### 4.1.c Composition of EN: Glutamine

July 2013

There were no new randomized controlled trials since the 2009 update but a caution against the use of any glutamine in patients with shock and MOF was added given the possibility of harm as demonstrated by the results of the REDOXS study of combined enteral and parenteral glutamine.

Recommendation 2013: Based on 2 level 1 and 7 level 2 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. In addition, we strongly recommend that any glutamine NOT be used in critically ill patients with shock and multi-organ failure (refer to section 9.4 b Combined Parenteral and Enteral Glutamine).

**Discussion 2013:** 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). There was a large treatment effect with respect to a reduced length in hospital stay however the data was quite skewed. Given that all studies were single centre trials, the likelihood of results being replicated in other settings is low. The cost and feasibility considerations were favourable despite potential limitations in acquiring the product. Given the results of the REDOXS study and harm associated with glutamine in patients with shock and multi-organ failure, we considered it unsafe to administer even EN glutamine to burns/trauma patients with shock and multi-organ failure. 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 to 0.5 gm/kg/day would be reasonable. The effect of parenteral glutamine is discussed separately (section 9-4).

Recommendation 2009: Based on 2 level 1 and 7 level 2 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 2009:** 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). There was a large treatment effect with respect to a reduced length in hospital stay however the data was quite skewed. Given that all studies were single centre trials, the likelihood of results being replicated in other settings is low. 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 to 0.5 gm/kg/day would be reasonable. The effect of parenteral glutamine is discussed separately (section 9-4).

# Semi Quantitative Scoring

	Definition	2009 Score (0,1,2,3)	2013 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listeda higher score indicates a larger effect size	2	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	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 outcomesa higher score indicates presence of more of these features in the trials appraised	2	2
Homogeneity or Reproducibility	Similar direction of findings among trialsa higher score indicates greater similarity of direction of findings among trials	1	1
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	2
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.	1	1
Low cost	Estimated cost of implementing the intervention listeda higher score indicates a lower cost to implement the intervention in an average ICU	3	3
Feasible	Ease of implementing the intervention listeda higher score indicates greater ease of implementing the intervention in an average ICU	3	3
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listeda higher score indicates a lower probability of harm	3	2

### 4.1.c Composition of EN: Glutamine

#### Question:

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

Summary of Evidence: There were 7 level 2 studies and 2 level 1 studies, 3 of which were in burn patients (Garrel 2003, Zhou 2003, Peng 2004), 3 in trauma patients (Houdijk 1998, Brantley 2000 and McQuiggan 2008) and the remaining 3 were in mixed ICU patients.

**Mortality:** When the data from all the 8 trials that reported on mortality were aggregated, there was no statistically significant difference in mortality between the groups receiving glutamine supplemented EN or not. (RR = RR 0.81, 95% CI 0.48, 1.34 p = 0.41) (figure 1). Subgroup analyses of the 3 studies of trauma patients showed that glutamine supplemented EN had no significant effect on mortality (RR= 0.79, 95% CI 0.16, 3.92, p = 0.77, some heterogeneity present, 21%) (figure 2). In the 2 studies of burn patients, patient deaths occurred in only one study (Garrel 2003) and these were significantly lower than the control group (RR 0.19, 95% CI 0.57-0.76, p =0.02).

**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) (figure 3). In one study in burn patients (Zhou 2003), and one study in trauma patients (Houdijk 1998), glutamine supplemented EN was associated with a significant reduction in infectious complications.

Length of Stay: There were 5 level 2 studies that demonstrated a significant reduction in length of hospital stay (WMD (weighted mean difference) - 4.50, 95% CI -7.29, -1.70, p= 0.002) (see figure 4). Two of these studied also reported on ICU LOS but there were no significant differences between the two groups.

#### 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.

3) Glutamine supplemented enteral nutrition is associated with a significant reduction in hospital length of stay 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

#### July 2013

### For overall effect of glutamine supplementation (enteral and parenteral), refer to pages 4.1(c)-6 and 4.1(c)-7.

Study	Population	Methods	Intervention	Mortalit		Infection	ıs # (%)‡	Hospital s	tay (days)
		(score)	-Dose (gm/kg/day) -Type of feeding	Experimental	Control	Experimental	Control	Experimental	Control
1) Houdijk 1998	Critically ill trauma N = 80	C.Random: Yes ITT: No Blinding: Yes (10)	<ul> <li>&gt; 0.25</li> <li>Altira Q (glutamine enriched formula) vs.</li> <li>isonitrogenous control (added amino acids)</li> <li>Same volume of feeding received in both groups</li> </ul>	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)

