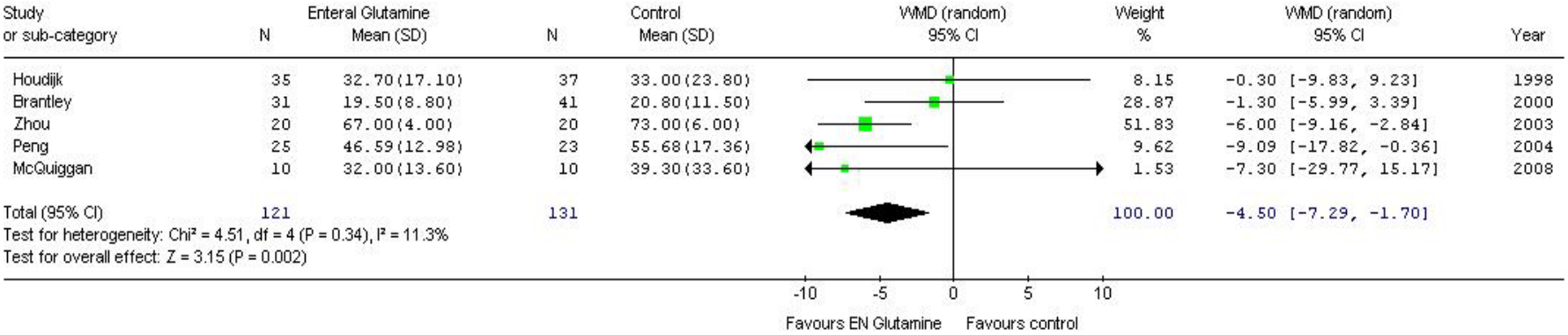
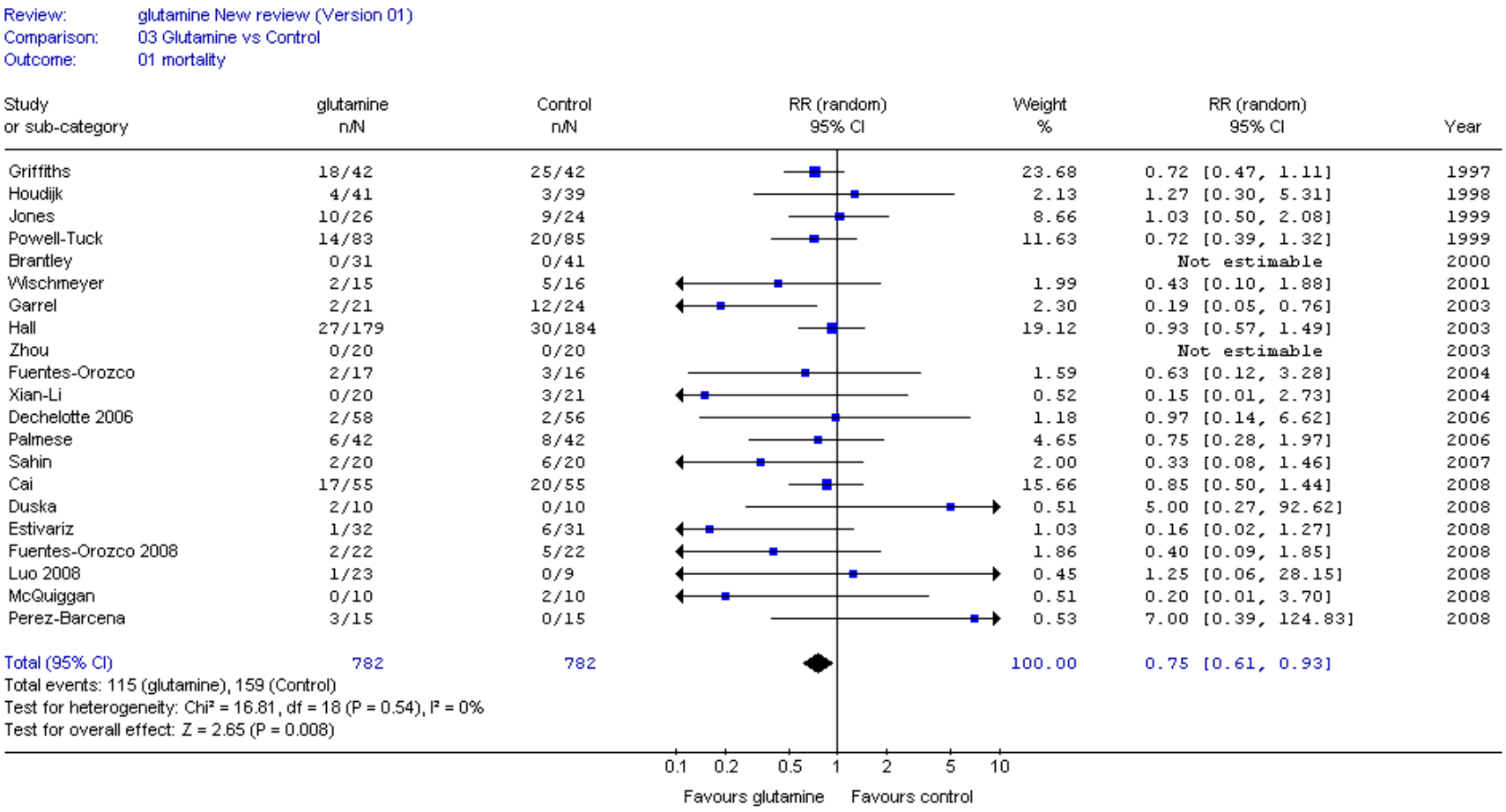


