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 listeda 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 outcomesa higher score indicates presence of more of these features in the trials appraised	2
Homogeneity or Reproducibility	Similar direction of findings among trialsa 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 listeda 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 listeda 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 =0.001) (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.

Study	Population	Methods	Intervention	Mortal	ity # (%)†	Infectior	ıs # (%) <u>‡</u>	Length of	Stay (days)
	•	(score)	Dose of Lglutamine gm/kg/day	Experiment	Control	Experiment	Control	Experiment	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	Avera 10 21.3 \pm 13.5 Hos 46 \pm 49.1 (33)	ge LOS* 20.8 ± 9.1 spital $39.4 \pm 31.1 (35)$
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)	7.2 ± 9.2 Hosp 16.5 ± 8.9	CU 7.3 ± 4.5 ital 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)	Hos 42 ± 7.0	bital 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)	# Comp 4	lications 11	Hosp 25.3 ± 7.6	ital 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)	10 12.5 (1-430) Hos 30 (1-560)	CU 11.5 (3-121) pital 26 (4-407)

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

9) Palmese 2006	Mixed ICU N = 84	C.Random: yes ITT: yes Blinding: single	PN, 0.14 IV glutamine + EN with FOS vs.	ICU 6/42 (14)	ICU 8/42 (19)	All infections 13/42 (31) Pneumonia	All infections 21/42 (50) Pneumonia	ICU 12 ± 4.6	ICU 13 ± 3.4
10) Cai 2007	Elderly, severe sepsis N = 110	(10) C.Random: not sure ITT: yes Blinding: no (10)	EN without FOS PN, 0.19 IV glutamine + PN or EN+PN vs. PN or EN+PN isocaloric,	28 day 17/55 (31)	28 day 20/55 (36)	2/42 (5) NR	6/42 (14) 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)

EN: Enteral nutrition; TPN Total parenteral nutrition

 \pm (): Mean \pm Standard deviation (number) NR: Not reported

NA: not applicable

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

ITT: Intent to treat

-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

† Hospital mortality unless stated otherwise

‡ Number of patients with infections unless stated otherwise

Figure '	1 Overall	Mortality
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glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 03 Mortality Review: Comparison: Outcome:

Study or sub-category	PN glutamine n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Griffiths	18/42	25/42		35.43	0.72 [0.47, 1.11]	1997
Powell-Tuck	14/83	20/85		17.40	0.72 [0.39, 1.32]	1999
Wischmeyer	2/15	5/16	← ■	2.98	0.43 [0.10, 1.88]	2001
Fuentes-Orozco	2/17	3/16		2.39	0.63 [0.12, 3.28]	2004
Xian-Li	0/20	3/21	←	0.77	0.15 [0.01, 2.73]	2004
Dechelotte 2006	2/58	2/56			0.97 [0.14, 6.62]	2006
Palmese	6/42	8/42		6.96	0.75 [0.28, 1.97]	2006
Sahin	2/20	6/20	← ● ↓	3.00	0.33 [0.08, 1.46]	2007
Cai	17/55	20/55	_	23.44	0.85 [0.50, 1.44]	2008
Duska	2/10	0/10			5.00 [0.27, 92.62]	2008
Estivariz	1/32	6/31	← ■ ───────────────────────────────────	1.54	0.16 [0.02, 1.27]	2008
Fuentes-Orozco 2008	2/22	5/22	← ● ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	2.79	0.40 [0.09, 1.85]	2008
Luo 2008	0/11	0/9			Not estimable	2008
Perez-Barcena	3/15	0/15		● 0.79	7.00 [0.39, 124.83]	2008
Total (95% Cl) Total events: 71 (PN glutamine	442), 103 (Control)	440	•	100.00	0.71 [0.55, 0.92]	
Test for heterogeneity: Chi ² = 9 Test for overall effect: Z = 2.6	9.84, df = 12 (P = 0.63), l² = 0' 3 (P = 0.008)	%				
			0.1 0.2 0.5 1 2	5 10		
			Favours PN glutamine Favours co	ntrol		

Figure 2. Hospital Mortality Review: glutamine New review (Version 01) Comperison: 02 Parenteral Glutamine vs Control 03 Mortality

