9.4 Composition of Parenteral Nutrition: Glutamine Supplementation January 31st 2009

Recommendation:

Based on 4 level 1 studies and 13 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is strongly 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 large reduction in mortality, hospital length of stay and a moderate reduction in infectious complications associated with the use of parenteral glutamine. There was concern about the large heterogeneity seen in the aggregated data on hospital length of stay. Given the similar signals on reduced mortality and infections from majority of the studies from various settings, the likelihood of the results being replicated in other settings is good. The cost and lack of availability of parenteral glutamine limits the applicability of this intervention. 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). Based on the three trials in which EN was used predominantly, whether parenteral glutamine has an effect in patients fed enterally is unknown. The effect of enteral glutamine is discussed separately (section 4.1(e)).

	Definition	Score 0, 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 Infections 3 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	3 Infections 3 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 or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	3
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	2
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	3
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.	2
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	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)
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

9.4 Composition of Parenteral Nutrition: Glutamine supplementation January 31st 2009

Question:
Compared to standard parenteral nutrition (PN), does glutamine-supplemented PN result in improved clinical outcomes in critically ill patients?

Summary of Evidence:
There were 17 studies on IV glutamine supplementation included that were done in ICU patients ranging from pancreatitis, trauma, burns and sepsis. While in majority of the studies, the intervention and control groups received parenteral nutrition/amino acids, in a few studies, patients predominantly received enteral nutrition (Wischmeyer 2001, Palmese 2006 and Cai 2007). In one study, the dosage of glutamine was questionably lower than the other studies (0.002 gm/kg/day) and hence the data from this study was not included in the meta-analyses (Yang 2007).

Mortality: When the 4 level 1 and 13 level 2 studies were aggregated, glutamine supplemented PN was associated with a significant reduction in overall mortality (RR 0.71, 95%CI 0.55, 0.92, p =0.008) (figure 1) and a significant reduction in hospital mortality (RR 0.71, 95% CI 0.54,0.92, p =0.01) (figure 2). When the studies in which patients predominantly received enteral nutrition were aggregated, glutamine supplemented PN had no effect on mortality (RR = 0.78, 95 % CI 0.50, 1,21, p = 0.27) (figure 3).

Infections: When the 3 level 1 studies and 6 level 2 studies were aggregated, glutamine supplemented PN was associated with a significant reduction in infectious complications (RR =0.76, 95%CI 0.62,0.93, p =0.008) (figure 4).

LOS: When the 3 level 1 studies and 6 level 2 studies were aggregated, glutamine supplemented PN was associated with a significant reduction in hospital LOS (WMD -3.14, 95% CI -6.03, -0.24, p =0.03) (See figure 5). Glutamine supplemented PN had no effect on ICU length of stay (WMD -0.30, 95 % CI -1.45, 0.85, p = 0.61) (figure 6).

