

9.4 Composition of Parenteral Nutrition: Glutamine Supplementation

January 26th, 2006

Recommendation:

Based on 4 level 1 studies and 5 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is recommended. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.

Discussion: The committee noted that in patients receiving PN, there was a moderate reduction in mortality associated with parenteral glutamine. The cost and lack of availability of parenteral glutamine limit the applicability of this intervention. Whether parenteral glutamine has an effect in patients fed enterally is unknown. The effect of enteral glutamine is discussed separately (section 4.1(e)). The committee decided that the range of glutamine of 0.2-0.57 gm/kg/day, as used in the studies reviewed, would be reasonable (see table 1).

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+ Infections 2+ Mortality
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+ Infections 2+ Mortality
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	2+
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	2+
Feasible	ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	0 (not available in Canada)
Cost	estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2+

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Question:

Compared to standard PN, does glutamine-supplemented PN result in improved clinical outcomes in critically ill patients?

Summary of Evidence:

Mortality: When the 4 level 1 and 5 level 2 studies were aggregated, glutamine supplemented PN was associated with a significant reduction in mortality in critically ill patients (RR 0.67, CI 0.48, 0.92, $p = 0.01$) See meta-analysis figure (page 9-17).

Infections: When the 2 level 1 study and 4 level 2 studies were aggregated, glutamine supplemented PN was associated with a trend towards a reduction in infectious complications (RR 0.75, 95% CI 0.54, 1.04, $p = 0.08$) See figure (page 9-17).

LOS: When the 2 level 1 studies and 4 level 2 studies were aggregated, glutamine supplemented PN had no effect on hospital LOS (See page 9-18).

Conclusions:

- 1) Glutamine supplemented PN is associated with a significant reduction in mortality in critically ill patients.
- 2) Glutamine supplemented PN may reduce infectious complications 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

For overall effect of glutamine supplementation (enteral and parenteral), refer to pages 9-19 and 9-20.

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

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡		Hospital stay (days)	
1) Dechelotte 2006	ICU patients, multiple trauma, surgery, sepsis, pancreatitis. N = 114	C.Random: N/A ITT: yes Blinding: double N/A	PN, 0.35	Hospital 2/58 (3) 6 month 16/58 (28)	Hospital 2/56 (3) 6 month 9/56 (16)	All infections 23/58 (40) Pneumonia 10/58 (17)	All infections 32/56 (58) Pneumonia 19/56 (34)	ICU 12.5 (1-430) hospital 11.5 (3-121) 30 (1-560) 26 (4-407)	
2) Griffiths 1997 and 2002	Mixed ICU Population N = 84	C.Random: Yes ITT: Yes Blinding: Yes (11)	dose of Lglutamine gm.kg/day PN, 0.26	Experiment Hospital 18/42(42.9)	Control Hospital 25/42(59.5)	Experiment 28/42(67)	control 26/42(62)	Experiment ICU 10.5 (6-19)*	Control ICU 10.5 (6-24)*
3) Powell-Tuck 1999	Mixed ICU/hosp population N = 168	C.Random: Yes ITT: Yes Blinding: Yes (8)	PN, 0.26	14/83 (16.9)	20/85 (23.5)	NA	NA	43.4+/-34.1 (83)	48.9+/-38.4 (85)
4) Wischmeyer 2001	Critically ill burns N = 31	Random: Not sure ITT: No Blinding Yes (8)	PN, 0.57 Intravenous glutamine while on EN	2/15 (13.0)	5/16 (31.0)	7/12 (58.3)	9/14 (64.3)	40+/-10 (12)	40+/-9 (14)
5) Goeters 2002	surgical ICU patients N = 68	C.Random: not sure ITT: no Blinding: no	PN, 0.2	ICU 7/33 (21)* 30 day 7/33 (21)* 6 m 11/33 (33)*	ICU 10/35 (29)* 30 day 11/35 (31)* 6 m 21/35 (60)*	NA	NA	Average LOS* ICU 21.3 ± 13.5 hospital 20.8 ± 9.1 46 ± 49.1 (33) 39.4 ± 31.1 (35)	
6) Fuentes-Oroczo 2004	Secondary peritonitis Requiring TPN N = 33	C.Random: yes ITT: yes Blinding: double (11)	PN, 0.27	2/17 (12)	3/16 (19)	4/17 (23)	12/16 (75)	ICU 7.2 ± 9.2 Hospital 16.5 ± 8.9	7.3 ± 4.5 16.7 ± 7
7) Ziegler 2004 (unpublished)**	Post-op patients requiring ICU care N = 63	C.Random: not sure ITT: no Blinding: double (9)	PN, 0.35	Hospital 1/32 (3)	Hospital 5/31(16)	8/30 (27)	13/29 (45)	ICU 12 ± 2	23 ± 6
8) Zhou 2004	Severe Burns N = 30	C.Random: yes ITT: yes Blinding: double (11)	PN, 0.35	NA	NA	3/15 (20)	4/15 (26)	Hospital 42 ± 7.0	46 ± 6.6
9) Xian-Li 2005	Severe acute pancreatitis N = 69	C.Random: yes ITT: no Blinding: no (5)	PN, 0.4	0/20	3/21 (14)	# complications 4	11	Hospital 25.3 ± 7.6	28.6 ± 6.9

