1522994 - **Parenteral Glutamine Supplementation in Critical Illness: A Systematic Review**

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Background: The potential benefit of parenteral glutamine (GLN) supplementation has been one of the most commonly studied nutritional interventions in the critical care setting. Glutamine deficiency at ICU admission has been associated with an increased risk of death. Further, a significant body of pre-clinical in vivo and in vitro has demonstrated GLN may play a vital role in mediating an optimal stress and immune response to critical illness and injury. The aim of this systematic review was to incorporate recent trials of parenteral GLN supplementation of in critical illness with previously existing data.

Methods: All prospective randomized controlled trials of parenterally administered GLN in critically ill patients conducted from 1997 to 2012 were identified. Studies of enteral GLN only or combined enteral (EN)/parenteral GLN were excluded. Methodological quality of studies was scored and data abstracted by independent reviewers. Our primary endpoint was overall mortality, which is hospital mortality but includes ICU or 28-day mortality if hospital mortality was not reported. A sensitivity analysis was conducted excluding studies of patients receiving EN as the only method of artificial nutrition (n=3).

Results: 27 studies in 2317 patients examining only parenteral GLN supplementation were identified in ICU patients with diagnoses ranging from pancreatitis, trauma, burns and sepsis. In the majority of these studies, the intervention and control groups received parenteral nutrition (PN) only. As shown in Figure 1, when all the 8 level 1 and 19 level 2 studies reporting mortality were aggregated, parenteral GLN supplementation was associated with a trend towards reduction of overall mortality (RR 0.88, 95% CI 0.75, 1.02, p=0.10). In studies examining only patients receiving PN, supplementation with GLN was associated with a trend towards a reduction in overall mortality (RR 0.85, 95% CI 0.71, 1.01, p=0.07) and a significant reduction in hospital mortality (Figure 2) in the studies, which reported this endpoint (RR 0.67, 95% CI 0.51, 0.90, p=0.007). When the three studies in which patients only received EN were aggregated, GLN supplementation had no effect on overall mortality or hospital mortality. In addition, GLN-supplemented PN was found to be associated with a trend towards a reduction in infectious complications (p = 0.21), ICU length of stay (LOS) (p = 0.16) and a significant reduction in hospital LOS (p = 0.03) (Figure 2). However, significant heterogeneity was present in the LOS analyses.

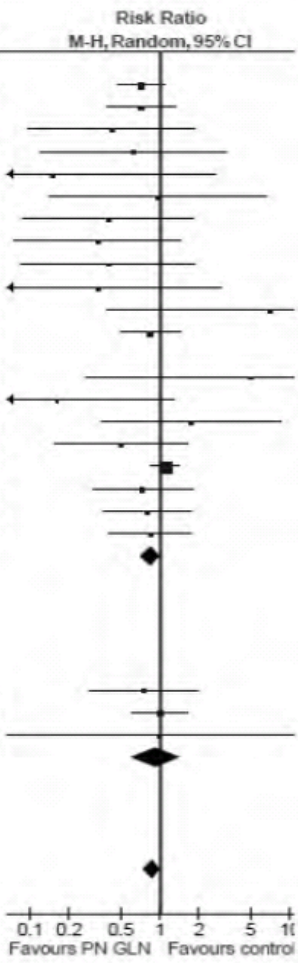
Conclusions: When all recent studies of parenteral GLN-supplementation are evaluated, GLN-supplementation of PN is associated with a significant reduction in hospital mortality and a trend towards a reduction in overall mortality. GLN-supplemented PN is also associated with a trend towards reduced infectious complications and was associated with a significant reduction in ICU and hospital LOS. The role of parenteral GLN supplementation of EN, appears safe, but clinical data supporting it's use are not yet sufficient to make a recommendation. Significant heterogeneity and statistical imprecision weaken any clinical inferences that can be made from

this analysis.