Conclusions:
1) Glutamine supplemented PN is associated with a significant reduction in mortality in critically ill patients.
2) Glutamine supplemented PN s associated with a significant reduction in infectious complications in critically ill patients.
3) Glutamine supplemented PN is associated with a significant reduction in hospital length of stay 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 Dose of Lglutamine gm/kg/day	Mortality # (%)† Experiment	Mortality # (%)† Control	Infections # (%)‡ Experiment	Infections # (%)‡ Control	Length of Stay (days) Experiment	Length of Stay (days) Control
1) Griffiths 1997 and 2002	Mixed ICU Population N = 84	C.Random: Yes ITT: Yes Blinding: Yes (11)	PN, 0.26 IV glutamine + PN vs. PN, isocaloric, isonitrogenous.	Hospital 18/42(42.9)	Hospital 25/42(59.5)	28/42(67)	26/42(62)	ICU 10.5 (6-19)*	ICU 10.5 (6-24)*
2) Powell-Tuck 1999	Mixed ICU/hosp population N = 168	C.Random: Yes ITT: Yes Blinding: Yes (8)	PN. 0.26 IV glutamine + PN vs. PN, isocaloric, isonitrogenous.	14/83 (16.9)	20/85 (23.5)	NR	NR	Hospital 43.4+/-34.1 (83)	Hospital 48.9+/-38.4 (85)
3)Wischmeyer 2001	Critically ill burns N = 31	Random: Not sure ITT: No Blinding Yes (8)	PN, 0.57 IV glutamine + EN or EN+PN vs. AAcids +PN or EN or EN+PN, isocaloric, isonitrogenous.	2/15 (13.0)	5/16 (31.0)	7/12 (58.3)	9/14 (64.3)	Hospital 40+/-10 (12)	Hospital 40+/-9 (14)
4) Goeters 2002*	Surgical ICU patients N = 68	C.Random: not sure ITT: no Blinding: no	PN, 0.2 IV glutamine + PN or EN or EN+PN vs. PN or EN or EN+PN	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)*	NR	NR	Average LOS* ICU 21.3 ± 13.5	20.8 ± 9.1 Hospital 46 ± 49.1 (33) 39.4 ± 31.1 (35)
5) Fuentes-Oroczo 2004	Secondary peritonitis Requiring TPN N =33	C.Random: yes ITT: yes Blinding: double (11)	PN, 0.27 IV glutamine + PN vs. PN, isocaloric, isonitrogenous.	2/17 (12)	3/16 (19)	4/17 (23)	12/16 (75)	ICU 7.2 ± 9.2	7.3 ± 4.5 Hospital 16.5 ± 8.9 16.7 ± 7
6) Zhou 2004	Severe Burns N = 30	C.Random: yes ITT: yes Blinding: double (11)	PN, 0.35 IV glutamine + PN vs. PN, isocaloric, isonitrogenous.	NR	NR	3/15 (20)	4/15 (26)	Hospital 42 ± 7.0	46 ± 6.6
7) Xian-Li 2005	Severe acute pancreatitis N = 69	C.Random: yes ITT: no Blinding: no (5)	PN, 0.4 IV glutamine + PN vs. PN	0/20	3/21 (14)	# Complications 4	11	Hospital 25.3 ± 7.6	28.6 ± 6.9
8) Dechelotte 2006	Multiple trauma, surgery,sepsis , pancreatitis from 16 ICUs N = 114	C.Random: NR ITT: yes Blinding: double N/A	PN, 0.35 IV glutamine + PN vs. PN, isocaloric, isonitrogenous.	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) 11.5 (3-121) Hospital 30 (1-560)	26 (4-407)

9) Palmese 2006	Mixed ICU N = 84	C.Random: yes ITT: yes Blinding: single (10)	PN, 0.14 IV glutamine + EN with FOS vs. EN without FOS	ICU 6/42 (14)	ICU 8/42 (19)	All infections 13/42 (31) Pneumonia 2/42 (5)	All infections 21/42 (50) Pneumonia 6/42 (14)	ICU 12 ± 4.6	ICU 13 ± 3.4
10) Cai 2007	Elderly, severe sepsis N = 110	C.Random: not sure ITT: yes Blinding: no (10)	PN, 0.19 IV glutamine + PN or EN+PN vs. PN or EN+PN isocaloric, isonitrogenous	28 day 17/55 (31)	28 day 20/55 (36)	NR	NR	ICU 22.1 ± 4.9	ICU 23.8 ± 5.1
11) Luo 2007***	Medical Surgical N=44	C.Random: not sure ITT: no Blinding: double (9)	PN, 0.50 IV glutamine + EN vs. IV 15% Clinisol (placebo) +EN isocaloric, isonitrogenous	Hospital 0/11	Hospital 0/9	NR	NR	ICU 7.6 ± 0.7 (14)	ICU 6.9 ± 0.9 (9)
12) Sahin 2007	Acute pancreatitis N = 40	C.Random: not sure ITT: yes Blinding: single (9)	PN, 0.3 IV glutamine + PN vs. PN, isocaloric, isonitorgenous.	Hospital 2/20 (10)	Hospital 6/20 (30)	NR	NR	Hospital 14.2 ± 4.4	Hospital 16.4 ± 3.9
13) Yang 2007α	Brain injury Neurosurgical ICU N= 46	C.Random: not sure ITT: yes Blinding: no (6)	PN, 0.002 IV glutamine + PN vs. PN	Hospital 5/23 (22)	Hospital 9/23 (39)	NR	NR	ICU 10 ± 3.5	ICU 18 ± 5.6
14) Duska 2008	Trauma N = 30	C.Random: not sure ITT: yes Blinding: single (8)	PN, 0.3 IV glutamine + PN vs. normal saline + supplemental PN isocaloric, isonitrogenous	ICU 2/10 (20)	ICU 0/10	NR	NR	ICU 23 (median)	ICU 24 (median)
15) Estivariz 2008	Pancreatic and non pancreatic surgery N = 63	C.Random: not sure ITT: no** Blinding: double (9)	PN, 0.5 IV glutamine + PN vs. PN isocaloric, isonitrogenous	Hospital 1/32 (3)	Hospital 6/31 (19)	Pneumonia 13/30 (43)	Pneumonia 16/29 (55)	Hospital* 20 ± 2 ICU* 12 ± 2	Hospital* 30 ± 6 ICU* 23 ± 6
16) Fuentes-Oroczo 2008	Acute pancreatitis requiring admission N = 44	C.Random: not sure ITT: yes Blinding: double (12)	PN, 0.4 IV glutamine + PN vs. PN isocaloric, isonitrogenous	ICU 2/22 (9)	ICU 5/22 (23)	9/22 (41)	16/22 (73)	Hospital 30.18 ± 10.42 ICU 11 ± 11.7	Hospital 26.59 ± 13.3 ICU 11.14 ± 7.41
17) Perez-BarceNR 2008	Mixed ICU N = 30	C.Random: not sure ITT: yes Blinding: single (10)	PN, 0.35 IV glutamine + PN vs. PN isocaloric, isonitrogenous	Hospital 3/15 (20)	Hospital 0/15	11/15 (73)	13/15 (87)	Hospital 35.5 ± 33.6 ICU 22.9 ± 20.6	Hospital 42.9 ± 28.8 ICU 20.5 ± 16.0