C.Random: concealed randomization median (range)

ITT: intent to treat

NA: not available

** preliminary data and subject to review of final manuscript. Data for mortality is ITT, infections is non-ITT.

EN: enteral nutrition; TPN Total parenteral nutrition

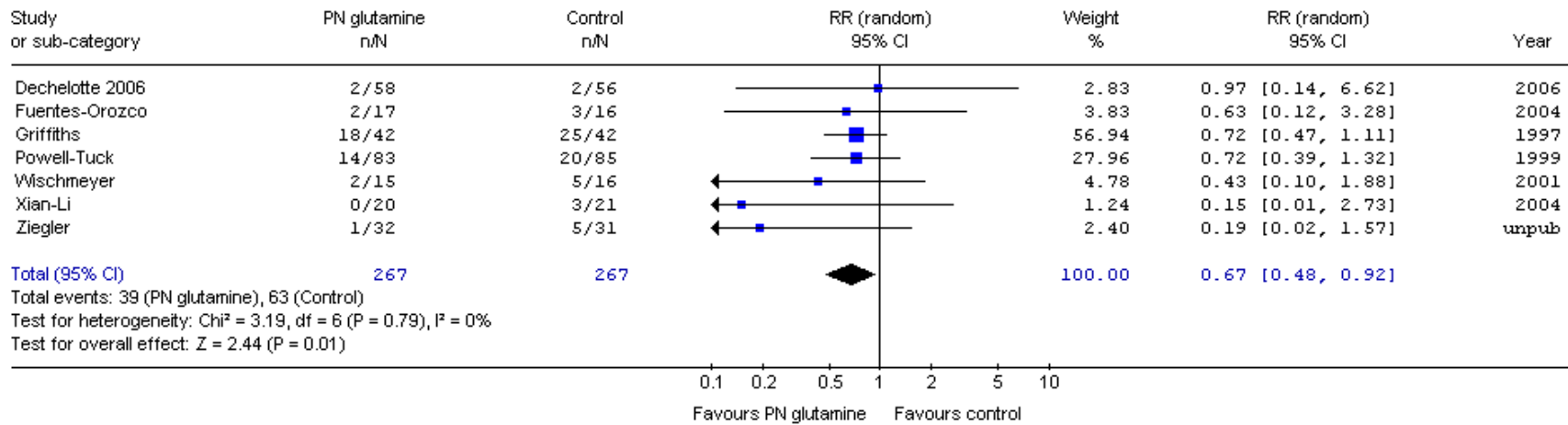
± () : mean ± Standard deviation (number)

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

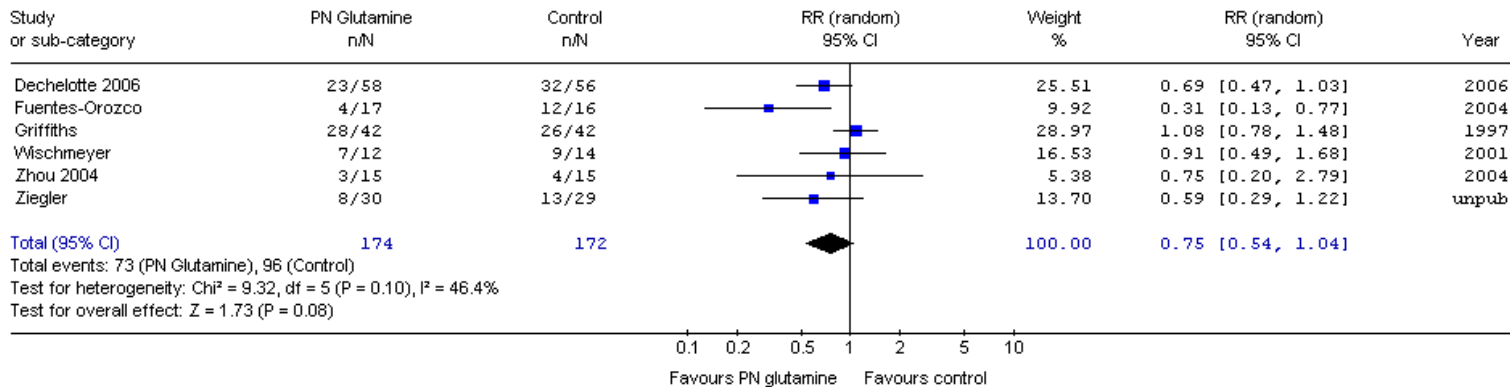
† hospital mortality unless stated otherwise

