4.1 (c) Composition of EN: Immune Enhancing Diets: Glutamine: January 26th, 2006

Recommendation:
Based on 5 level 2 studies and 2 level 1 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). 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 gm/kg/day would be reasonable. The effect of parenteral glutamine is discussed separately (section 9-4).

Values	definition	Score: 0, +, ++, +++
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	similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1+
Safe	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+
Feasible	ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3+
Cost	estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	3+

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January 26th , 2006

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 5 level 2 studies and 2 level 1 studies that demonstrated no statistical difference in mortality between the groups receiving glutamine supplemented EN or not (RR = 0.80, 95%CI 0.45,1.43, p = 0.46). See meta-analysis figure (page 4.1(c)-4). In one study in burn patients (Garrel), a significant reduction in mortality was observed (RR 0.19, 95% CI 0.57-0.76).

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). See meta-analysis figure (page 4.1(c)-4). In one study in burn patients (Zhou), and one study in trauma patients (Houdijk), glutamine supplemented EN was associated with a significant reduction in infectious complications.

LOS: There were 4 level 2 studies that demonstrated a trend towards a reduction in length of stay (SMD = -0.42, 95% CI -0.89, 0.04, p=0.08)(see figure page 4.1(c)-5).

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.

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

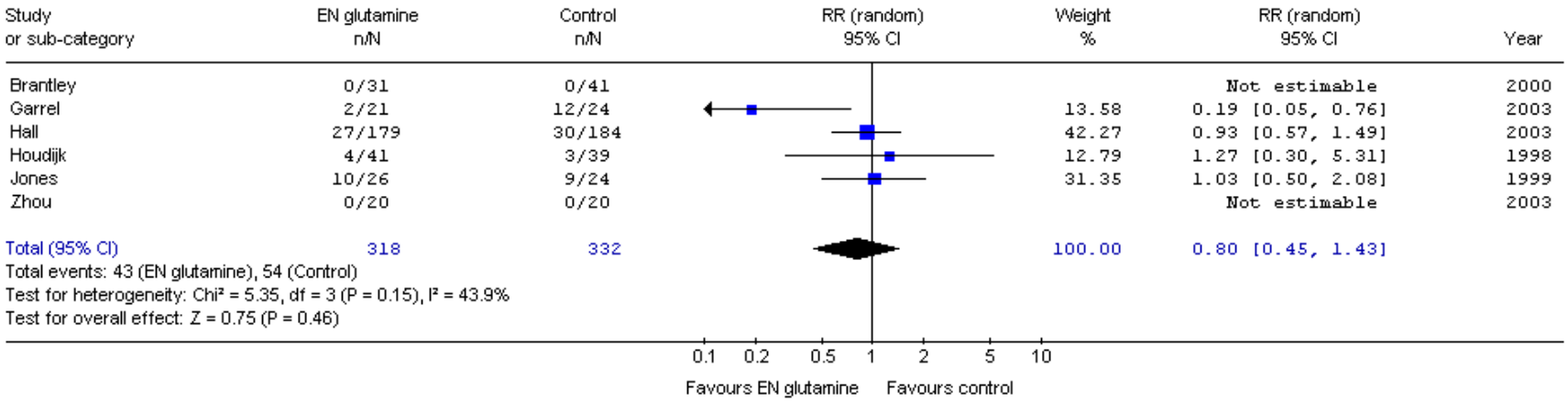
Study	Population	Methods (score)	Intervention –Dose (gm/kg/day) -Type of feeding	Mortality # (%)† Experimental	 Control	Infections # (%)‡ Experimental	 Control	Hospital stay (days) Experimental	 Control
1) Houdijk 1998	Critically ill trauma N = 80	C.Random: Yes ITT: No Blinding: Yes (10)	> 0.25 Altira 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)

C.Random: concealed randomization median (range)
ITT: intent to treat
± ( ) : mean ± Standard deviation (number)
NA: not available

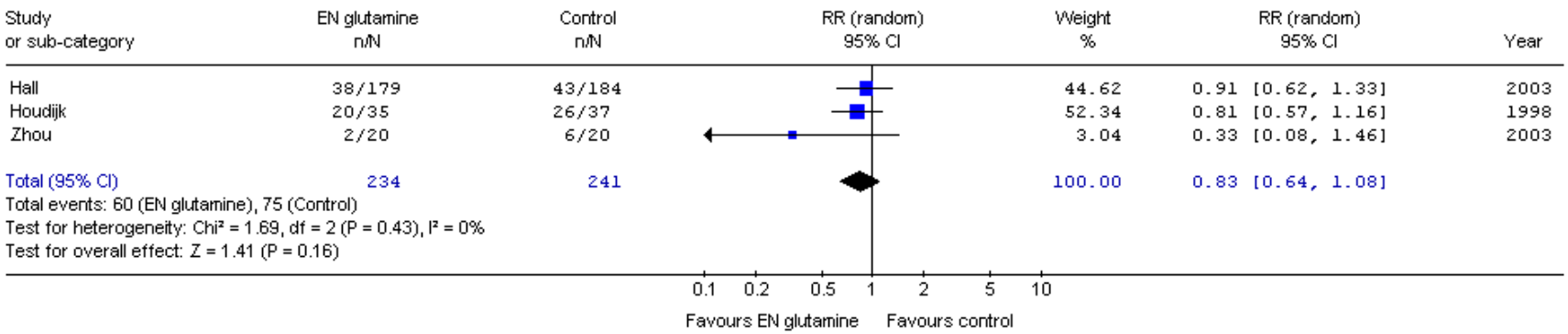
EN: enteral nutrition
TPN: Total parenteral nutrition
* median and range hence not included in meta analysis
† hospital mortality unless otherwise stated