Figure 1: Mortality Outcomes

Overall Mortality

Study or Subgroup	PN GLN Events	PN GLN Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.3.1 PN GLN							
Griffiths	18	42	25	42	12.8%	0.72 [0.47, 1.11]	1997
Powell-Tuck	14	83	20	85	6.3%	0.72 [0.39, 1.32]	1999
Wischmeyer	2	15	5	16	1.1%	0.43 [0.10, 1.88]	2001
Fuentes-Orozco 2004	2	17	3	16	0.9%	0.63 [0.12, 3.28]	2004
Xian-Li	0	20	3	21	0.3%	0.15 [0.01, 2.73]	2004
Dechelotte	2	58	2	56	0.6%	0.97 [0.14, 6.62]	2006
Tian	2	20	5	20	1.0%	0.40 [0.09, 1.83]	2006
Sahin	2	20	6	20	1.1%	0.33 [0.08, 1.46]	2007
Fuentes-Orozco 2008	2	22	5	22	1.0%	0.40 [0.09, 1.85]	2008
Yang 2008	1	25	3	25	0.5%	0.33 [0.04, 2.99]	2008
Perez-Barcena 2008	3	15	0	15	0.3%	7.00 [0.39, 124.83]	2008
Cai	17	55	20	55	8.5%	0.85 [0.50, 1.44]	2008
Luo	0	11	0	9		Not estimable	2008
Duska	2	10	0	10	0.3%	5.00 [0.27, 92.62]	2008
Estivariz	1	32	6	31	0.6%	0.16 [0.02, 1.26]	2008
Perez-Barcena 2010	4	23	2	20	0.9%	1.74 [0.36, 8.51]	2010
Cekman	3	15	6	15	1.7%	0.50 [0.15, 1.64]	2011
Andrews	88	250	80	252	38.7%	1.11 [0.87, 1.42]	2011
Wernerman	8	205	11	208	3.0%	0.74 [0.30, 1.80]	2011
Grau	9	59	13	68	3.9%	0.80 [0.37, 1.73]	2011
Ziegler	11	75	13	75	4.4%	0.85 [0.41, 1.77]	2012
Subtotal (95% CI)		1072		1081	87.9%	0.85 [0.71, 1.01]	
Total events	191		228				
Heterogeneity: Tau² = 0.00; Chi² = 19.46, df = 19 (P = 0.43); I² = 2%							
Test for overall effect: Z = 1.82 (P = 0.07)							
2.3.2 EN GLN							
Palmese	6	42	8	42	2.5%	0.75 [0.28, 1.97]	2006
Ozgultekin	12	20	12	20	9.2%	1.00 [0.60, 1.66]	2008
Eroglu	1	20	1	20	0.3%	1.00 [0.07, 14.90]	2009
Subtotal (95% CI)		82		82	12.1%	0.94 [0.61, 1.47]	
Total events	19		21				
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Total (95% CI)		1154		1163	100.0%	0.88 [0.75, 1.02]	
Total events	210		249				
Heterogeneity: Tau² = 0.00; Chi² = 19.88, df = 22 (P = 0.59); I² = 0%							
Test for overall effect: Z = 1.67 (P = 0.10)							
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%							



Hospital Mortality

Study or Subgroup	PN GLN Events	PN GLN Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Griffiths	18	42	25	42	44.2%	0.72 [0.47, 1.11]	1997
Powell-Tuck	14	83	20	85	21.7%	0.72 [0.39, 1.32]	1999
Wischmeyer	2	15	5	16	3.7%	0.43 [0.10, 1.88]	2001
Xian-Li	0	20	3	21	1.0%	0.15 [0.01, 2.73]	2004
Fuentes-Orozco 2004	2	17	3	16	3.0%	0.63 [0.12, 3.28]	2004
Dechelotte	2	58	2	56	2.2%	0.97 [0.14, 6.62]	2006
Sahin	2	20	6	20	3.7%	0.33 [0.08, 1.46]	2007
Perez-Barcena 2008	3	15	0	15	1.0%	7.00 [0.39, 124.83]	2008
Estivariz	1	32	6	31	1.9%	0.16 [0.02, 1.26]	2008
Luo	0	11	0	9		Not estimable	2008
Yang 2008	1	25	3	25	1.7%	0.33 [0.04, 2.99]	2008
Perez-Barcena 2010	0	23	1	20	0.8%	0.29 [0.01, 6.78]	2010
Ziegler	11	75	13	75	15.0%	0.85 [0.41, 1.77]	2012
Total (95% CI)		436		431	100.0%	0.67 [0.51, 0.90]	
Total events	56		87				
Heterogeneity: Tau² = 0.00; Chi² = 8.02, df = 11 (P = 0.71); I² = 0%							
Test for overall effect: Z = 2.70 (P = 0.007)							