‡ number of patients with infections unless stated otherwise

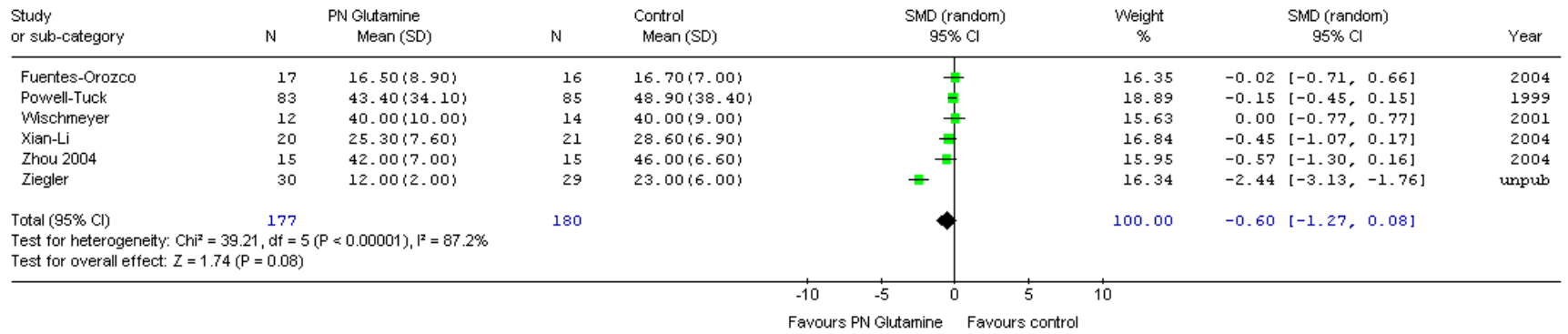
Review: glutamine New review
 Comparison: 02 Parenteral Glutamine vs Control
 Outcome: 03 Mortality



Review: glutamine New review
 Comparison: 02 Parenteral Glutamine vs Control
 Outcome: 01 Infectious Complications