Study or sub-category	PN glutarnine n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Griffiths	18/42	25/42		38.08	0.72 [0.47. 1.11]	1997
Powell-Tuck	14/83	20/85		18.70	0.72 [0.39, 1.32]	1999
Wischmever	2/15	5/16	←	3.20	0.43 [0.10, 1.88]	2001
Fuentes-Órozco	2/17	3/16	·	2.56	0.63 [0.12, 3.28]	2004
Xian-Li	0/20	3/21	← ■	0.83	0.15 [0.01, 2.73]	2004
Dechelotte 2006	2/58	2/56	· ·	1.89	0.97 [0.14, 6.62]	2006
Sahin	2/20	6/20	←	3.22	0.33 [0.08, 1.46]	2007
Cai	17/55	20/55	·	25.19	0.85 [0.50, 1.44]	2008
Duska	2/10	0/10		→ 0.82	5.00 [0.27, 92.62]	2008
Estivariz	1/32	6/31	← ■	1.65	0.16 [0.02, 1.27]	2008
Fuentes-Orozco 2008	2/22	5/22	▲	3.00	0.40 [0.09, 1.85]	2008
Luo 2008	0/11	0/9			Not estimable	2008
Perez-Barcena	3/15	0/15			7.00 [0.39, 124.83]	2008
Total (95% CI)	400	398	•	100.00	0.71 [0.54, 0.92]	
Total events: 65 (PN glutamine)), 95 (Control)		+			
Test for heterogeneity: Chi ² = 9	9.83, df = 11 (P = 0.55), l ² = 0	%				
Test for overall effect: Z = 2.57	7 (P = 0.01)					
				<u> </u>		
			0.1 0.2 0.5 1 2	5 10		

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

Comparison: Outcome:	glutamine New review 02 Parenteral Glutamine vs Control 03 Mortality						
Study or sub-category	PN glutamine n/N	Control n/N		RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Wischmeyer	2/15	5/16	•		8.92	0.43 [0.10, 1.88]	2001
Palmese	6/42	8/42	-	_	20.85	0.75 [0.28, 1.97]	2006
Cai	17/55	20/55			70.23	0.85 [0.50, 1.44]	2008
Total (95% Cl) Total events: 25 Test for heterog Test for overall 6	112 (PN glutamine), 33 (Control) eneity: Chi ² = 0.75, df = 2 (P = 0.69), effect: Z = 1.11 (P = 0.27)	113 ² = 0%		-	100.00	0.78 [0.50, 1.21]	
			0.1 0.2	0.5 1 2	5 10		
			Favours PN	glutamine Favours co	ntrol		
Figure 4 Review:	glutamine New review (Version 01)	I					
Figure 4 Review: Comparison: Outcome: Study or sub-category	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N	Control n/N		RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Figure 4 Review: Comparison: Outcome: Study or sub-category	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28 (42	Control n/N		RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmever	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12	Control n/N 26/42 9/14		RR (random) 95% Cl	Weight % 20.25 8.45	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49] 1.68]	Year 1997 2001
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmeyer Eventes-Orozoc	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12 4/17	Control n/N 26/42 9/14 12/16		RR (random) 95% Cl	Weight % 20.25 8.45 4.44	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49, 1.68] 0.31 [0.13, 0.77]	Year 1997 2001 2004
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmeyer Fuentes-Orozoc Zhou 2004	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12 0 4/17 3/15	Control n/N 26/42 9/14 12/16 4/15		RR (random) 95% Cl	Weight % 20.25 8.45 4.44 2.22	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49, 1.68] 0.31 [0.13, 0.77] 0.75 [0.20, 2,79]	Year 1997 2001 2004 2004
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmeyer Fuentes-Orozoc Zhou 2004 Dechelotte 2006	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12 0 4/17 3/15 6 23/58	Control n/N 26/42 9/14 12/16 4/15 32/56		RR (random) 95% Cl	Weight % 20.25 8.45 4.44 2.22 16.18	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49, 1.68] 0.31 [0.13, 0.77] 0.75 [0.20, 2.79] 0.69 [0.47, 1.03]	Year 1997 2001 2004 2004 2006
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmeyer Fuentes-Orozco Zhou 2004 Dechelotte 2006 Palmese	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12 0 4/17 3/15 6 23/58 13/42	Control n/N 26/42 9/14 12/16 4/15 32/56 21/42		RR (random) 95% Cl	Weight % 20.25 8.45 4.44 2.22 16.18 10.29	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49, 1.68] 0.31 [0.13, 0.77] 0.75 [0.20, 2.79] 0.69 [0.47, 1.03] 0.62 [0.36, 1.07]	Year 1997 2001 2004 2004 2006 2006
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmeyer Fuentes-Orozco Zhou 2004 Dechelotte 2006 Palmese Estivariz	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12 0 4/17 3/15 3 23/58 13/42 13/30	Control n/N 26/42 9/14 12/16 4/15 32/56 21/42 16/29		RR (random) 95% Cl	Weight % 20.25 8.45 4.44 2.22 16.18 10.29 10.86	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49, 1.68] 0.31 [0.13, 0.77] 0.75 [0.20, 2.79] 0.69 [0.47, 1.03] 0.62 [0.36, 1.07] 0.79 [0.46, 1.33]	Year 1997 2001 2004 2004 2006 2008
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmeyer Fuentes-Orozco Zhou 2004 Dechelotte 2006 Palmese Estivariz Fuentes-Orozco	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12 0 4/17 3/15 3 23/58 13/42 13/30 0 2008 9/22	Control n/N 26/42 9/14 12/16 4/15 32/56 21/42 16/29 16/22		RR (random) 95% Cl	Weight % 20.25 8.45 4.44 2.22 16.18 10.29 10.86 9.74	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49, 1.68] 0.31 [0.13, 0.77] 0.75 [0.20, 2.79] 0.69 [0.47, 1.03] 0.62 [0.36, 1.07] 0.79 [0.46, 1.33] 0.56 [0.32, 0.99]	Year 1997 2001 2004 2004 2006 2008 2008
Figure 4 Review: Comparison: Outcome: Study or sub-category Griffiths Wischmeyer Fuentes-Orozoc Zhou 2004 Dechelotte 2006 Palmese Estivariz Fuentes-Orozoc Perez-Barcena	glutamine New review (Version 01) 02 Parenteral Glutamine vs Control 01 Infectious Complications PN Glutamine n/N 28/42 7/12 0 4/17 3/15 5 23/58 13/42 13/30 0 2008 9/22 11/15	Control n/N 26/42 9/14 12/16 4/15 32/56 21/42 16/29 16/22 13/15		RR (random) 95% Cl	Weight % 20.25 8.45 4.44 2.22 16.18 10.29 10.86 9.74 17.57	RR (random) 95% Cl 1.08 [0.78, 1.48] 0.91 [0.49, 1.68] 0.31 [0.13, 0.77] 0.75 [0.20, 2.79] 0.69 [0.47, 1.03] 0.62 [0.36, 1.07] 0.79 [0.46, 1.33] 0.56 [0.32, 0.99] 0.85 [0.59, 1.22]	Year 1997 2001 2004 2004 2006 2006 2008 2008 2008 2008