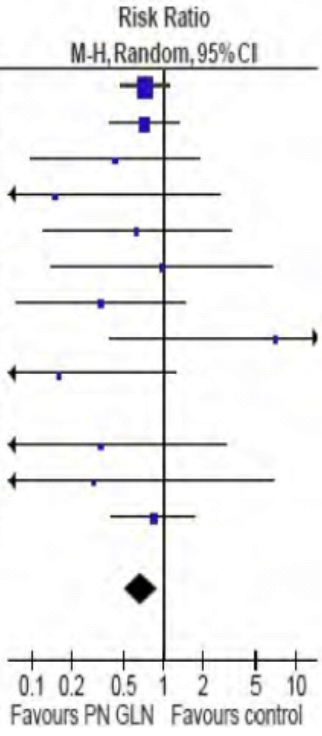
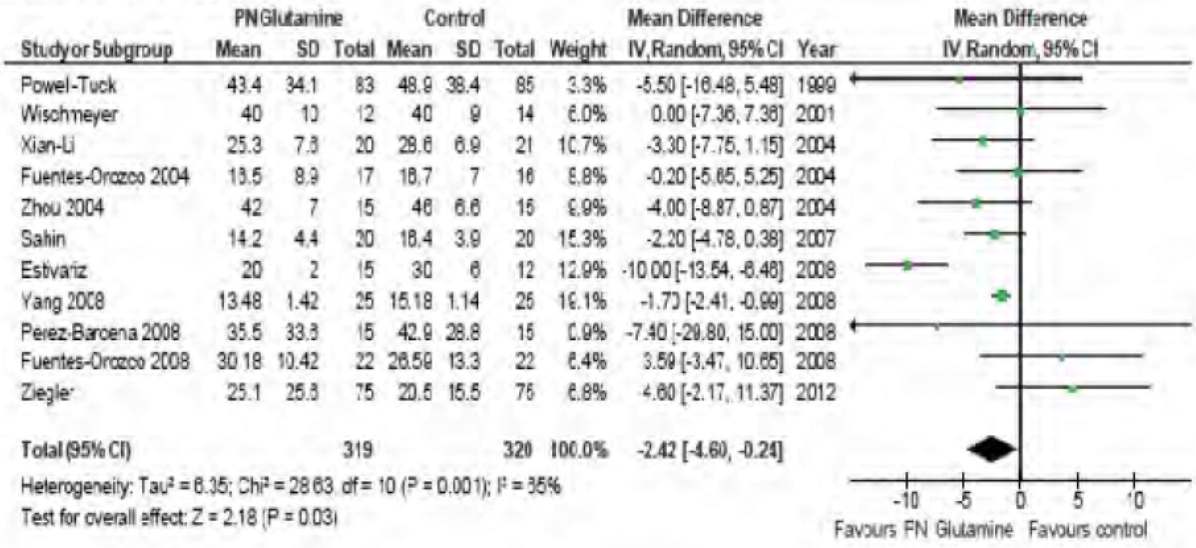


Figure 2 Overall Complications

Hospital Length of Stay



Study or Subgroup	PN Glutamine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Powel-Tuck	43.4	34.1	83	48.9	38.4	85	3.3%	-5.50 [-16.48, 5.48]	1999
Wischmeyer	40	10	12	40	9	14	6.0%	0.00 [-7.36, 7.36]	2001
Xian-Li	25.3	7.8	20	29.6	6.9	21	10.7%	-3.30 [-7.75, 1.15]	2004
Fuentes-Orozco 2004	13.5	8.9	17	18.7	7	16	6.8%	-0.20 [-5.65, 5.25]	2004
Zhou 2004	42	7	15	46	6.6	15	6.9%	-4.00 [-8.87, 0.87]	2004
Sahin	14.2	4.4	20	18.4	3.9	20	15.3%	-2.20 [-4.78, 0.38]	2007
Estivariz	20	2	15	30	6	12	12.9%	-10.00 [-13.54, -6.46]	2008
Yang 2008	13.48	1.42	25	15.18	1.14	25	16.1%	-1.70 [-2.41, -0.99]	2008
Perez-Barcena 2008	35.5	33.8	15	42.9	28.8	15	0.9%	-7.40 [-29.80, 15.00]	2008
Fuentes-Orozco 2008	30.18	10.42	22	26.59	13.3	22	6.4%	3.59 [-3.47, 10.65]	2008
Ziegler	25.1	25.8	75	20.6	15.5	75	6.8%	4.60 [-2.17, 11.37]	2012
Total (95% CI)			319			320	100.0%	**-2.42 [-4.60, -0.24]**	