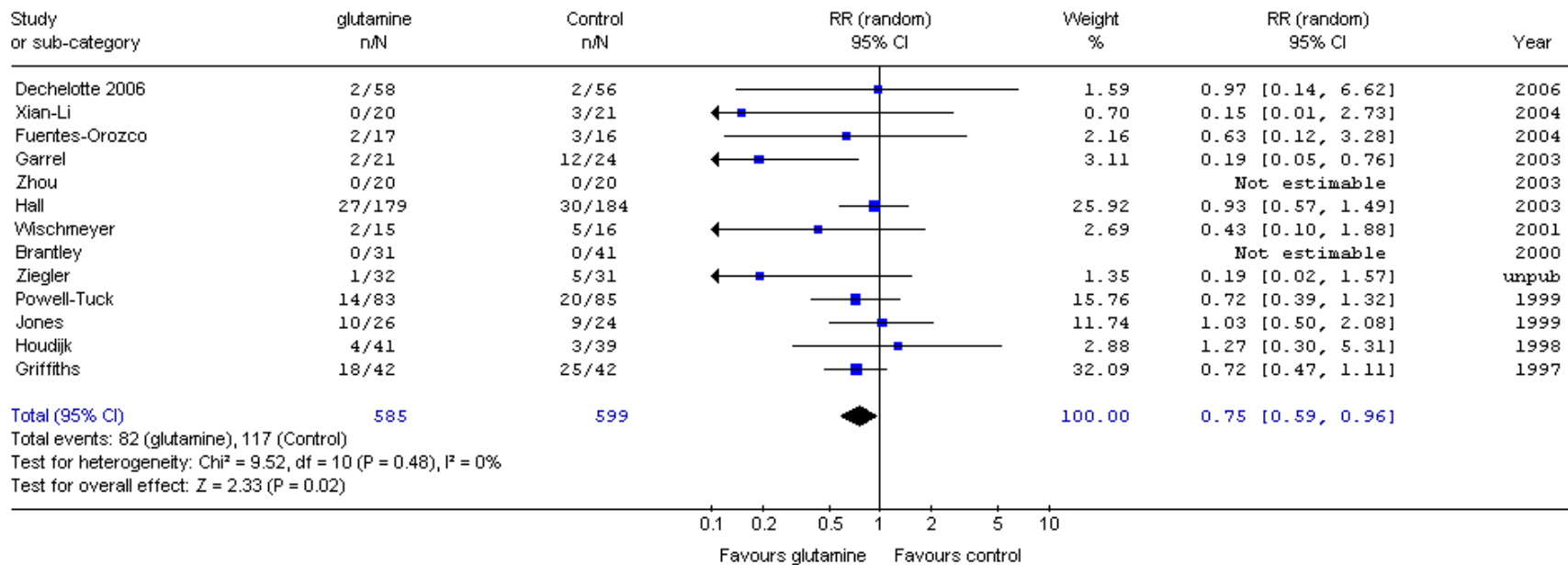


Review: glutamine New review
 Comparison: 02 Parenteral Glutamine vs Control
 Outcome: 02 LOS

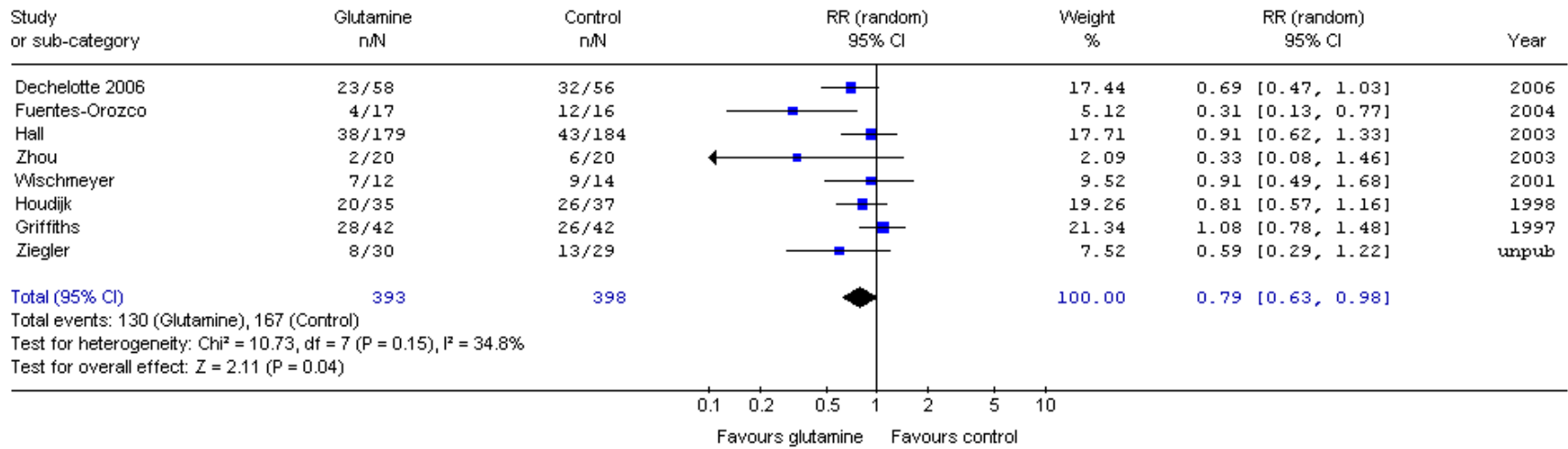


Overall Glutamine Supplementation (studies of Enteral and Parenteral supplementation)