Favours PN glutamine Favours control

Figure 5. Hospital Length of Stay

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

Study or sub-category	N	PN Glutamine Mean (SD)	N	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl	Year
Powell-Tuck	83	43.40(34.10)	85	48.90(38.40)	• • •	5.26	-5.50 [-16.48, 5.48]	1999
Wischmeyer	12	40.00(10.00)	14	40.00(9.00)	_	9.01	0.00 [-7.36, 7.36]	2001
Fuentes-Orozco	17	16.50(8.90)	16	16.70(7.00)		12.24	-0.20 [-5.65, 5.25]	2004
Xian-Li	20	25.30(7.60)	21	28.60(6.90)	_	14.30	-3.30 [-7.75, 1.15]	2004
Zhou 2004	15	42.00(7.00)	15	46.00(6.60)	_	13.41	-4.00 [-8.87, 0.87]	2004
Sahin	20	14.20(4.40)	20	16.40(3.90)	_ _	18.45	-2.20 [-4.78, 0.38]	2007
Estivariz	15	20.00(2.00)	12	30.00(6.00)	←	16.33	-10.00 [-13.54, -6.46]	2008
Fuentes-Orozco 2008	22	30.18(10.42)	22	26.59(13.30)		9.45	3.59 [-3.47, 10.65]	2008
Perez-Barcena	15	35.50(33.60)	15	42.90(28.80)	<	1.55	-7.40 [-29.80, 15.00]	2008
Total (95% Cl)	219		220			100.00	-3.14 [-6.03, -0.24]	
Test for heterogeneity: Chi2 =	20.34, df = 8 (P = 0.009), I² = 60.7%			_			
Test for overall effect: Z = 2.	12 (P = 0.03)							
					-10 -5 0 5	10		
					Favours PN Glutamine Favours c	ontrol		

Figure 6. ICU Length of Stay

Review:	glutamine New review (Version 01)
Comparison:	02 Parenteral Glutamine vs Control
Outcome:	04 ICH LOS