Heterogeneity: Tau² = 6.35; Chi² = 28.63, df = 10 (P = 0.001); I² = 65%

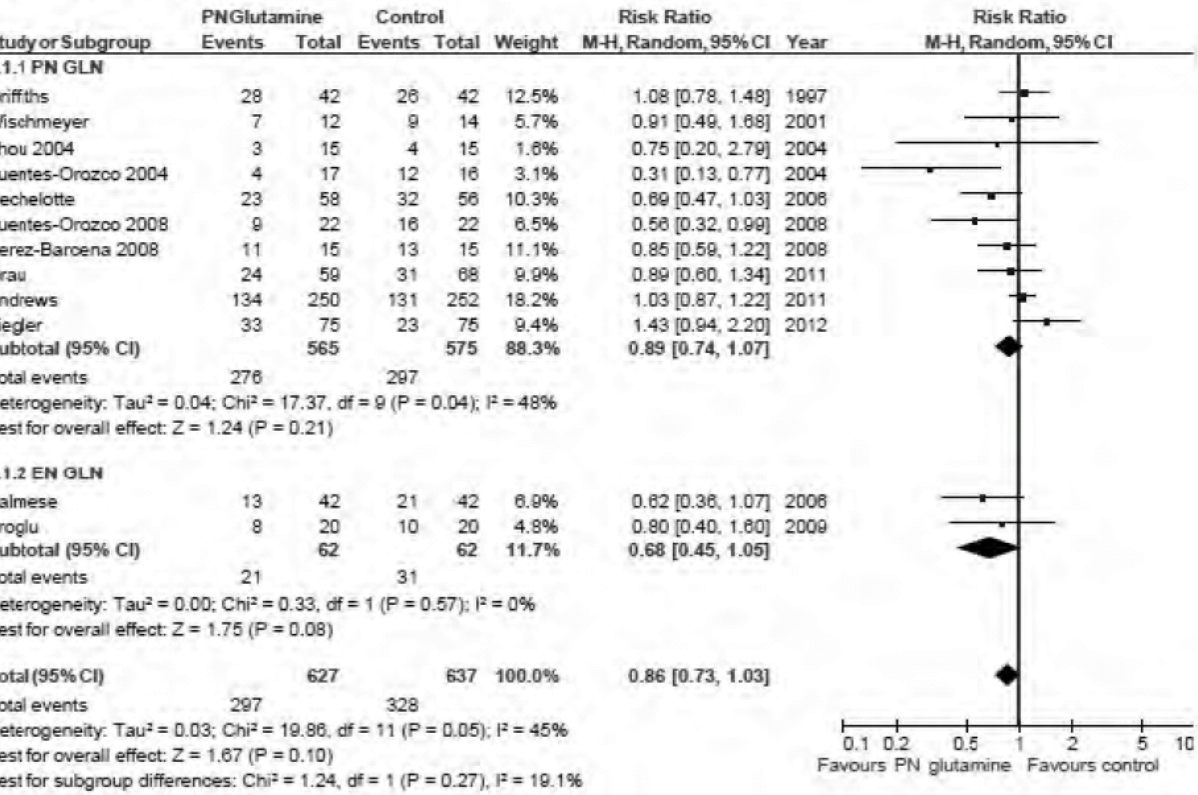
Test for overall effect: Z = 2.18 (P = 0.03)

Mean Difference IV, Random, 95% CI

-10 -5 0 5 10

Favours PN Glutamine Favours control

Infectious Complications



Study or Subgroup	PN Glutamine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.1.1 PN GLN							
Griffiths	28	42	26	42	12.5%	1.08 [0.78, 1.48]	1997
Wischmeyer	7	12	9	14	5.7%	0.91 [0.49, 1.68]	2001
Zhou 2004	3	15	4	15	1.6%	0.75 [0.20, 2.79]	2004
Fuentes-Orozco 2004	4	17	12	16	3.1%	0.31 [0.13, 0.77]	2004
Dechelotte	23	58	32	56	10.3%	0.69 [0.47, 1.03]	2006
Fuentes-Orozco 2008	9	22	16	22	6.5%	0.56 [0.32, 0.99]	2008
Perez-Barcena 2008	11	15	13	15	11.1%	0.85 [0.59, 1.22]	2008
Grau	24	59	31	68	9.9%	0.89 [0.60, 1.34]	2011
Andrews	134	250	131	252	18.2%	1.03 [0.87, 1.22]	2011
Ziegler	33	75	23	75	9.4%	1.43 [0.94, 2.20]	2012
Subtotal (95% CI)		565		575	88.3%	**0.89 [0.74, 1.07]**	
Total events	276		297				
Heterogeneity: Tau² = 0.04; Chi² = 17.37, df = 9 (P = 0.04); I² = 48%							
Test for overall effect: Z = 1.24 (P = 0.21)							
2.1.2 EN GLN							
Palmese	13	42	21	42	6.9%	0.62 [0.36, 1.07]	2006
Eroglu	8	20	10	20	4.8%	0.80 [0.40, 1.60]	2009
Subtotal (95% CI)		62		62	11.7%	**0.68 [0.45, 1.05]**	
Total events	21		31				
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%							
Test for overall effect: Z = 1.75 (P = 0.08)							
Total (95% CI)		627		637	100.0%	**0.86 [0.73, 1.03]**	
Total events	297		328				
Heterogeneity: Tau² = 0.03; Chi² = 19.86, df = 11 (P = 0.05); I² = 45%							
Test for overall effect: Z = 1.67 (P = 0.10)							
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.1%							

Risk Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours PN glutamine Favours control