C.Random: Concealed randomization median (range)
ITT: Intent to treat
NA: not applicable
EN: Enteral nutrition; TPN Total parenteral nutrition
± ( ) : Mean ± Standard deviation (number)
NR: Not reported
† Hospital mortality unless stated otherwise
‡ Number of patients with infections unless stated otherwise

* Data from a sub group, hence not included in meta-analysis
**-Data for mortality is ITT, infections is non-ITT.
*** Data from EN glutamine group not shown here, appears in EN glutamine section
α Unable to confirm the low dose from authors (0.002 gm/kg/day) hence data not included in the meta-analyses
∂ Data from growth hormone group not shown here

Figure 1 Overall Mortality

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

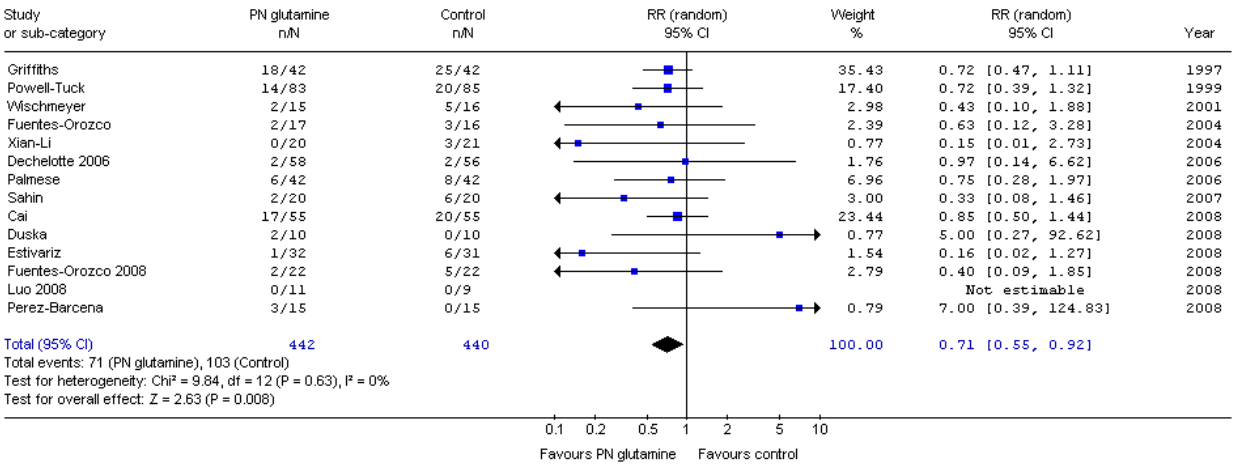


Figure 2. Hospital Mortality

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

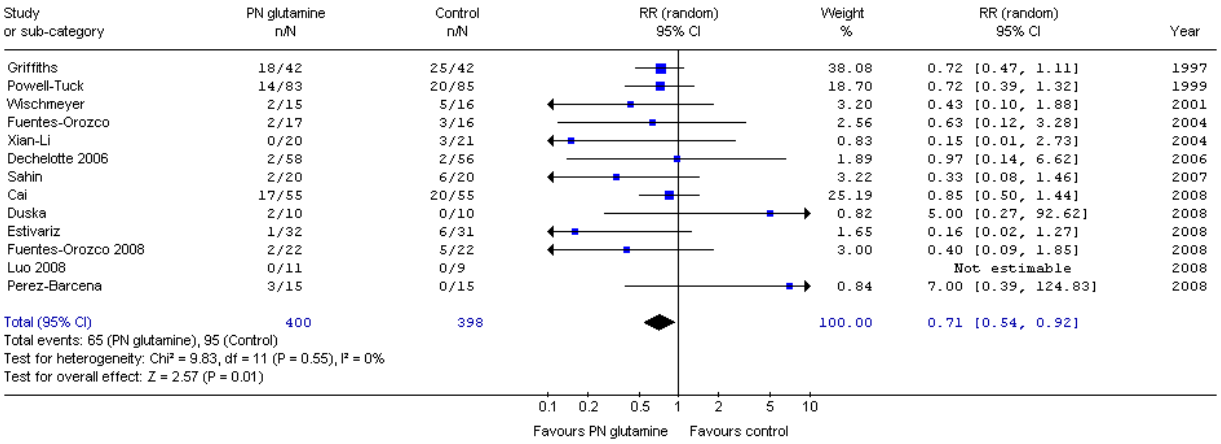


Figure 3 Subgroup of studies in which patients predominantly received Enteral nutrition

