4.1 (c) Composition of EN: Glutamine: January 31st 2009

Recommendation:

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: 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).

	Definition	Score 1, 2 or 3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	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
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
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	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
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	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
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
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	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

4.1(c) Composition of EN: Glutamine

January 31st 2009

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

Summary of Evidence:
Mortality: 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. When the data from all these trials 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.

LOS: 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)
ITT: intent to treat
± ( ) : mean ± Standard deviation (number)
EN: enteral nutrition
TPN: Total parenteral nutrition
† hospital mortality unless otherwise stated
NA: not available

* 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

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

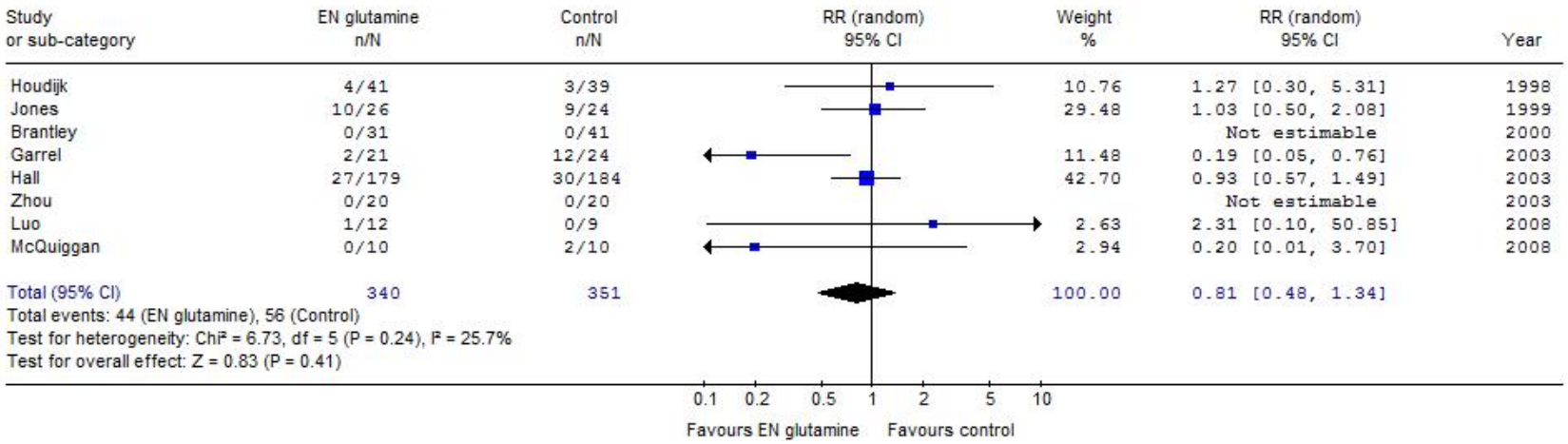


Figure 2. Subgroup analysis of studies of Trauma patients

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

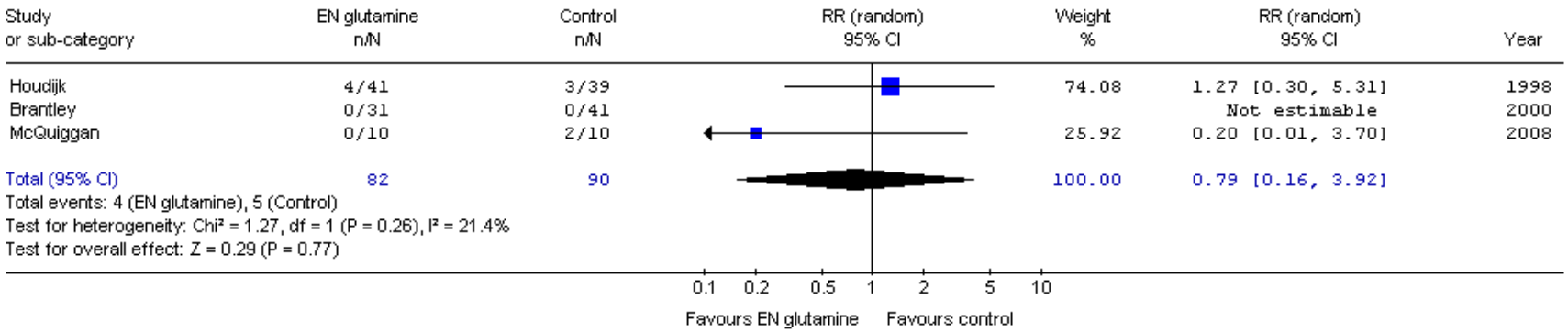


Figure 3

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

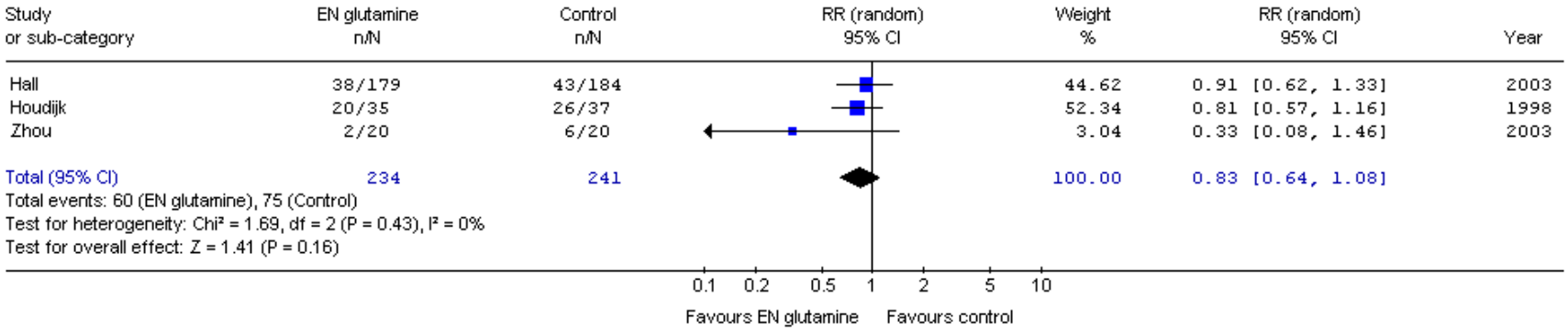
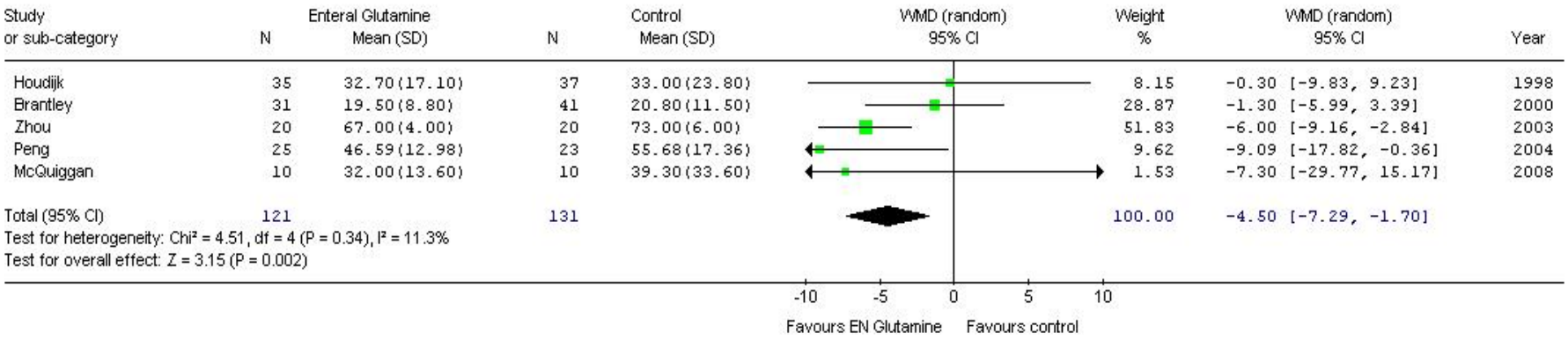