Study or sub-category	N	PN Glutamine Mean (SD)	N	Control Mean (SD)		M	MD (random) 95% Cl)	Weight %		VVMD (random) 95% Cl	Year
Fuentes-Orozco	17	7.20(9.20)	16	7.30(4.50)			_		5.00	-0.10	[-5.00, 4.80]	2004
Palmese	42	12.00(4.60)	42	13.00(3.40)			_-+		24.19	-1.00	[-2.73, 0.73]	2006
Cai	55	22.10(4.90)	55	23.80(5.10)		_			22.16	-1.70	[-3.57, 0.17]	2008
Fuentes-Orozco 2008	22	11.00(11.70)	22	11.14(7.41)			+		3.68	-0.14	[-5.93, 5.65]	2008
Luo 2008	11	7.60(0.70)	9	6.90(0.90)			₽		44.22	0.70	[-0.02, 1.42]	2008
Perez-Barcena	15	22.90(20.60)	15	20.50(16.00)	←				→ 0.75	2.40	[-10.80, 15.60]	2008
Total (95% CI)	162		159				•		100.00	-0.30	[-1.45, 0.85]	
Test for heterogeneity: Chi ² =	7.81, df = 5 (P	= 0.17), I² = 36.0%					1					
Test for overall effect: Z = 0.5	51 (P = 0.61)											
					-10	-5	0	5	10			
					Favours	PN Glutar	mine Favo	urs cont	rol			

Overall Glutamine Supplementation (studies of Enteral and Parenteral supplementation)

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

RR (random) Weight Study glutamine Control RR (random) or sub-category n/N n/N 95% CI % 95% CI Year Griffiths 18/42 25/42 23.68 0.72 [0.47, 1.11] 1997 Houdijk 4/41 3/39 2.13 1.27 [0.30, 5.31] 1998 Jones 10/26 9/24 8.66 1.03 [0.50, 2.08] 1999 Powell-Tuck 14/83 20/85 11.63 0.72 [0.39, 1.32] 1999 Brantley 0/31 0/41 Not estimable 2000 Wischmeyer 2/15 5/16 1.99 0.43 [0.10, 1.88] 2001 Garrel 0.19 [0.05, 0.76] 2/21 12/24 2.30 2003 Hall 27/179 30/184 19.12 0.93 [0.57, 1.49] 2003 Zhou 0/20 0/20 Not estimable 2003 Fuentes-Orozco 2/17 0.63 [0.12, 3.28] 2004 3/16 1.59 Xian-Li 0/20 3/21 0.52 0.15 [0.01, 2.73] 2004 Dechelotte 2006 2/58 2/56 1.18 0.97 [0.14, 6.62] 2006 Palmese 6/42 8/42 4.65 2006 0.75 [0.28, 1.97] Sahin 2/20 6/20 2.00 0.33 [0.08, 1.46] 2007 Cai 17/55 20/55 15.66 0.85 [0.50, 1.44] 2008 Duska 2/10 0/10 0.51 5.00 [0.27, 92.62] 2008 Estivariz 1/32 6/31 1.03 0.16 [0.02, 1.27] 2008 Fuentes-Orozco 2008 2/22 5/22 1.86 0.40 [0.09, 1.85] 2008 Luo 2008 2008 1/23 0/9 0.45 1.25 [0.06, 28.15] McQuiggan 0/10 2/10 0.51 0.20 [0.01, 3.70] 2008 Perez-Barcena 3/15 0/15 0.53 7.00 [0.39, 124.83] 2008 -Total (95% CI) 782 782 100.00 0.75 [0.61, 0.93] Total events: 115 (glutamine), 159 (Control) Test for heterogeneity: $Chi^2 = 16.81$, df = 18 (P = 0.54), $l^2 = 0\%$ Test for overall effect: Z = 2.65 (P = 0.008)0.2 0.5 Ś 0.1 2 10 1