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

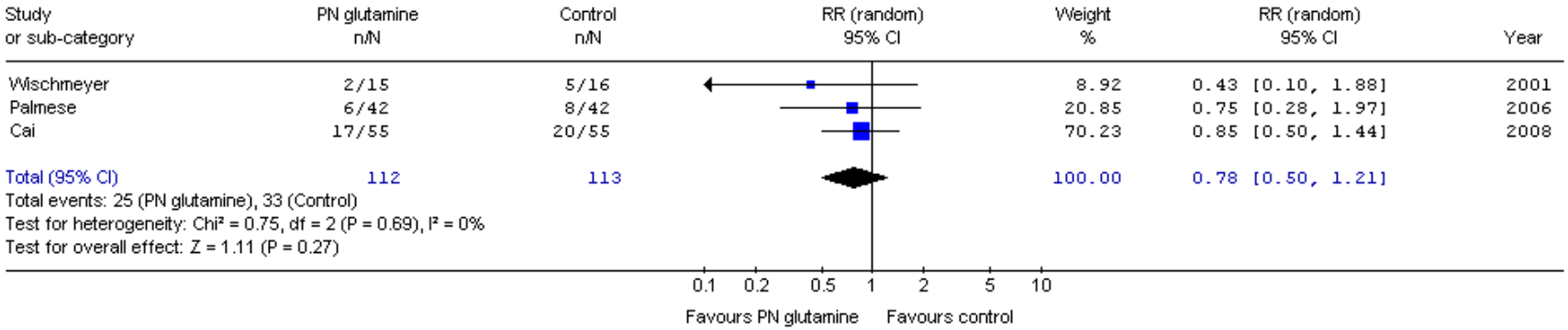


Figure 4