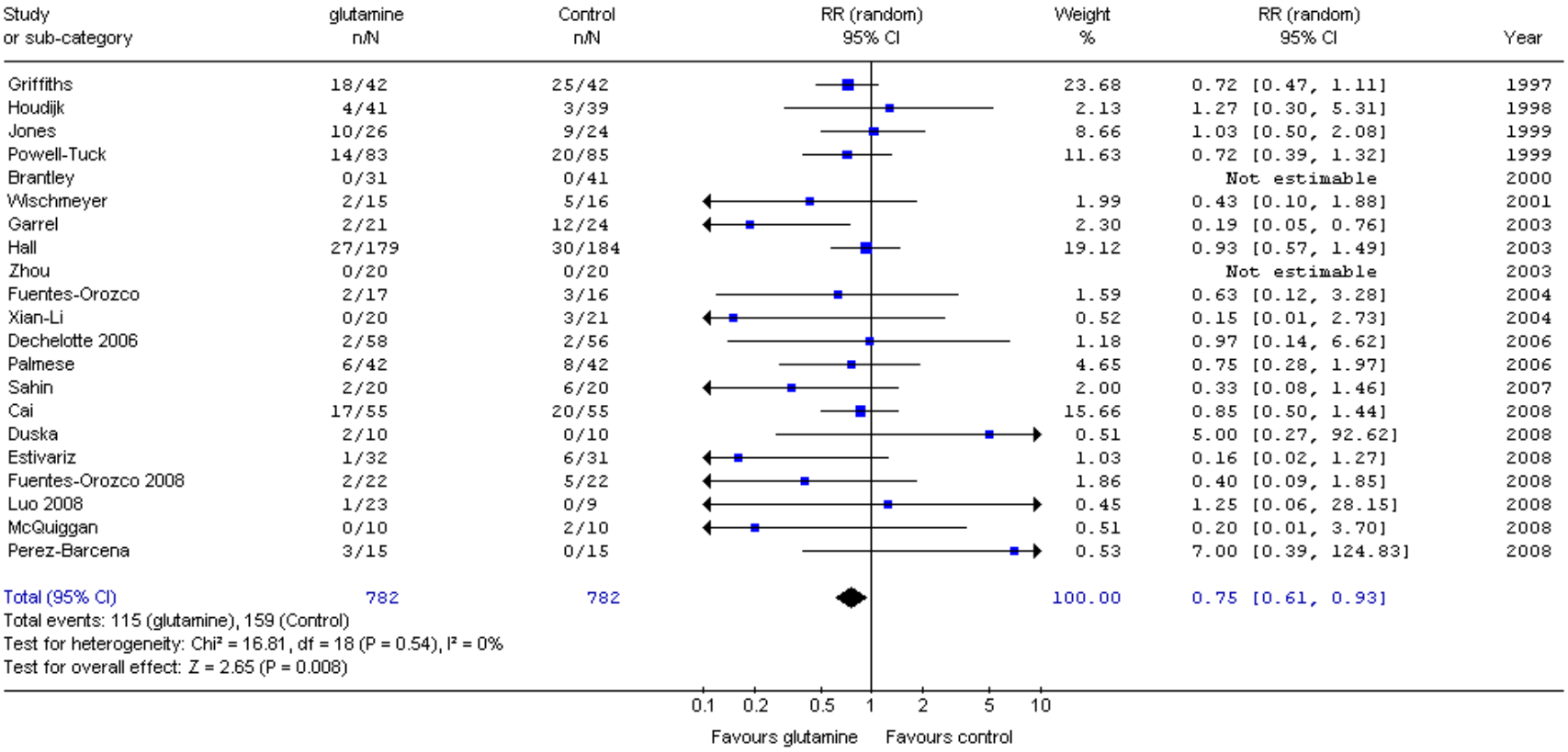
Figure 4

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

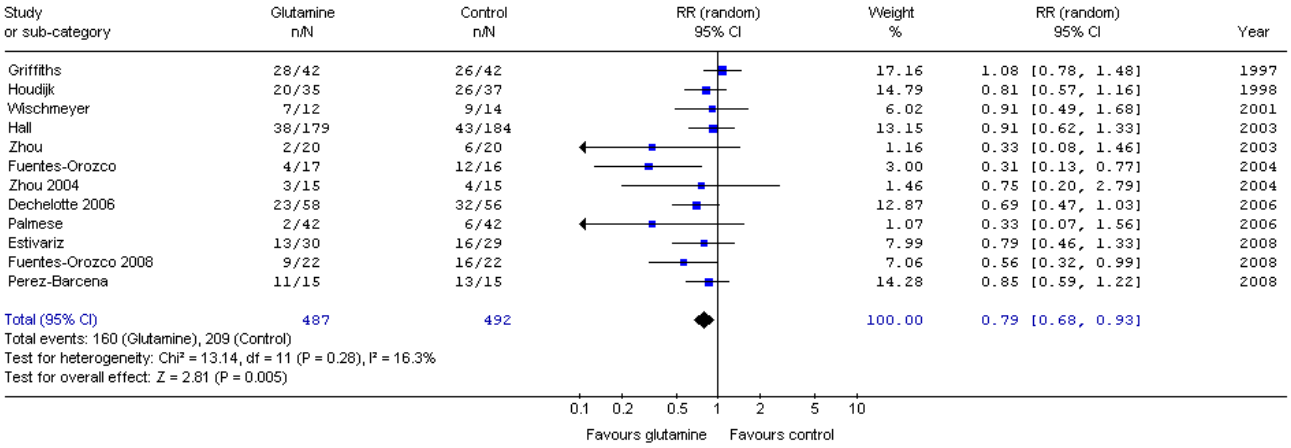


Overall Glutamine Supplementation (studies of Enteral and Parenteral supplementation)

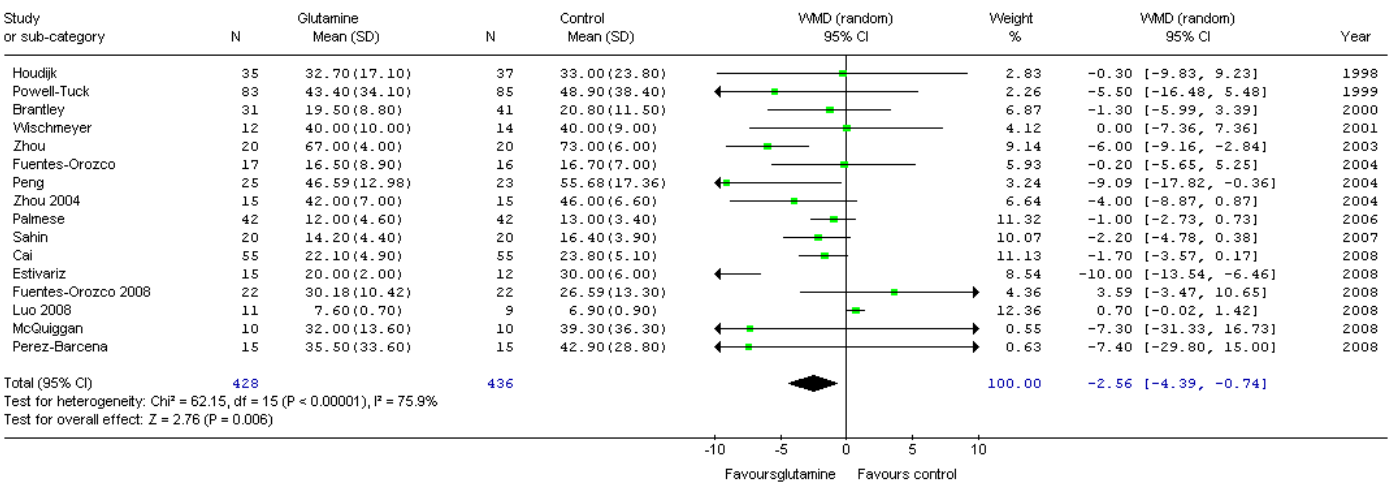
Review: glutamine New review (Version 01)
Comparison: 03 Glutamine vs Control
Outcome: 01 mortality



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



TOPIC: 4.1 (c) Composition of EN: Immune Enhancing diets: Glutamine

Article inclusion log
Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill, ventilated patients (no elective surgery patients)
Intervention: TPN and /or EN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