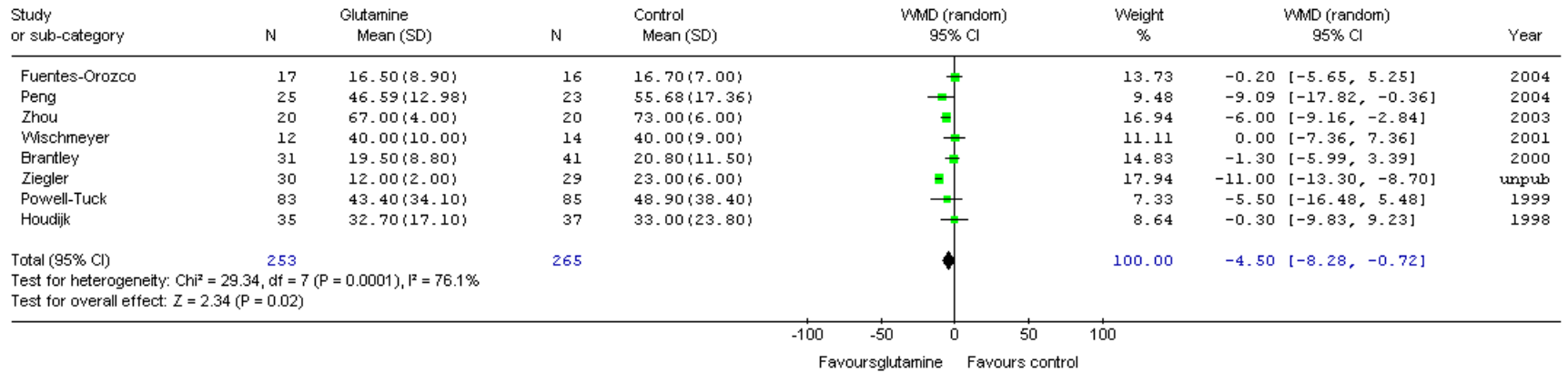
Review: glutamine New review
 Comparison: 03 Glutamine vs Control
 Outcome: 01 mortality



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 PN: Glutamine

(Reviewers: Ulrich Suchner, Minto Jain)

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.	Griffiths	Nutrition 1997	√		
2.	Griffiths	Nutrition 2002	√		
3.	Powell-Tuck	Gut 1999	√		
4.	Wischmeyer	Crit Care Med 2001	√		
5.	Goeters	CC Medicine 2002	√		
6.	Dechelotte	CC Medicine 2006	√		
7.	Umpleby	Nutrition 2002		√	No significant outcomes
8.	Ziegler	Abstract N. Week	√		
9.	Fuentes-Orozco	Clin Nutr 2004	√		
10.	Ockenga	Clin Nutr 2002		√	Not ICU patients
11.	Zhou	Clin Nutr Suppl 2004	√		
12.	Xian-Li	Clin Nutr Suppl 2004	√		
13.	Jing-Xiang	Clin Nutr Suppl 2004		√	Not ICU patients
14.	Jiang	Clin Nutr Suppl 2004		√	Surgical Patients
15.	DeBeaux	Nutrition 1998		√	Not ICU patients (excluded respiratory failure patients)
16.	Tjader	Intensive Care Med 2004		√	Intervention consisted of varying doses of glutamine
17.	Zeigler	Intensive Care Med 2005		√	Sub group of earlier study already included

I = included, E = excluded

References

1. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* Apr;13(4):295-302, 1997.
2. Griffiths RD, Allen KD, Andrews FJ, Jones C. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. *Nutrition*. 2002 Jul-Aug; 18(7-8): 546-52.
3. Powell-Tuck J, Jamieson CP, Bettany GE, Obeid O, Fawcett HV, Archer C, Murphy DL. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. *Gut*. 1999 Jul; 45(1): 82-8.
4. Wischmeyer PE, Lynch J, Liedel J, Wolfson R, Riehm J, Gottlieb L, Kahana M. Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. *Crit Care Med*. 2001 Nov; 29(11): 2075-80.
5. Goeters C, Wenn A, Mertes N, Wempe C, Van Aken H, Stehle P, Bone HG. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med*. 2002 Sep; 30(9): 2032-7.
6. Fuentes-Orozco C, Anaya-Prado R, Gonzalez-Ojeda A, Arenas-Marquez H, Cabrera-Pivaral C, Cervantes-Guevara G, Barrera-Zepeda LM. L-alanyl-L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. *Clin Nutr*. 2004 Feb;23(1):13-21.
7. Zeigler TR, Fernandez-Estivariz C, Griffith P et al. Parenteral Nutrition Supplemented with alanyl-glutamine dipeptide decreases infectious morbidity and improves organ function in critically ill post-operative patients: results of a double-blind, randomized, controlled pilot study. *Nutrition Week Abstracts 2004*: 023: 52.
8. Zhou Ye-Ping et al. The effects of supplemental glutamine dipeptide on gut integrity and clinical outcomes after major escharectomy in severe burns: a randomized, double blind, controlled clinical trial. *Clinical Nutrition Supplements 2004*(1):55.
9. Xian-Li He et al. Effect of total parenteral nutrition (TPN) with and without glutamine dipeptide supplementation on outcome in severe acute pancreatitis (SAP). *Clinical Nutrition Supplements 2004*(1):43.
10. Dechelotte P, Hasselman M et al. L-Alanyl-L-glutamine dipeptide-supplemented totalparenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients : The French controlled, randomized, double-blind, multicentre study. *Critical Care Medicine* 2006.