** data from a subgroup, hence not included in meta-analysis

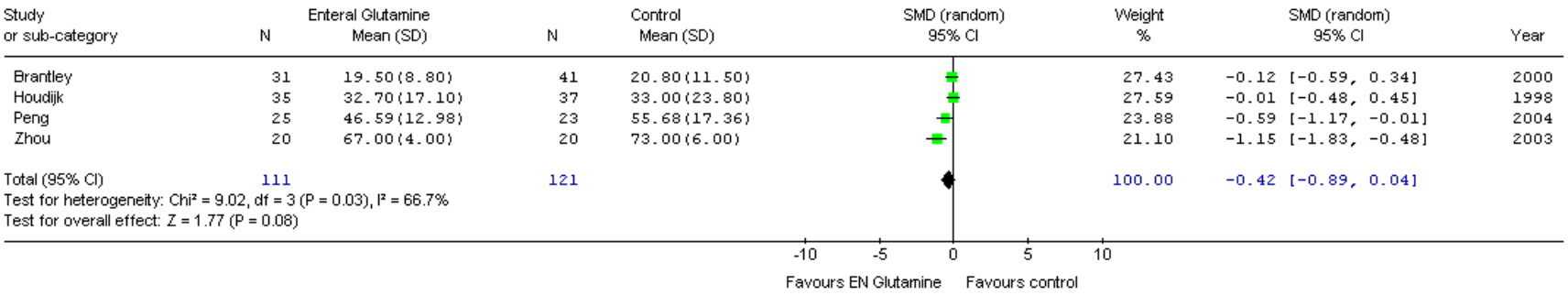
Review: glutamine New review
Comparison: 01 Enteral Glutamine vs Control
Outcome: 03 Mortality



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

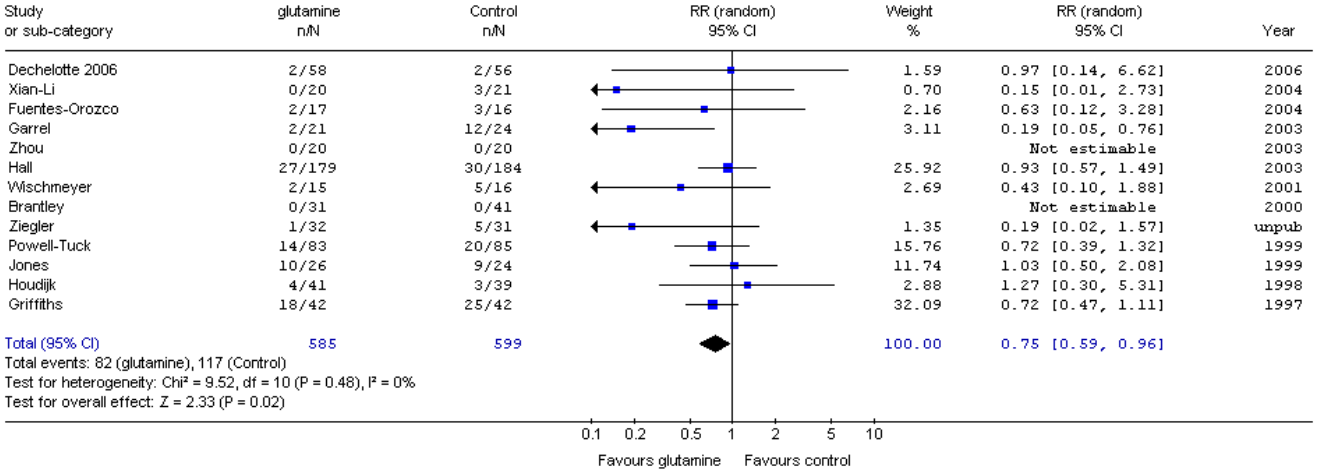


Review: glutamine New review
Comparison: 01 Enteral Glutamine vs Control
Outcome: 02 LOS