Figure 4. Hospital LOS

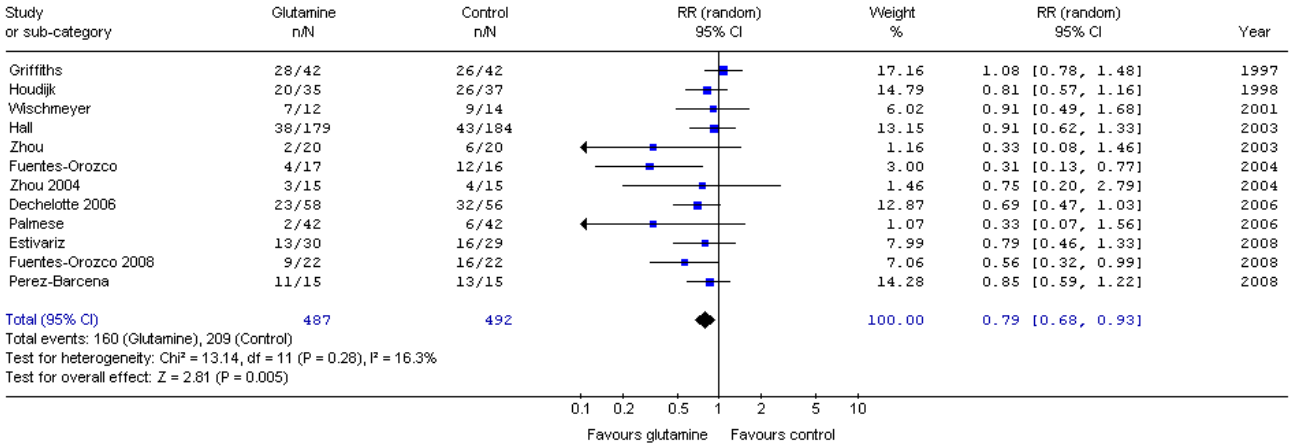
Review: glutamine New review (Version 01)
Comparison: 01 Enteral Glutamine vs Control
Outcome: 02 Hospital LOS



Overall Glutamine Supplementation (studies of Enteral and Parenteral supplementation)



Review: glutamine New review (Version 01)
Comparison: 03 Glutamine vs Control
Outcome: 02 Infectious Complications



Review: glutamine New review (Version 01)
Comparison: 03 Glutamine vs Control
Outcome: 03 Length of Stay