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

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)
8) Luo 2007***	Medical Surgical N=44	C.Random: not sure ITT: no Blinding: double (9)	0.32 glutamine + IV saline + vs. Nutren + 15% Clinisol (placebo) (isocaoric, isonitrogenous) 1.7 gm/kg/d protein	1/12	0 /9	NA	NA	ICU 8.1 ± 0.4 (12)	ICU 6.9 ±0.9 (9)
9) McQuiggan 2008	Shock trauma patients N = 20	C.Random: Not sure ITT: yes Blinding: no (10)	0.5 (actual 0.4) Impact + glutasolve via NJ tube (1.3 gm/kg/day protein), bolus with H20 vs. Impact + protein supplements {isonitrogenous,isocaloric, 0.85 gm/kg/day protein}	0/10	2/10 (20)	NA	NA	Hospital 32 ± 13.6 (10) ICU 14.8± 6.7 (10)	Hospital $39.3 \pm 33.6 (10)$ ICU $10.4 \pm 6.2 (10)$

C.Random: concealed randomization median (range) ITT: intent to treat

EN: enteral nutrition TPN: Total parenteral nutrition NA: not available

then to treat and the section (number)
 the section in the section (number)
 the section included in meta analysis (Hall 2003 p = NS)
 the section included in meta-analysis
 the section included in meta-analysis
 the section included in meta-analysis

itudy	EN glutamine	Control		RR (random)	Weight	RR (random)	
r sub-category	n/N	n/N		95% CI	%	95% CI	Year
Houdijk	4/41	3/39			- 10.76	1.27 [0.30, 5.31]	1998
lones	10/26	9/24			29.48	1.03 [0.50, 2.08]	1999
Brantley	0/31	0/41				Not estimable	2000
Garrel	2/21	12/24	· · ·		11.48	0.19 [0.05, 0.76]	2003
Hall	27/179	30/184			42.70	0.93 [0.57, 1.49]	2003
Zhou	0/20	0/20		200 C		Not estimable	2003
Luo	1/12	0/9	87 <u>-</u>		2.63	2.31 [0.10, 50.85]	2008
McQuiggan	0/10	2/10	< <del>· · · ·</del>		2.94	0.20 [0.01, 3.70]	2008
otal (95% Cl)	340	351		-	100.00	0.81 [0.48, 1.34]	
otal events: 44 (EN glutar	nine), 56 (Control)						
est for heterogeneity: Ch	i <sup>2</sup> = 6.73, df = 5 (P = 0.24), l <sup>2</sup> = 25	.7%					
est for overall effect: Z =	0.83 (P = 0.41)						

# Figure 1. Mortality

Figure 2. S	Subgroup analysis of studie	es of Trauma patients
Review:	alutamine New review	

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

Study or sub-category	EN glutamine n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Houdijk	4/41	3/39			1.27 [0.30, 5.31]	1998
Brantley	0/31	0/41	1-		Not estimable	2000
McQuiggan	0/10	2/10	← ■		0.20 [0.01, 3.70]	2008
Total (95% Cl)	82	90		100.00	0.79 [0.16, 3.92]	
Total events: 4 (EN glutarnin Tost for betergepeitur, Chi	ne), 5 (Control) ² = 1.27, df = 1 (P = 0.26), l² = 21./	49/				
Test for overall effect: Z =		470				
			0.1 0.2 0.5 1 2	5 10		
			Favoura EN dutamina - Favou	re control		

Favours EN glutamine Favours control

Comparison: 01 Enteral (	lew review Glutamine vs Control us complications					
Study or sub-category	EN glutamine n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Hall	38/179	43/184		44.62	0.91 [0.62, 1.33]	2003
Houdijk	20/35	26/37	_ <b>_</b>	52.34	0.81 [0.57, 1.16]	1998
Zhou	2/20	6/20	< <b>- - + − +</b>	3.04	0.33 [0.08, 1.46]	2003
Total (95% Cl) Total events: 60 (EN glutamir	234 ne), 75 (Control)	241	•	100.00	0.83 [0.64, 1.08]	
Test for heterogeneity: Chi <sup>2</sup>	= 1.69, df = 2 (P = 0.43), l <sup>2</sup> = 0%					
Test for overall effect: Z = 1	.41 (P = 0.16)					
			0.1 0.2 0.5 1 2	5 10		
			Favours EN glutamine Favours c	ontrol		