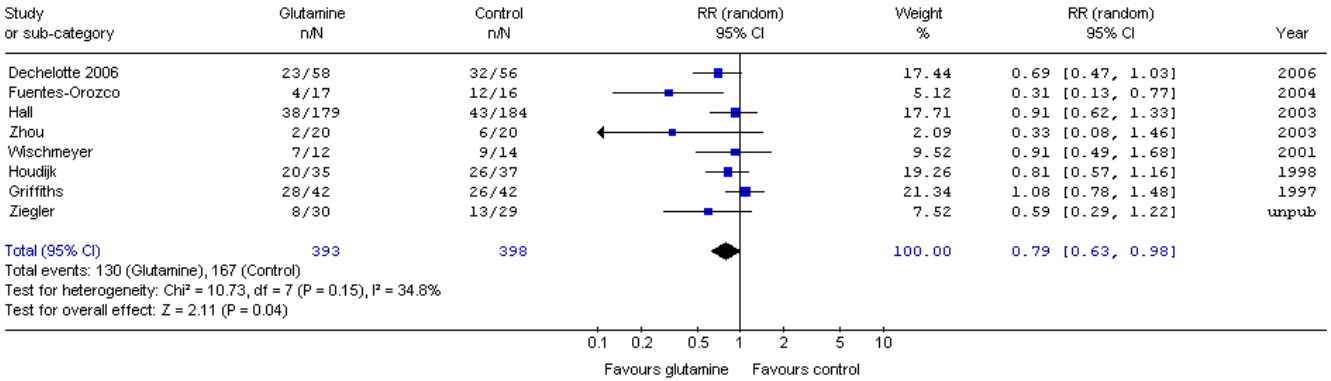


Overall Glutamine Supplementation (studies of Enteral and Parenteral supplementation)

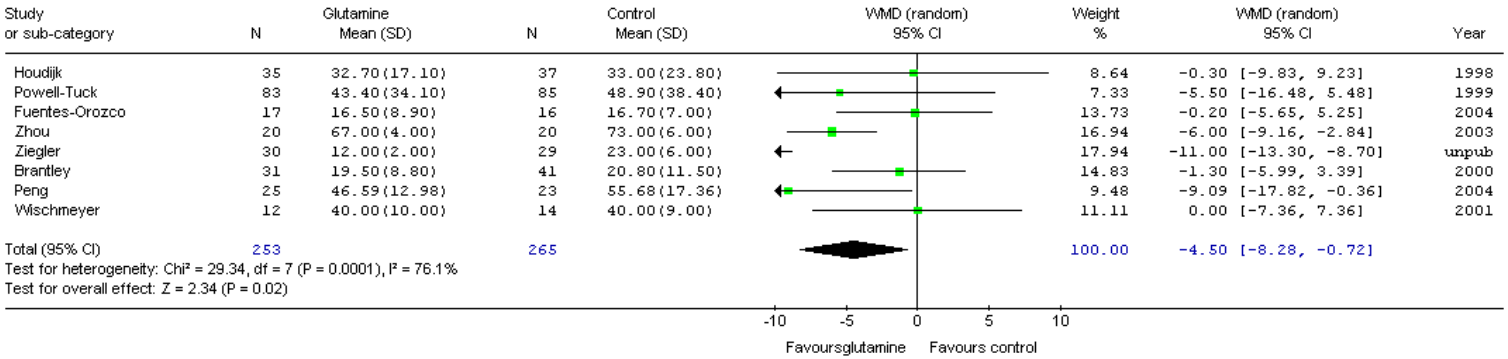
Review: glutamine New review
Comparison: 03 Glutamine vs Control
Outcome: 01 mortality



Review: glutamine New review
Comparison: 03 Glutamine vs Control
Outcome: 02 Infectious Complications



Review: glutamine New review
Comparison: 03 Glutamine vs Control
Outcome: 03 Length of Stay



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

(Reviewers: Deborah Schroter-Noppe, Carmen Christman, Dominique Garrel)

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.	Houdijk	Lancet 1998	√		
2.	Jones	Nutrition 1999	√		
3.	Brantley	Nutr Clin Prac 2000	√		
4.	Hall	In submission 2002	√		
5.	Garrel	CC Medicine 2003	√		
6.	Novak	CC Medicine 2002	√		Studies on critically ill patients were included from this review
7.	Boelens	J of Nutrition 2002		√	No significant outcomes
8.	Long	JPEN 1995		√	No significant outcomes
9.	Savy	Nut in Clin Pract 1997		√	Not RCT
10.	Velasco	Nutrition 2001		√	No significant outcomes
11.	Jensen	Am J Clin Nutr 1996		√	No significant outcomes
12.	Chiolero	Nutrition 2002		√	Not RCT
13.	Peng	Burns 2004	√		
14.	Peng	Burns 2005		√	Duplicate study of earlier publication already included
15.	Zhou	Natl Med J China 1999		√	Earlier study of 2003 RCT already included

I = included, E = excluded

Composition of Enteral Nutrition: Immune Enhancing Diets: Glutamine
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12. 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.