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

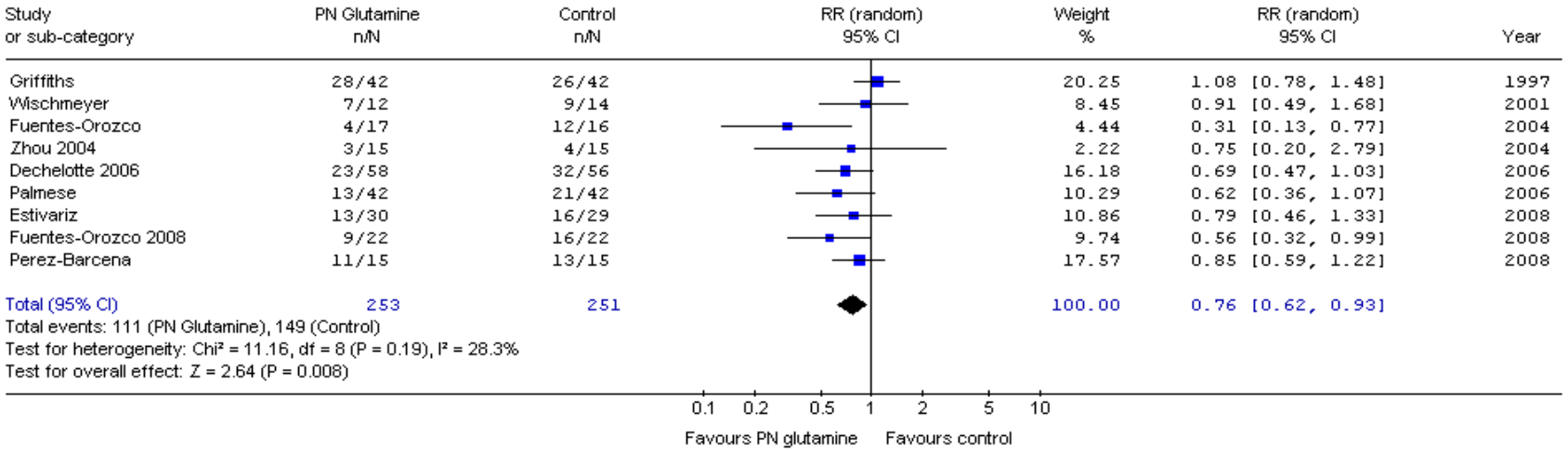


Figure 5. Hospital Length of Stay