## Figure 4. Hospital LOS

	310°YE4							
Study	E	Enteral Glutamine		Control	VVMD (random)	Weight	WMD (random)	
or sub-category	N	Mean (SD)	N	Mean (SD)	95% CI	%	95% CI	Year
Houdijk	35	32.70(17.10)	37	33.00(23.80) -			-0.30 [-9.83, 9.23]	1998
Brantley	31	19.50(8.80)	41	20.80(11.50)		28.87	-1.30 [-5.99, 3.39]	2000
Zhou	20	67.00(4.00)	20	73.00(6.00)		51.83	-6.00 [-9.16, -2.84]	2003
Peng	25	46.59(12.98)	23	55.68(17.36) 🔶	a contraction of the second seco	9.62	-9.09 [-17.82, -0.36]	2004
McQuiggan	10	32.00(13.60)	10	39.30(33.60) 🔸	•	→ 1.53	-7.30 [-29.77, 15.17]	2008
Total (95% Cl)	121		131			100.00	-4.50 [-7.29, -1.70]	
Test for heterogeneity:	Chi <sup>2</sup> = 4.51, df = 4 (P	' = 0.34), I <sup>2</sup> = 11.3%			Contra a contra			
Test for overall effect: 2	= 3.15 (P = 0.002)							

## Overall Glutamine Supplementation (studies of Enteral and Parenteral supplementation)

 Review:
 glutamine New review (Version 01)

 Comparison:
 03 Glutamine vs Control

 Outcome:
 01 mortality

Study or sub-category	glutamine n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	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	-	11.00	Not estimable	2000
Wischmeyer	2/15	5/16	•	1.99	0.43 [0.10, 1.88]	2001
Garrel	2/21	12/24		2.30	0.19 [0.05, 0.76]	2001
Hall	27/179	30/184		19.12	0.93 [0.57, 1.49]	2003
Zhou	0/20	0/20		10.16	Not estimable	2003
Fuentes-Orozco	2/17	3/16		1.59	0.63 [0.12, 3.28]	2003
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]	2004
Palmese	6/42	8/42		4.65	0.75 [0.28, 1.97]	2006
Sahin	2/20	6/20		2.00	0.33 [0.08, 1.46]	2008
Cai	17/55	20/55		15.66	0.85 [0.50, 1.46]	2007
Duska	2/10	20/35		→ 0.51		2008
Estivariz	1/32	6/31			5.00 [0.27, 92.62]	2008
		•			0.16 [0.02, 1.27]	
Fuentes-Orozco 2008 Luo 2008	2/22	5/22		1.86	0.40 [0.09, 1.85]	2008
	1/23	0/9		→ 0.45	1.25 [0.06, 28.15]	2008
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% Cl)	782	782	•	100.00	0.75 [0.61, 0.93]	
Total events: 115 (glutamine), 1	, ,	~~				
Test for heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z = 2.65	1 1 11	0%				
			0.1 0.2 0.5 1 2	5 10		

Favours glutamine Favours control

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

Study or sub-category	Glutarnine n/N	Control n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	Year
Griffiths	28/42	26/42	_ <b>_</b> _	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	<b>_</b> _	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	<b>_</b>	3.00	0.31 [0.13, 0.77]	2004
Zhou 2004	3/15	4/15	<b>_</b>	1.46	0.75 [0.20, 2.79]	2004
Dechelotte 2006	23/58	32/56	_ <b>_</b>	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	<b>_</b>	7.99	0.79 [0.46, 1.33]	2008
Fuentes-Orozco 2008	9/22	16/22	<b>_</b>	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% Cl)	487	492	•	100.00	0.79 [0.68, 0.93]	
Total events: 160 (Glutamine), 2	209 (Control)					
Test for heterogeneity: $Chi^2 = 1$ Test for overall effect: $Z = 2.81$		16.3%				
			0.1 0.2 0.5 1 2	5 10		
			Foucure aliteraise - Foucure cor	teal		

Favours glutamine Favours control

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)	<b>_</b>	6.87	-1.30 [-5.99, 3.39]	2000
Wischmeyer	12	40.00(10.00)	14	40.00(9.00)	<b>_</b>	- 4.12	0.00 [-7.36, 7.36]	2001
Zhou	20	67.00(4.00)	20	73.00(6.00)	<b>_</b>	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)	<b>+-</b>	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)	— <b>—</b> —	11.32	-1.00 [-2.73, 0.73]	2006
Sahin	20	14.20(4.40)	20	16.40(3.90)	<b>_</b>	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)	<b>← −</b> − − −	→ 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% CI)	428		436		-	100.00	-2.56 [-4.39, -0.74]	
Test for heterogeneity: Chi <sup>2</sup> = Test for overall effect: Z = 2.7		(P < 0.00001), I <sup>2</sup> = 75.9%			-			
					-10 -5 0 5	10		
					Favoursclutamine Favours con	trol		

Favoursglutamine Favours control