9.4c: Enteral Glutamine vs. Parenteral Dipeptide Supplementation May 2015

NEW SECTION in 2015

2015 Recommendation: There are insufficient data to make a recommendation on the use of enteral glutamine vs. parenteral dipeptide supplementation. However given concerns of glutamine supplementation in general as per sections 4.1c EN glutamine, 9.4a PN glutamine and 9.4b EN+PN glutamine, *we strongly recommend that glutamine supplementation NOT be used in critically ill patients, hence we do not recommend the use of enteral glutamine or parenteral dipeptides.*

2015 Discussion: There was one new small pilot study that compared a similar dose of enteral glutamine dipeptide supplementation with .IV glutamine dipeptide infusion over 5 days in surgical and critically ill trauma patients (Uranjek 2014). The committee noted the presence of a trend towards a reduction in ICU mortality, ICU and hospital LOS with the enteral supplemented group. The generalizability of the findings from this small, underpowered study were felt to be limited and in light of the safety concerns of enteral or parenteral glutamine supplementation (see section 4.1c, 9.4a and 9.4b), the committee decided to caution against the use of any glutamine and hence did not put forward a recommendation for enteral administration over supplementation of parenteral dipeptides.

Semi Quantitative Scoring

Values	Definition	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	2 (ICU 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	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 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	NA
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	1
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3)	1
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
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	3
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3
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

9.4c: Enteral vs. Parenteral Glutamine Supplementation

Question: Does enteral or parenteral glutamine-supplementation result in improved clinical outcomes in critically ill patients?

Summary of evidence: There was one level 1 study that compared the use of IV glutamine dipeptide infusion and polymeric formula (Ensure) to enteral glutamine supplemented formula (Alitraq) x 5 days (Uranjek 2013) in surgical and critically ill trauma patients.

Mortality: Glutamine supplementation administered enterally was associated with a trend towards a reduction in ICU mortality (p = 0.07) (RR 0.19, 95% CI 0.02, 1.52) when compared to parenteral dipeptides but had no effect on 6-month survival (RR 0.70, 95% CI 0.27, 1.83). (p = 0.51)

Infections: Glutamine supplementation administered enterally had no effect on overall infectious complications (RR 0.74, 95% CI 0.40 1.38, p=0.35) or ventilator associated pneumonia (RR 1.68, 95% CI 0.36, 1.30, p=0.24) when compared to parenteral glutamine administration

Length of Stay: Enteral glutamine supplementation was associated with a trend towards a reduction in ICU LOS and hospital LOS when compared to supplementation with parenteral dipeptides (both, p =0.10)

Duration of ventilation: Enteral glutamine supplementation vs. parenteral dipeptides had no effect on ventilation (p =0.29)

Conclusions:
1) Enteral glutamine supplementation versus parenteral dipeptides is associated with a trend towards a reduction in ICU mortality, though no effect was seen on 6-month mortality
2) Enteral glutamine supplementation versus parenteral dipeptides is associated with a trend towards a reduction in ICU and hospital LOS.
3) Enteral glutamine supplementation versus parenteral dipeptides has no effect on infectious outcomes or duration of ventilation.

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 Enteral vs. Parenteral glutamine in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)*		Infections # (%)†	
				EN GLN	PN GLN	EN GLN	PN GLN
1) Uranjek 2013	Surgical and critically ill trauma patients N=90	C.Random: yes ITT: other Blinding: single (outcomes) (9)	EN formula containing supplemental GLN (Alitraq) x 5 days w dose dependent on EN prescription, supplemental PN as needed vs EN (Ensure) + IV glutamine dipeptide infusion x 5 days, supplemental PN as needed Grams glutamine /kg/d received EN GLN 0.22 (0.12–0.23) IV GLN 0.19 (0.18–0.23)	ICU 1/42 (2) 6-month 6/42 (14)	ICU 5/39 (13) 6-month 8/39 (21)	All 12/42 (29) Pneumonia 11/42 (26)	All 15/39 (38) Pneumonia 15/39 (38)

Table 1. Randomized studies evaluating Enteral vs. Parenteral glutamine in critically ill patients (continued)

Study	LOS days		Ventilator days		Other Outcomes	
	EN GLN	PN GLN	EN GLN	PN GLN	EN GLN	PN GLN
1) Uranjek 2013	ICU 11.5 (8.0–21.25) Hospital 29.5 (16.0–50.0)	ICU 17.0 (10.0–25.0) Hospital 30.0 (21.0–40.0)	6.0 (4.75-13.25)	9.0 (4.0–20.4)	Kcal/kg/d 17.32 (15.22–22.08) Grams nitrogen/kg/d 0.15 (0.11–0.17) EN start (h) 10.5 (6–15)	17.81 (14.72–20.66) 0.13 (0.12–0.14) 12.00 (6–20)

* presumed hospital mortality unless otherwise specified
† refers to the # of patients with infections unless specified