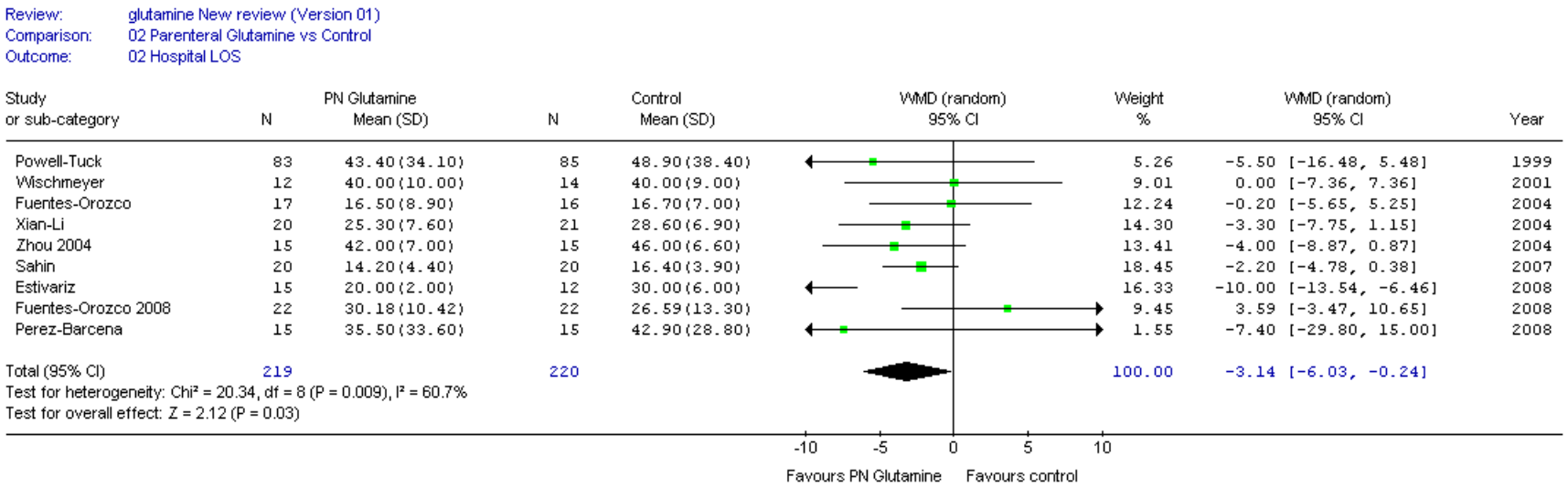
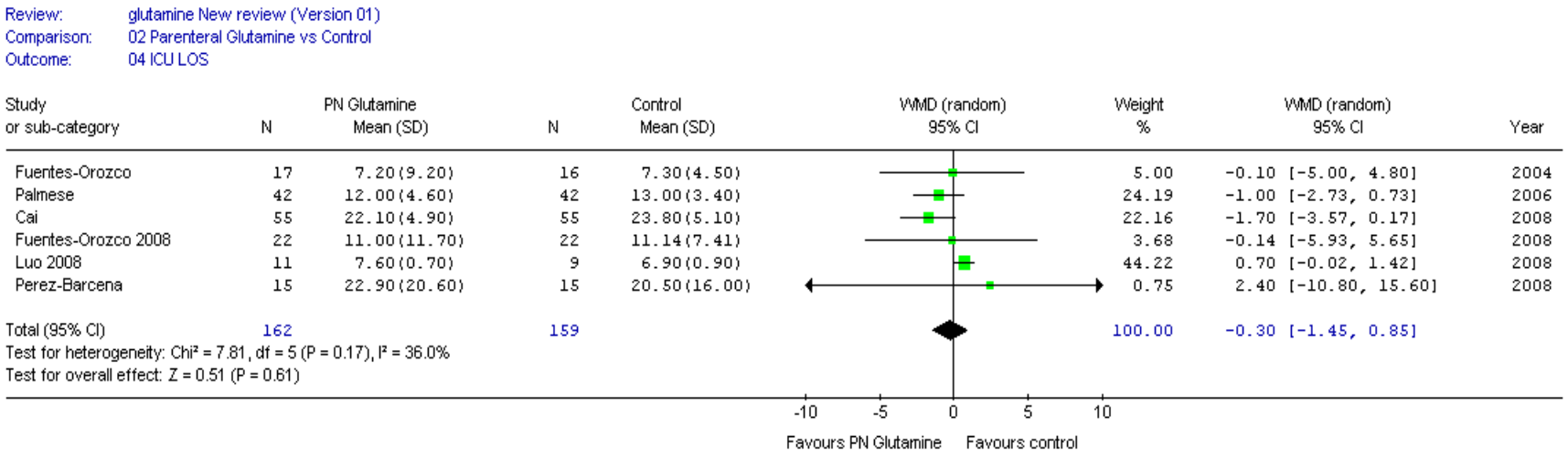
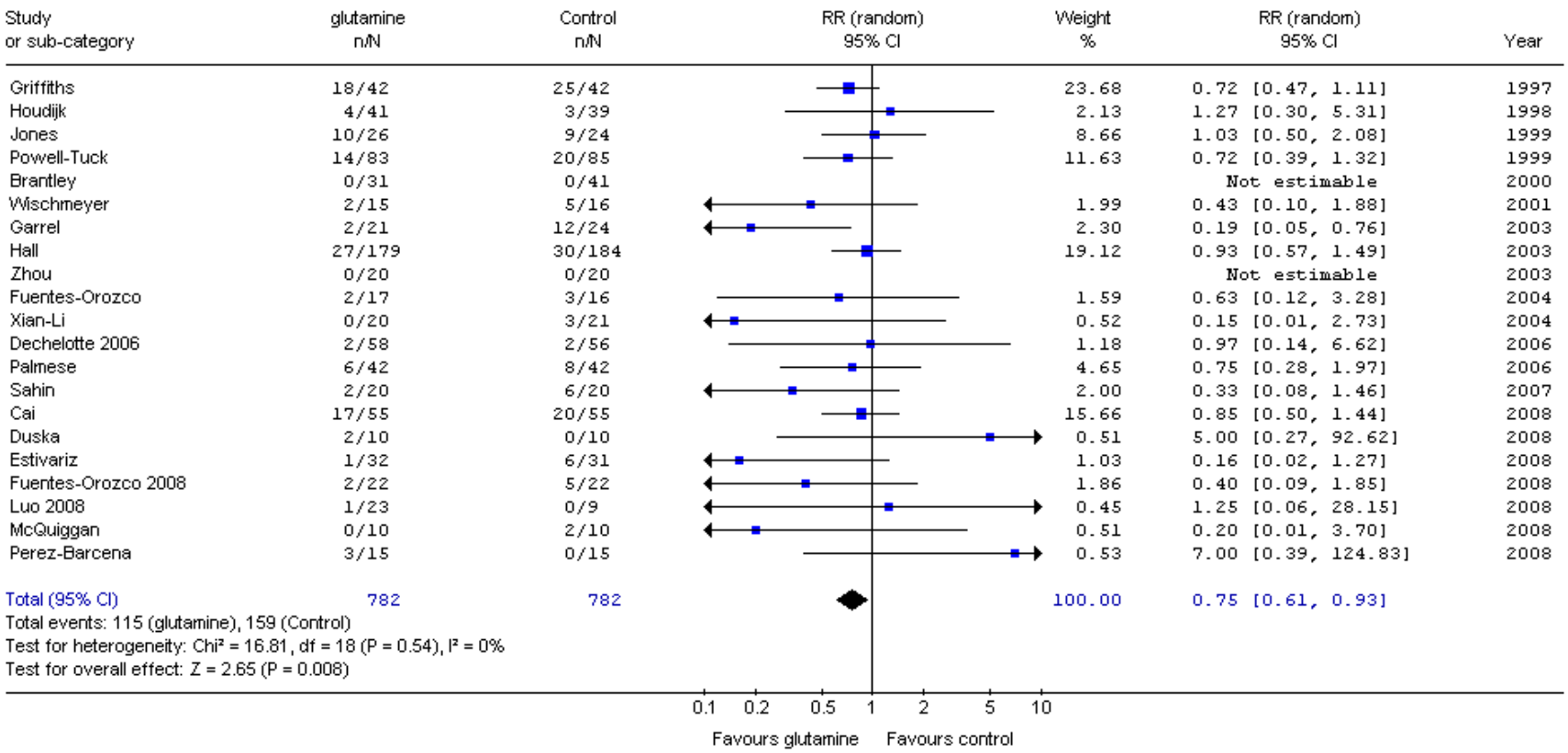