	Author	Journal	I	E	Why Rejected
1	Jebb	Clinical Nutrition 1995		√	Transplant/elective surgery pts
2	Long	JPEN J Parenter Enteral Nutr 1995		√	No clinical outcomes
3	Jensen	Am J Clin Nutr 1996		√	No clinical outcomes
4	Fish	AJCN 1997			Cancer pts
5	Scolapio	Gastroenterology 1997			Crossover design
6	Anderson	Bone Marrow Transplantation 1998			Surgical pts
7	Anderson	Cancer 1998			Pediatric cancer pts
8	Houdijk	Lancet 1998	√		
9	Den Hond	JPEN 1999			Not ICU pts
10	Jones	Nutrition 1999	√		
11	Schloerb	JPEN 1999			Cancer/surgery pts
12	Zhou	Natl Med J China 1999		√	Earlier study of 2003 RCT already included
13	Scolapio	JPEN 1999			Crossover design
14	Brantley	Nutr Clin Prac 2000	√		
15	Jackson	Am J Physiol Endocrinol Metab 2000			Surgery patients, No clinical outcomes
16	Szkudlarek	Gut 2000			Crossover design
17	Scolapio	Clin Nutr 2001			Crossover design
18	Velasco	Nutrition 2001		√	No clinical outcomes, Duplicate of Houdjik
19	Hall	In submission 2002	√		
20	Novak	Crit Care Med 2002	√		Studies on critically ill patients were included from this review
21	Boelens	J Nutr 2002		√	No clinical outcomes
22	Flaring	Clinical Science 2003		√	Elective surgery pts
23	Garcia-de-Lorenzo	Nutrition 2003			Systematic review, Individuals studies looked at
24	Garrel	Critical Care Med 2003	√		
25	Zhou	JPEN 2003	√		
26	Peng	Burns 2004	√		
27	Boelens	Clinical Nutrition 2004			Duplicate of Houdijk study
28	Peng	Burns 2004	√		
29	Falcao de Arruda	Clin Sci (Lond) 2004		√	Includes probiotics
30	Peng	Burns 2005		√	Duplicate study of earlier publication already included
31	Luo	Clin Nutr 2008	√		
32	McQuiggan	JPEN J Parenter Enteral Nutr 2008	√		

I = included, E = excluded

Reference List

1. 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. 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. 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. 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. 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. 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. 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. Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, Teerlink T, Meuwissen SG, Haarman HJ, Thijs LG, van Leeuwen PA. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet. 1998 Sep 5;352(9130):772-6.

9. 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..

10. Jones C, Palmer TE, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. Nutrition. 1999 Feb;15(2):108-15.

11. 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.

12. Zhou. National Medical Journal of China. 1999

13. 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.

14. Brantley S, Pierce J: Effects of enteral glutamine on trauma patients. Nutrition in Clinical Practice 2000; 15, S13.

15. 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.

16. 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.

17. Scolapio JS, McGreevy K, Tennyson GS, Burnett OL. Effect of glutamine in short-bowel syndrome. Clin Nutr. 2001 Aug;20(4):319-23.

18. 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.

19. Hall JC, Dobb G, Hall J, De Sousa R, Brennan L, McCauley R. A prospective randomized trial of enteral glutamine in critical illness. Intensive Care Med. 2003 Oct;29(10):1710-6.

20. 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.

21. 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.

22. 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

23. 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.

24. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, D'Elia M,Bernier J. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit Care Med. 2003 Oct;31(10):2444-9.

25. Zhou YP, Jiang ZM, Sun YH, Wang XR, Ma EL, Wilmore D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. JPEN J Parenter Enteral Nutr. 2003 Jul-Aug;27(4):241-5.

26. Peng X, Yan H, You Z, Wang P, Wang S. Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. Burns. 2004 Mar;30(2):135-9.

27. 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.

28. Peng X, Yan H, You Z, Wang P, Wang S. Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. Burns. 2004 Mar;30(2):135-9.

29. 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.

30. 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.

31. Luo M, Bazargan N, Griffith DP, Estivariz CF et al. Metabolic effects of enteral versus parenteral alanyl-glutamine dipeptide administration in critically ill patients receiving enteral feeding: a pilot study. Clin Nutr 2008;27(2):297-306.

32. McQuiggan M, Kozar R, Sailors RM, Ahn C, McKinley B, Moore F. Enteral glutamine during active shock resuscitation is safe and enhances tolerance of enteral feeding. JPEN J Parenter Enteral Nutr 2008;32(1):28-35.