Favours glutamine Favours control

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

Study	Glutamine	Control	RR (random)	VVeight	RR (random)	Voor
	100 N	10/4	35%0	/0	33.60	i cai
Griffiths	28/42	26/42	_ _	17.16	1.08 [0.78, 1.48]	1997
Houdijk	20/35	26/37		14.79	0.81 [0.57, 1.16]	1998
Wischmeyer	7/12	9/14	_	6.02	0.91 [0.49, 1.68]	2001
Hall	38/179	43/184		13.15	0.91 [0.62, 1.33]	2003
Zhou	2/20	6/20	← ● ───────────────────────────────────	1.16	0.33 [0.08, 1.46]	2003
Fuentes-Orozco	4/17	12/16		3.00	0.31 [0.13, 0.77]	2004
Zhou 2004	3/15	4/15		1.46	0.75 [0.20, 2.79]	2004
Dechelotte 2006	23/58	32/56		12.87	0.69 [0.47, 1.03]	2006
Palmese	2/42	6/42	← ● ───────────────────────────────────	1.07	0.33 [0.07, 1.56]	2006
Estivariz	13/30	16/29		7.99	0.79 [0.46, 1.33]	2008
Fuentes-Orozco 2008	9/22	16/22		7.06	0.56 [0.32, 0.99]	2008
Perez-Barcena	11/15	13/15		14.28	0.85 [0.59, 1.22]	2008
Total (95% CI)	487	492	•	100.00	0.79 (0.68, 0.93)	
Total events: 160 (Glutamine), 2	209 (Control)					
Test for heterogeneity: Chi2 = 1	3.14, df = 11 (P = 0.28), l ² =	16.3%				
Test for overall effect: Z = 2.81	(P = 0.005)					
			0.1 0.2 0.5 1 2	5 10		
			Favours glutamine Favours con	trol		

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

Study or sub-category	N	Glutamine Mean (SD)	N	Control Mean (SD)	WMD (random) 95% Cl	Weight %	WMD (random) 95% Cl	Year
Houdijk	35	32.70(17.10)	37	33.00(23.80)		2.83	-0.30 [-9.83, 9.23]	1998
Powell-Tuck	83	43.40(34.10)	85	48.90(38.40)	← ■ ─────────	2.26	-5.50 [-16.48, 5.48]	1999
Brantley	31	19.50(8.80)	41	20.80(11.50)		6.87	-1.30 [-5.99, 3.39]	2000
Wischmeyer	12	40.00(10.00)	14	40.00(9.00)	+	- 4.12	0.00 [-7.36, 7.36]	2001
Zhou	20	67.00(4.00)	20	73.00(6.00)	_	9.14	-6.00 [-9.16, -2.84]	2003
Fuentes-Orozco	17	16.50(8.90)	16	16.70(7.00)	_	5.93	-0.20 [-5.65, 5.25]	2004
Peng	25	46.59(12.98)	23	55.68(17.36)	4	3.24	-9.09 [-17.82, -0.36]	2004
Zhou 2004	15	42.00(7.00)	15	46.00(6.60)		6.64	-4.00 [-8.87, 0.87]	2004
Palmese	42	12.00(4.60)	42	13.00(3.40)		11.32	-1.00 [-2.73, 0.73]	2006
Sahin	20	14.20(4.40)	20	16.40(3.90)		10.07	-2.20 [-4.78, 0.38]	2007
Cai	55	22.10(4.90)	55	23.80(5.10)		11.13	-1.70 [-3.57, 0.17]	2008
Estivariz	15	20.00(2.00)	12	30.00(6.00)	←	8.54	-10.00 [-13.54, -6.46]	2008
Fuentes-Orozco 2008	22	30.18(10.42)	22	26.59(13.30)		→ 4.36	3.59 [-3.47, 10.65]	2008
Luo 2008	11	7.60(0.70)	9	6.90(0.90)	-	12.36	0.70 [-0.02, 1.42]	2008
McQuiggan	10	32.00(13.60)	10	39.30(36.30)	← - - -	→ 0.55	-7.30 [-31.33, 16.73]	2008
Perez-Barcena	15	35.50(33.60)	15	42.90(28.80)	← •	• 0.63	-7.40 [-29.80, 15.00]	2008
Total (95% Cl) Test for heterogeneity: Chi ² = Test for overall effect: Z = 2.3	428 62.15, df = 15 76 (P = 0.006)	(P < 0.00001), I ² = 75.9%	436		•	100.00	-2.56 [-4.39, -0.74]	
					-10 -5 0 5	10		

Favoursglutamine Favours control

TOPIC: <u>9.4 (c) Composition of PN: Glutamine</u> 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		Ε	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	V	1	
6	Umpleby	Nutrition 2002		N	No significant outcomes
/	Ockenga	Clin Nutr 2002	,	V	Not ICU patients
8	Griffths	Nutrition 2002	V		
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	V		
			· ·		

36	Yeh	Langenbecks Arch Surg 2008		Elective surgery pts
I – inclu	ided E – evoluded			

I = included, E = excluded

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