Figure 6. ICU Length of Stay

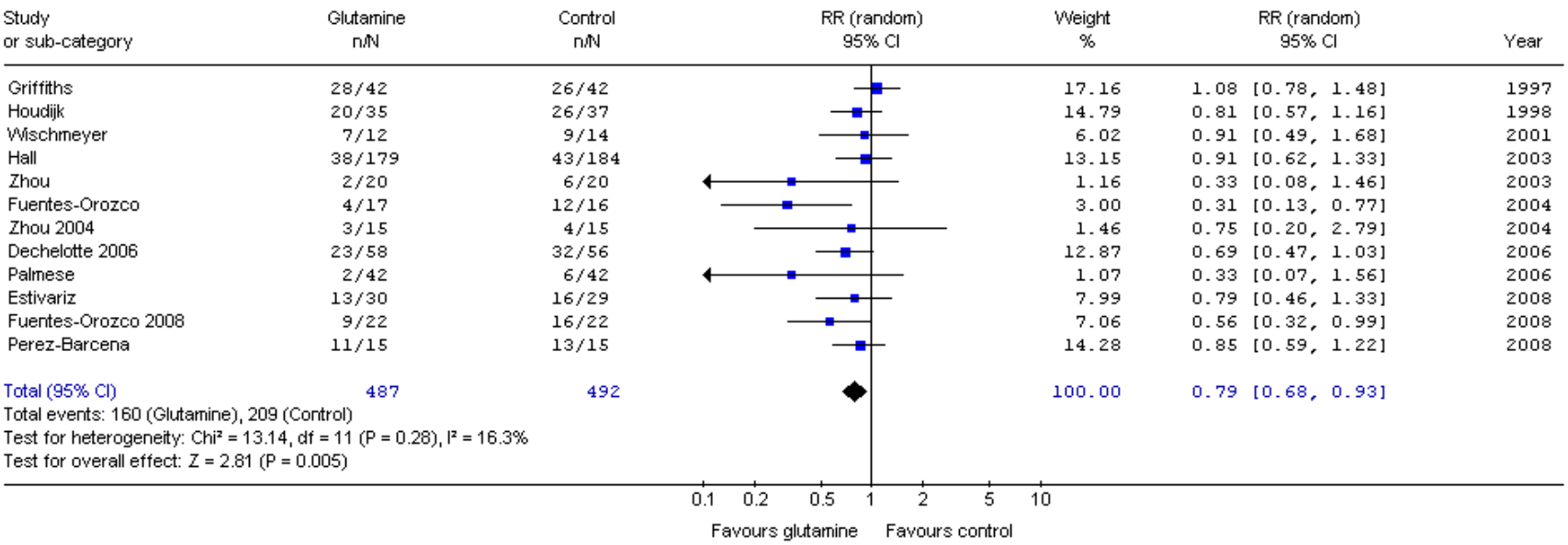


Overall Glutamine Supplementation (studies of Enteral and Parenteral supplementation)

