9.4b Combined Parenteral and Enteral Glutamine Supplementation May 2015

2015 Recommendation: : *Based on one level 1 study and 1 level 2 study, we recommend that high dose combined parenteral and enteral glutamine supplementation NOT be used in critically ill patients*

2015 Discussion: The committee noted the inclusion of one single centre study in septic, malnourished ICU patients in which patients were given a total of 30 grams of glutamine via the enteral and parenteral route (Koskal 2014). When the data from this study was combined with the earlier study (Heyland 2014), there was no effect on mechanical ventilation. The lack of reporting of other clinical outcomes in this study was acknowledged as was the lower dose of administered glutamine compared to the Heyland 2014 study. The committee agreed that the increase of mortality seen across all time points with the use of high dose combined glutamine supplementation in the multicentre study of severely ill patients with at least two organ failures was still a concern, and hence the recommendation against the use of combined enteral and parenteral glutamine was not changed.

2013 Recommendation: *Based on one level 1 study, we strongly recommend that high dose combined parenteral and enteral glutamine supplementation NOT be used in critically ill patients with shock and multi-organ failure.*

2013 Discussion: The committee agreed that due to the unique methodology of the REDOXS trial (Heyland, 2013), in which combined parenteral and enteral glutamine supplementation was provided, this study not be included with other studies of parenteral glutamine supplementation in section 9.4a. The committee noted the large multicentre nature of this trial in which there was an increase in mortality across all time points with the use of high dose glutamine supplementation in severely ill patients with at least two organ failures.

Semi Quantitative Scoring

Values	Definition	2013 Score (0,1,2,3)	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	1	1
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	3
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	3	3
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	n/a	n/a
Adequacy of control group	Extent to which the control group presented 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 consistencies=2, very consistent=3)	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)	3	3
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	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	0	0
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	0	0

9.4b Combined Parenteral and Enteral Glutamine Supplementation

Question: Compared to placebo, does combined enteral and parenteral glutamine-supplementation result in improved clinical outcomes in critically ill patients?

Summary of evidence: There was one level 1 study and 1 level 2 study on glutamine supplementation administered via both PN and EN that were included.

Mortality: Based on the single study that reported on this outcome, glutamine supplementation administered via both PN and EN was associated with a significant increase in hospital (RR 1.20, 95% CI 1.02, 1.40, p=0.02), 28-day (RR 1.19, 95% CI 1.00, 1.42, p=0.05), 3-month (RR 1.20, 95% CI 1.04, 1.38, p=0.01), and 6-month mortality (RR 1.19, 95% CI 1.03, 1.36, p=0.02); and was associated with a trend towards a increase in 14-day mortality (RR 1.21, 95% CI 0.99, 1.48, p=0.07).

Infections: Based on the single study that reported on this outcome, glutamine supplementation administered via both PN and EN had no effect on overall infectious complications (RR 1.10, 95% CI 0.92, 1.31, p=0.32) or ventilator associated pneumonia (RR 1.08, 95% CI 0.82, 1.43, p=0.59).

Length of Stay: Based on the single study that reported on this outcome, glutamine supplementation administered via both PN and EN was associated with a trend towards an increase in ICU length of stay (WMD 1.80, 95% CI -0.76, 4.36, p=0.17), but had no effect on hospital length of stay (WMD 1.30, 95% CI -4.05, 6.65, p=0.63).

Duration of ventilation: Based on the 2 studies, no effect in duration of ventilation was seen with (WMD 0.28, 95% CI -2.85, 3.41, p=0.86; figure 1).

Conclusions:
1) Combined parenteral and enteral glutamine supplementation is associated with a significant increase in hospital, 28-day, 3-month, and 6-month mortality, as well as a trend towards a increase in 14-day mortality.
2) Combined parenteral and enteral glutamine supplementation has no effect on overall infectious complications, ventilator associated pneumonia or duration of mechanical ventilation.
3) Combined parenteral and enteral glutamine supplementation is associated with a trend towards an increase in ICU length of stay but has no effect on hospital length of stay.

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.

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

Study	Population	Methods (score)	Intervention	Mortality # (%)*		Infections # (%)†	
				GLN PN+EN	Placebo	GLN PN+EN	Placebo
1) Heyland 2013	Multicentre mixed ICUs N=1218	C.Random: yes ITT: yes Blinding: double (12)	GLN supplementation (0.35 g/kg/day) parenterally vs placebo; additional GLN supplementation (30 g/day) enterally vs placebo	Hospital 227/611 (37) RR 1.20, 95% CI 1.02, 1.40, p=0.02 14-day 157/611 (26) RR 1.21, 95% CI 0.99, 1.48, p=0.07 28-day 198/611 (32) RR 1.19, 95% CI 1.00, 1.42, p=0.05 3-month 252/611 (39) RR 1.20, 95% CI 1.04, 1.38, p=0.01 6-month 264/611 (44) RR 1.19, 95% CI 1.03, 1.36, p=0.02	Hospital 188/607 (31) 14-day 129/607 (21) 28-day 165/607 (27) 3-month 209/607 (32) 6-month 221/607 (37)	All 183/611 (30) RR 1.10, 95% CI 0.92, 1.31, p=0.32 VAP 88/611 (14) RR 1.08, 95% CI 0.82, 1.43, p=0.59	All 166/607 (27) VAP 78/607 (13)
2) Koksal 2014	Septic, malnourished ICU patients N=120	C.Random: yes ITT: other Blinding: single (outcomes) (9)	15 g/day parenteral glutamine + 15 g/day enteral glutamine + EN vs EN, no placebo, no supplemental glutamine	NR		NR	

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

Study	LOS days‡		Ventilator days‡	
	GLN PN+EN	Placebo	GLN PN+EN	Placebo
1) Heyland 2013	ICU 14.9 ± 29.1 (611) WMD 1.80, 95% CI -0.76, 4.36, p=0.17 Hospital 31.0 ± 52.6 (611) WMD 1.30, 95% CI -4.05, 6.65, p=0.63	ICU 13.1± 14.0 (607) Hospital 29.7 ± 42.1 (607)	11.6 ± 26.3 (611)	9.8 ± 12.3 (607)
2) Koksal 2014	NR		12.9±5.3	14.3±5.4

* presumed hospital mortality unless otherwise specified
† refers to the # of patients with infections unless specified
‡ LOS and ventilation statistics calculated using all patients who were discharged; for patients who died, death date was substituted for discharge date.

Figure 1: Duration of Mechanical Ventilation