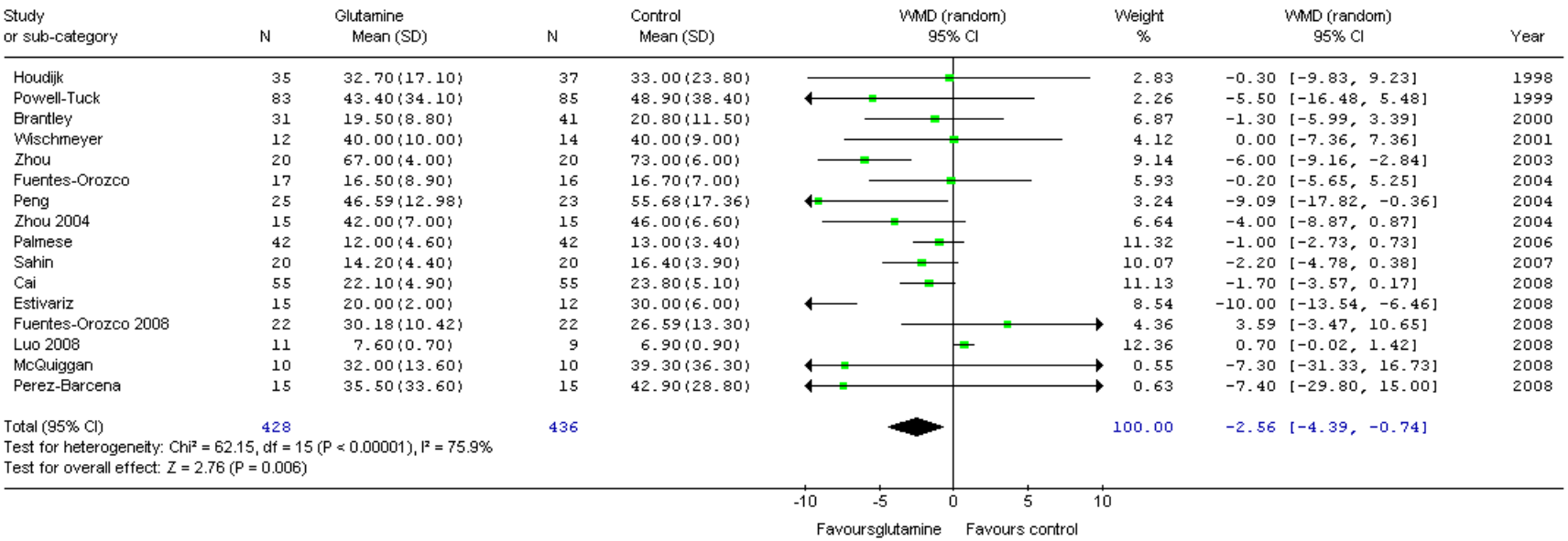
Review: glutamine New review (Version 01)
Comparison: 03 Glutamine vs Control
Outcome: 01 mortality



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: 9.4 (c) Composition of PN: 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: PN/IV Glutamine supplementation
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	DeBeaux	Nutrition 1998		√	Not ICU patients (excluded respiratory failure patients)
3	Powell-Tuck	Gut 1999	√		
4	Hajek	Anesteziologie a neodkladne pece			Couldn't get mortality information from authors
5	Wischmeyer	Crit Care Med 2001	√		
6	Umpleby	Nutrition 2002		√	No significant outcomes
7	Ockenga	Clin Nutr 2002		√	Not ICU patients
8	Griffths	Nutrition 2002	√		
9	Goeters	CC Medicine 2002	√		
10	Flaring	Clinical Science 2003		√	Cancer pts
11	Fuentes-Orozco	Clin Nutr 2004	√		
12	Hulsewe	Clin Nutr 2004			Elective surgery pts
13	Jiang	Clin Nutr Suppl 2004		√	Surgical patients
14	Jing-Xiang	Clin Nutr Suppl 2004		√	Not ICU patients
15	Tjader	Intensive Care Med 2004		√	Intervention consisted of varying doses of glutamine
16	Xian-Li	Clin Nutr Suppl 2004	√		
17	Ziegler	Abstract Nutr Week 2004		√	Preliminary study, replaced by Estivariz 2008
18	Zhou	Clin Nutr Suppl 2004	√		
19	Berg	Amino Acids 2005		√	No clinical outcomes
20	Blijlevens	Support Care Cancer 2005		√	Not ICU pts
21	Lin	World J Gastroenterol 2005		√	Surgery pts
22	Ockenga	Eur J Clin Nutr 2005		√	Not ICU pts
23	Yao	Clinical Nutr 2005		√	Surgery pts
24	Ziegler	Intensive Care Med 2005		√	Sub-group of earlier study already included
25	Dechelotte	Crit Care Med 2006	√		
26	Palmese	Nutr Therapy & Metabolosm 2006	√		
27	Zheng	World J Gastroenterol 2006		√	Elective surgery pts
28	Sahin	Eur J Clin Nutr 2007	√		
29	Yang	Chin J Traumatology 2007	√		
30	Cai	J Organ Dysfunction 2008	√		
31	Duska	Crit Care Med 2008	√		
32	Estivariz	JPEN J Parenter Enteral Nutr 2008	√		
33	Fuentes-Oroczo	JPEN J Parenter Enteral Nutr 2008	√		
34	Luo	Clin Nutr 2008	√		
35	Perez-Barcena	Nutrition 2008	√		

36	Yeh	Langenbecks Arch Surg 2008		√	Elective surgery pts

I = included, E = excluded

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